Endoscopic ultrasonography in esophageal carcinoma: a narrative review

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Objective: The goal of this review is to summarize and discuss the role of endoscopic ultrasound (EUS) in the staging and diagnosis of esophageal carcinoma.

Background: EUS has a well-established role in the diagnosis and staging of esophageal carcinoma. Technological advancements over the last three decades have increased the ability and utility of EUS; it is a mainstay in the workup of esophageal carcinoma.

Methods: Literature review and summary of the available information relating to the use of EUS in practice, along with a review of its limitations in practice.

Conclusions: The technology that underlies EUS has evolved over the last three decades. In particular, EUS plays a vital role in determining the extent of local extension of the tumor, which is defined using the T-staging system. Furthermore, it can accurately identify metastases to nearby lymph nodes and liver, and provides the capability of tissue sampling of metastatic disease with fine needle aspiration (FNA), thereby expanding its diagnostic power. As EUS has developed, it has surpassed other modalities for the purposes of both T and N staging of esophageal cancers as delineated by the American Joint Committee on Cancer/ Union for International Cancer Control (AJCC/UICC). EUS is a cornerstone in the multimodal approach to the diagnosis and staging of esophageal cancer which also includes upper endoscopy, cross-sectional imaging, positron emission tomography (PET) scanning, mediastinoscopy and laparoscopy. Limitations of EUS include operator dependence, understaging of the disease in obstructing tumors, difficulty differentiating between T2 and T3 disease, and reduced yield in patients following chemoradiation therapy.

Keywords: Esophageal carcinoma; endoscopic ultrasound (EUS); cancer staging

Introduction

Endoscopic ultrasound (EUS) was first introduced in the 1980s as a diagnostic technique, utilizing the hypothesis that superior ultrasound resolution and images could be obtained by directly visualizing the gastrointestinal lumen in close proximity, avoiding intervening tissues. It was first utilized in the United States in the early 1990s to image the pancreas. Initial studies were performed to assess EUS as a diagnostic tool in pancreatic cancer. The field of EUS blossomed over time to assume an integral role in the diagnosis and staging of numerous intraluminal and extraluminal diseases of the gastrointestinal tract and surrounding structures. EUS was first used in the staging of esophageal cancer as a supplement to computed tomography (CT) scans, as the ultrasound images provided a superior modality for differentiating layers of the esophageal wall, and by extension, enabling more accurate staging of the
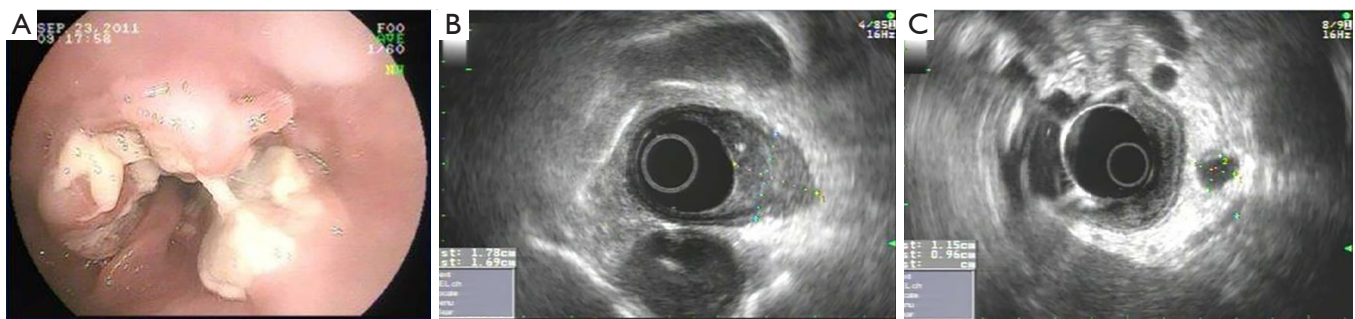
Figure 1 T3 esophageal adenocarcinoma with malignant lymph node. (A) Endoscopic image of T3 esophageal adenocarcinoma. (B) EUS in the same patient, demonstrating T3 disease with tumor infiltration through the muscularis propria into the adventitia. (C) Malignant lymph node in the same patient. Note diameter >1 cm, round contour with well-defined margins. EUS, endoscopic ultrasound.

disease. In addition to visualization, EUS-guided fine needle aspiration (FNA) with cytologic analysis has also become a commonplace method for tissue acquisition (1). The ability to obtain tissue has proven to be instrumental, increasing the specificity of EUS for diagnosing malignant lymph nodes and adjacent structures. On the whole, EUS has become an integral component in the diagnosis and staging of esophageal carcinoma. The role of EUS in the staging and diagnosis of esophageal carcinoma is described herein. We present the following article in accordance with the Narrative Review reporting checklist (available at https://aoe.amegroups.com/article/view/10.21037/aoe-21-25/rc).

Methods

The information used to write this review was gathered from available resources and literature sourced in validated databases, most notably PubMed. Articles included in this review include original articles, meta-analyses, and systematic reviews of the literature. All articles used in the composition of this narrative review are peer reviewed and include information that is central to the objectives of this article.

Discussion

Staging of esophageal cancer

The 'TNM' staging system, as described and developed by the American Joint Committee on Cancer/Union for International Cancer Control (AJCC/UICC), is the universally adopted method of staging esophageal cancer (2). The primary tumor (T) is staged 0–4, with an exception TX used to denote tumors that cannot be properly assessed

due to imaging limitations or specific aspects of the tumor. T0 is the absence of invasive cancer. Tis refers to high-grade dysplasia in the tissue specimen, but without frank tumor. T1 refers to mucosal tumor and is divided into T1a and T1b, with the former invading the lamina propria and/or muscularis mucosae and the latter invading submucosa. T2 tumors invade but do not penetrate through the muscularis propria. T3 tumors invade through the muscularis propria into the adventitia. T4 tumors are the most advanced, marked by invasion of adjacent structures. The most updated guidelines differentiate between T4 tumors, with T4a denoting resectable tumors invading pleura, pericardium, or diaphragm, and T4b referring to unresectable tumor in tissues such as the aorta, vertebrae, or trachea). There are no differences in the T-staging of squamous cell carcinoma (SCC) of the esophagus and adenocarcinoma/esophago-gastric junction (EGJ) tumors.

Regional lymph nodes (N) are staged from N0 to N3, again including NX for lymph nodes that cannot be assessed. N0 refers to no lymph node metastasis. N1 denotes metastases to 1–2 regional lymph nodes. N2 designates metastases to 3–6 regional lymph nodes. N3 refers to metastasis to 7 or more regional lymph nodes. Squamous cell and adenocarcinoma/EGJ tumors are N-staged similarly.

The M category is binary, with M0 referring to no known distant metastasis and M1 referring to distant metastasis, either to non-regional lymph nodes or distant organs. An overview of the TNM staging system can be seen in *Figure 1*.

Using the combination of the TNM stage and histologic grade of the tumor, an overall clinical stage is assigned to the tumor, ranging from T1a to 4b. Tumor stage is critical

Table 1 AJCC/UICC TNM staging of esophageal cancer (2)

Category	Description
T	
TX	Tumor cannot be assessed
T0	No evidence of tumor in esophagus
Tis	High-grade dysplasia, no extension beyond basement membrane
T1	Tumor invading the lamina propria, muscularis mucosae, or submucosa
T1a	Tumor invading the lamina propria or muscularis mucosae
T1b	Tumor invading the submucosa
T2	Tumor invading the muscularis propria
T3	Tumor invading the adventitia
T4	Tumor invading adjacent structures
T4a	Tissue involved: pleura, pericardium, azygous vein, diaphragm, peritoneum
T4b	Tissue involved: aorta, vertebral body, trachea, other
N	
NX	Regional nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis identified in 1–2 regional lymph nodes
N2	Metastasis identified in 3–6 regional lymph nodes
N3	Metastasis identified in 7 or more regional lymph nodes
M	
M0	No distant metastasis
M1	Distant metastasis present

in determining the optimal therapy such as primary surgery, neoadjuvant chemoradiation followed by surgery, definitive chemoradiation, or palliative chemotherapy. Staging is also a strong determinant of prognosis. A further discussion of the details of this staging system and treatment implications are beyond the scope of this discussion. Nonetheless, it is this overall stage that subtly differentiates between SCC and adenocarcinoma/EGJ tumors. In this system, proximal and mid-esophagus SCCs are considered to be more aggressive than distal esophageal SCC in the stage I and II categories; conversely the location of adenocarcinomas/EGJ tumors along the length of the esophagus is not included in their prognostic staging. The specifics of staging of esophageal carcinoma are detailed in the text and summarized in *Table 1* below.

Staging of esophageal cancer generally requires a multimodal approach, including imaging and invasive procedures (3). The initial diagnosis of esophageal cancer is usually made by upper endoscopy, with imaging following upper endoscopy with mucosal biopsies confirming the diagnosis of cancer. The available diagnostic studies include CT scan, full body integrated fluorodeoxyglucose positron emission tomography (FDG-PET) CT, EUS, and diagnostic laparoscopy and mediastinoscopy. Although CT is easily obtained and noninvasive, it lacks sensitivity and accuracy for identifying tumor stage in esophageal carcinoma (4,5). With regard to diagnosis of early esophageal cancer (T2 disease and below), EUS has been considered the gold standard with sensitivity of 80%, significantly outperforming CT (6). Despite the added benefits of FDG-PET, EUS outperforms that modality as well in detection of locoregional spread of primary tumor and regional lymph node metastasis and N3 describes more than 7 lymph nodes involvement (7). Numerous studies

have shown superior accuracy of EUS in the staging of esophageal cancer. One significant meta-analysis of 44 studies reported overall T-stage accuracy of 79%; T1a stage sensitivity and specificity of 84% and 91%, and T1b stage pooled sensitivity and specificity of 83% and 89% (8). FDG-PET and CT scan provide obvious benefits in the diagnosis of distant metastatic disease, as well as staging early cancers which are potentially curable (9). A few factors contribute to the superiority of EUS over these modalities for the primary tumor and regional lymph nodes. First, EUS enables differentiation of esophageal wall layers that classify the T stage of the tumors. With regard to locoregional extension and lymph node involvement, FDG-PET/CT has shown significantly high rate of false positivity (10). This, combined with the improved sensitivity and specificity of EUS solidifies the importance of EUS in diagnostic staging. When FDG-PET/CT is used as the first modality, findings should be confirmed by EUS. EUS is the most accurate modality for locoregional staging of esophageal cancer.

Based on the above findings and those confirmed by a large meta-analysis, EUS, CT, and FDG-PET are complementary components of the diagnostic approach to esophageal cancer (11). Whereas EUS is the most sensitive modality, CT and FDG-PET are more specific for the diagnosis of lymph node metastases. EUS-FNA (as addressed below) can supplement CT and FDG-PET in confirming a diagnosis of malignant lymphadenopathy whereas EUS alone is useful in ruling out metastatic disease. CT and FDG-PET are invaluable for diagnosing distant metastases, that are beyond the reach of EUS. Several studies have compared CT and FDG-PET for this purpose, but this is beyond the scope of this discussion.

EUS technology

EUS employs radial or curved linear array echoendoscopes to relay signal that projects an image of the esophagus and surrounding tissues. In the USA, the radial echoendoscope is the most commonly used for a diagnostic exam, whereas curved linear echoendoscopes have wider use in Europe. In radial echoendoscopes the image produced is a 360-degree transverse plane perpendicular to the endoscope. Only linear echoendoscopes have capability for FNA. Frequencies of the sonography range from 5–20 MHz with higher frequency transducers (12–30 MHz) that can be introduced into small catheters that can be passed through the scope. The product is a high-resolution image of the esophageal wall (12).

EUS capabilities

Depending on the type of endoscope, echoendoscopes can visualize the esophageal wall as either a five- or a nine-layered structure. Generally, tissue with high content of connective tissue appears hyperechoic, while tissue with high water content (muscle) appears hypoechoic on the EUS image. Endoscopes operating at 7.5–12 MHz can visualize a five-layered esophagus as follows:

(I)   First, hyperechoic layer, superficial mucosa;
(II)   Second, hypoechoic layer, deep mucosa;
(III)   Third, hyperechoic layer, submucosa;
(IV)   Fourth, hypoechoic layer, muscularis propria;
(V)   Fifth, hyperechoic layer, adventitia.

Endoscopes can employ high frequency mini-probes (20+ MHz) can be inserted through the working channel of the echoendoscopes and provide more detailed 9-layer wall as follows:

(I)   First, hyperechoic, superficial mucosa;
(II)   Second, hypoechoic, deeper superficial mucosa;
(III)   Third, hyperechoic, lamina propria;
(IV)   Fourth, hypoechoic, muscularis mucosa;
(V)   Fifth, hyperechoic, submucosa;
(VI)   Sixth, hypoechoic, inner circular muscle [myenteric plexus (MP)];
(VII)   Seventh, hyperechoic, intermuscular connective tissue;
(VIII)   Eighth, hypoechoic, outer longitudinal muscle (MP);
(IX)   Ninth, hyperechoic, adventitia.

Although the high frequency mini-probes are available, they are not as widely used in practice. Even using the more available lower frequency echoendoscopes, the degree of detail in imaging the esophageal wall has significant implications in the realm of T-staging tumors. The very specific layer that a tumor invades has dictates the modality of therapy, whether ablative, endoscopic resection, or surgical approach is appropriate. For example, if EUS detects a tumor with only mucosal disease, endoscopic mucosal resection is the treatment of choice rather than a surgical approach. This is based on robust data reporting excellent outcomes in patients who underwent removal of T1a cancers with endoscopic mucosal resection (13,14). Ell *et al.* reported 99% cure rate in these patients (13). Conversely, if EUS detects a T3 lesion, the surgical
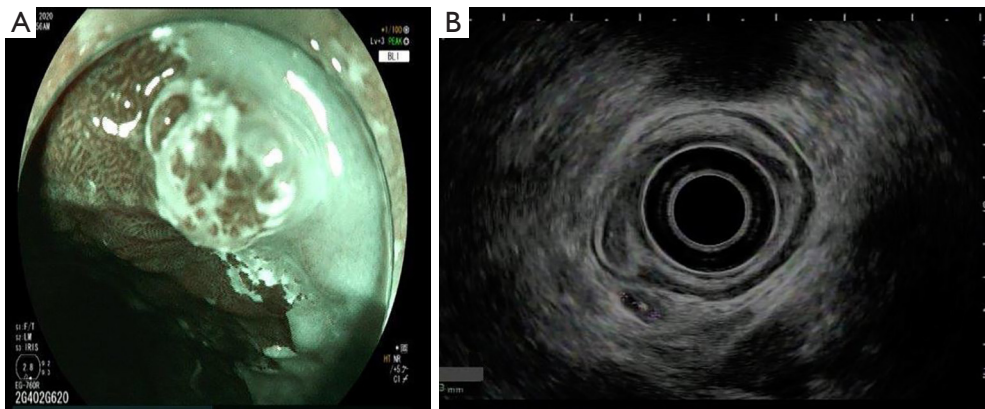
Figure 2 T1b esophageal adenocarcinoma with submucosal invasion. (A) Endoscopic image of T1b esophageal adenocarcinoma. (B) EUS in the same patient, demonstrating tumor invading submucosa (3rd endosonographic layer) at the 7 o'clock position. This was staged T1bN0 carcinoma. EUS, endoscopic ultrasound.

approach is the preferred modality and a neoadjuvant chemotherapeutic regimen may be considered. T1b lesions and lesions with indeterminate invasion present situations that are best dealt with in an interdisciplinary fashion with consideration of local expertise and patient preferences and comorbidities. *Figure 2*, below, includes a direct endoscopic view and an EUS depiction of T1b esophageal carcinoma. Generally speaking, a combination of surgery and chemoradiation is the standard of care for most lesions beyond T1a stage (15-17).

EUS can also identify lymph nodes, both regional and those located at the celiac axis, which can aid in N-staging the tumor. Malignant lymph nodes have a typical appearance that can be detected on ultrasound. Regional lymph nodes cannot be visualized by standard upper endoscopy. The characteristics that are evaluated on EUS include size, shape, border appearance, and echogenicity of the node (18,19). The number of lymph nodes present combined with the features of the lymph nodes evaluated will increase or decrease the yield of EUS in the diagnostic staging of esophageal cancer. The nodal sites that can be evaluated during an EUS include cervical paraesophageal, right recurrent laryngeal, left paratracheal, upper paraesophageal, lower paraesophageal, infra-aortic, infracarinal, lower posterior mediastinal, and perigastric. As previously noted, the presence of malignant lymph nodes and resultant upstaging of the clinical tumor stage carries significant implications for prognosis. Numerous studies have demonstrated that both the number and the location of regional lymph nodes affect prognosis (20,21).

Aside from identifying the lymph node groups noted above, celiac lymph nodes are of particular interest. Celiac nodes, when identified, increase the likelihood of malignancy independent of the characteristics of the lymph node. In one study, 90% of celiac lymph nodes identified by EUS were found to be malignant (22). Although traditional CT and PET-CT could be used to identify celiac lymph nodes, studies have compared EUS and CT/PET-CT, supporting the superiority of EUS (4,23,24).

Concerning endosonographic features of a lymph node that increase their likelihood of being malignant include diameter greater than 1 cm, round appearance, smooth edges, and poor echogenicity. Small, irregular, elongated, more echogenic lymph nodes lower the likelihood of malignancy. Without the inclusion of number of lymph nodes, endosonographic characteristics support an 80% to 100% likelihood of malignancy when one of the four concerning features is present (18,19). No studies have been done since 2010, when the decision was made by AJCC/UICC to include lymph node number in staging criteria; but it stands to reason that including the number of lymph nodes in assessment of risk would increase the yield of EUS in N staging of the tumor.

Regardless of the appearance of the lymph node(s) in question, EUS has the added benefit of the ability to obtain tissue using FNA. Accuracy of EUS nodal staging of esophageal cancer increases when combined with FNA, from 74% to 90% (25). Studies using EUS-FNA have compared EUS guided FNA with surgical specimens or cytology as the gold standard and EUS has exceeded 85% in sensitivity, specificity, and accuracy. A prospective study

Figure 3 FNA of a malignant lymph node. FNA, fine needle aspiration.

performed in 2003 showed that EUS-FNA improved lymph node staging of esophageal carcinoma over EUS alone or CT-guided FNA (25). EUS FNA has been studied in comparison with surgical resection/cytology as the gold standard and has yielded robust results (26-28). *Figure 3* depicts a FNA of a malignant regional lymph node.

Pitfalls of EUS

EUS requires an advanced skill set that is not available to all providers and in all settings. Training for EUS is generally provided during a fourth year of advanced endoscopy training after completing a standard gastroenterology fellowship. Even among expert gastroenterologists, there are significant rates of inter-observer variability in staging esophageal cancers (22). More specifically, tumors in the T2 category are subject to the greatest variability, and extension to T3 is not always obvious. It may be difficult to differentiate between T2 and T3 lesions even for expert providers. This challenge may not diminish the value of EUS in this context, as there are no current differences in management between T2 and T3 lesions.

Another conundrum encountered when performing EUS is the use of EUS following neoadjuvant chemotherapy or radiation. As noted above, T-staging of esophageal cancer is important in that it has implications for preoperative therapeutic interventions. In patients who received these therapies, EUS may be performed to monitor response to therapy and restage the tumor. Unfortunately, the accuracy of EUS in the initial assessment of esophageal cancer and lymph nodes is not matched after neoadjuvant chemoradiation. Certainly, residual lymphadenopathy predicts a more complicated post-surgical course and worse post-operative survival (29). However, T-stage accuracy by EUS is low after neoadjuvant chemoradiation. In the largest meta-analysis available, analyzing 16 studies that compared EUS assessments to surgical pathology, sensitivity and specificity of T-staging varied widely depending on the T-stage assigned to the tumor. T1 and T4 tumors had the highest specificity (95% and 96%, 93–97% and 94–97%), whereas T3 tumors had higher sensitivity (81%, 72–88%) (30). Regardless of the number, the more outstanding finding is that there was significant variance, lowering the overall accuracy, and possibly utility, of EUS in this setting. The cause of the inaccuracies are theoretical, but include tissue destruction and inflammation following chemoradiation as well as observer bias as no studies have blinded endoscopists to the patient's pre-EUS history. Still, despite the inaccuracies, EUS in conjunction with upper endoscopy remains the best modality for reassessing disease following chemoradiation. Here again, EUS-FNA has a role in providing information about remaining lymph nodes after therapy, increasing the value of visual inspection alone.

One final limitation of EUS is that it depends upon the ability of the echoendoscope to traverse the tumor. Unfortunately, many patients diagnosed with esophageal cancer present with advanced disease and tight malignant esophageal stenosis (31). Echoendoscopes are approximately 12 mm in diameter, and stiffer than diagnostic gastroscopes, thereby limiting the ability to traverse firm, narrow stenoses with the echoendoscope. Dilations can be utilized to transiently expand the esophageal luminal diameter, but this intervention carries significant risk (32,33). The risk of dilation may not be worth any potential diagnostic benefit. Even in such cases, EUS retains some accuracy in staging the tumor (34). However, the diagnostic approach relies more heavily on imaging or direct surgical visualization for staging.

Summary

In the last 30 years, EUS has come to assume a central role in the diagnosis and staging of esophageal carcinoma. It is not highly invasive, and is extremely accurate in providing T and N staging. The technique of EUS FNA is an accurate nonsurgical modality of tissue acquisition for confirmation of metastatic disease from adjacent lymph nodes and other nearby structures such as liver. Despite its limitations in obstructing tumors and reassessment of disease following neoadjuvant therapy, EUS is likely to remain a cornerstone in the care of our patients with esophageal cancer.

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