REVIEW

Is endoscopic ultrasound examination necessary in the management of esophageal cancer?

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Abstract

Despite substantial efforts at early diagnosis, accurate staging and advanced treatments, esophageal cancer (EC) continues to be an ominous disease worldwide. Risk factors for esophageal carcinomas include obesity, gastroesophageal reflux disease, hard-alcohol use and tobacco smoking. Five-year survival rates have improved from 5% to 20% since the 1970s, the result of advances in diagnostic staging and treatment. As the most sensitive test for locoregional staging of EC, endoscopic ultrasound (EUS) influences the development of an optimal oncologic treatment plan for a significant minority of patients with early cancers, which appropriately balances the risks and benefits of surgery, chemotherapy and radiation. EUS is costly, and may not be available at all centers. Thus, the yield of EUS needs to be thoughtfully considered for each patient. Localized intramucosal cancers occasionally require endoscopic resection (ER) for histologic staging or treatment; EUS evaluation may detect suspicious lymph nodes prior to exposing the patient to the risks of ER. Although positron emission tomography (PET) has been increasingly utilized in staging EC, it may be unnecessary for clinical staging of early, localized EC and carries the risk of false-positive metastasis (over staging). In EC patients with evidence of advanced disease, EUS or PET may be used to define the radio-therapy field. Multimodality staging with EUS, cross-sectional imaging and histopathologic analysis of ER, remains the standard-of-care in the evaluation of early esophageal cancers. Herein, published data regarding use of EUS for intramucosal, local, regional and metastatic esophageal cancers are reviewed. An algorithm to illustrate the current use of EUS at The

University of Texas MD Anderson Cancer Center is presented.

Core tip: Endoscopic ultrasound (EUS) is not necessary or adds little in management of many cases, such as, in patients with distant metastases or following pre-operative (neoadjuvant) chemoradiotherapy. EUS is the most sensitive test to exclude local tumor invasion and regional nodal disease that would make endoscopic resection (ER) unsafe or unnecessary. Thus, for early esophageal cancer staging, EUS followed by ER and histopathologic analysis, remains the standard-of-care. For a minority of locally advanced cancers, EUS-fine-needle aspiration can define the radiotherapy field by providing tissue samples of suspicious lymph nodes that are remote from the primary tumor.

INTRODUCTION

Dysphagia to solid food is the most common presenting symptom of patients with advanced esophageal cancer (EC). As the sixth most lethal cancer diagnosed worldwide, there are more than 450000 cases of EC diagnosed annually[1,2]. The American Cancer Society estimates 16910 cases of EC will be diagnosed in the United States in 2016[2-4]. The incidence of esophageal adenocarcinoma (EAC) has increased six-fold from 1975 to 2000, making it the most rapidly increasing cancer incidence in America[5,6]. Obesity, defined as body mass index > 30 kg/m^2, has been strongly linked to EAC, with an odds ratio of 16.2 (95%CI: 6.3-41.4) compared with the leanest persons with body mass index < 22 kg/m^2[7]. Meanwhile, the incidence of squamous cell carcinoma (SCC) in the US is declining[8].

Men are more commonly effected by EC; the median age at diagnosis is 67 and lifetime incidence is 1 in 125 (a rate 3 to 4 times higher than for women)[3,9]. Fifteen percent of EC are diagnosed in people younger than 55 years old. Additional risk factors for EC depend upon histologic subtype and include: European ancestry, gastroesophageal reflux disease, sleep apnea, and intestinal metaplasia (Barrett's esophagus) for EAC; *vs* African ancestry, tobacco smoking, distilled alcohol consumption, palmoplantar keratosis (tylosis),

and Plummer-Vinson syndrome for SCC[2,4,10-13]. Less common EC (such as sarcoma, melanoma, and lymphoma) may occur, although data regarding use of endoscopic ultrasound (EUS) in these cancers are limited.

The majority of patients (about 60%) have advanced cancer when diagnosed, as early EC are frequently asymptomatic[14,15]. Five-year relative survival rates for localized, regional, and distant stages of all types of esophageal cancers are currently estimated at 40%, 21%, and 4%, respectively[3]. Overall five-year survival rates for patients with EC have improved four-fold over the past four to five decades (Figure 1)[3,9]. This substantial improvement in life expectancy likely represents advances in accurate staging and treatment by dedicated professionals with research support from cancer societies, patient groups, industry, and local and national agencies. Per the National Institutes of Health (NIH)/National Cancer Institute, resource utilization and expenditures in 2010 for EC topped $1.3 billion, which is projected to increase to $1.8 billion by 2020[16].

Since the mid-1980s, EUS has evolved to occupy an important niche in EC staging, particularly in evaluating tumor invasion and surrounding lymph nodes. According to NIH/Surveillance, Epidemiology, and End Results program data, local and regional esophageal carcinomas, which are most amenable to EUS evaluation, are found in half of the patients (Figure 2)[9]. With radial and linear endoechoscopes, the five major layers of the esophagus are visible (Figure 3) and represent: (1) the innermost superficial mucosa or squamous epithelium; (2) the deep mucosa or lamina propria; (3) the submucosa, which contains an innumerable number of lymphatics, blood vessels, nerves and mucous glands, and is the most common route of extra-esophageal cancer spread; (4) the hypoechoic muscularis propria; and (5) the hyperechoic adventitia. Cytology specimens may be obtained from suspicious nodes using fine-needle aspiration (FNA).

EC JARGON

The seventh edition of the tumor-node-metastasis (TNM) staging system, developed by the American Joint Committee on Cancer (AJCC) and the Union for International Cancer Control, is the most commonly used staging system[17-19].

In general, *localized disease* refers to esophageal carcinoma, including intra-esophageal (T1-2) and penetrating cancers (T3-4, also known as, *locally advanced* cancers). *Regional disease* describes surrounding lymph node involvement (N-stages), such as celiac and thoracic lymph nodes. Together *locoregional* cancers fall into the AJCC anatomic stage/prognostic group Ⅰ-Ⅲ (so called stage Ⅰ-Ⅲ cancers; Figure 4). *Distant/metastatic disease* (M1) is identified by cancer spread to adjacent organs, distant lymph nodes (*i.e.*,
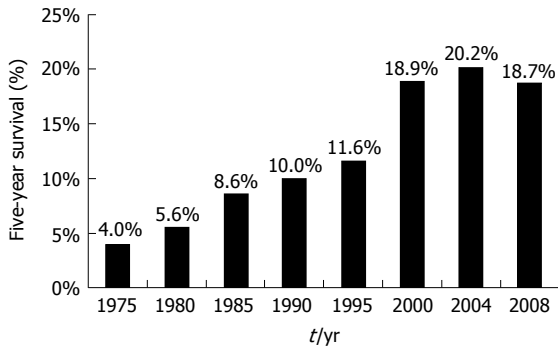
Figure 1 Five-year survival trends in esophageal cancer. Data from Surveillance, Epidemiology, and End Results Cancer Statistics Factsheets: Esophageal Cancer. National Cancer Institute. Bethesda, MD[9].

lungs or supraclavicular lymph nodes) or below the diaphragm (*i.e.*, liver or mesenteric lymph nodes); stage Ⅳ is the anatomic stage/prognostic group[20]. While the TNM components for staging EAC *vs* SCC are identical, the AJCC anatomic stage/prognostic groups differ depending on histologic type because of differing mortality rates between EAC and SCC stages.

An understanding of evolving TNM sub-stages is necessary, such as, *EUS* stage (*i.e., uT4*), *vs clinical* stage [*i.e.*, cT4; based upon pre-surgical evaluation, including endoscopic resection (ER)], *vs postoperative* stage (*i.e.*, pT4; based upon pathologic examination of surgical specimen), *vs neoadjuvant postoperative* stage (*i.e.*, ypT4)[14,21]. Cancers involving the submucosa (T1b) are further divided into *sm1* to *sm3* stages based upon the depth of invasion[22].

LITERATURE SEARCH

A literature search was completed using Google, PubMed and Cochrane Library for combinations of "EUS" and "EC". Study titles and abstracts were screened for relevance. Then, full text publications in English were selected for in-depth review and the references were further scrutinized to identify pertinent studies.

DISCUSSION

In 1980, a group of investigators from SRI International (formerly of Stanford University) and Mayo Clinic developed the "Ultrasonic Endoscope" prototype. It was felt with planned improvements in size and design that this device "should improve the investigation of cardiac, gastrointestinal, and genitourinary diseases"[23]. In 1986, EUS was used for evaluation of lesions of the upper gastrointestinal tract by Gordon, Rifkin and Goldberg, who described the endosonographic anatomy of the upper gastrointestinal tract in 25 patients[24]. Since then, a median of 50 manuscripts per year have been indexed for PubMed on the topics of "EC" and "EUS" (total 1286, range 1-83).

Radial EUS scopes provide a circumferential view of the visceral wall and surrounding tissues, similar to axial images obtained by computed tomography (CT). Often considered easier to interpret by early users, radial EUS images are more similar to transverse/ cross-sectional imaging displays. The linear array echo-endoscope is commonly used for tissue acquisition *via* fine needle aspiration (FNA) or biopsy, as it allows for direct needle visualization during passes into the target abnormality[25,26].

Higher frequency EUS devices yield increased superficial anatomic resolution, but lack deeper sonographic tissue penetration, limiting regional assessment. For example, most radial and curvilinear array echoendoscopes operate at frequencies of 7.5-12 megahertz (MHz), and penetrate 3-4 cm of surrounding tissue with good resolution. Very high frequency, through the scope, EUS miniature probes (mini-probes) can readily distinguish seven layers of the esophagus with a frequency of 20-30 MHz. However, useful sound wave breadth and depth with EUS mini-probes are substantially reduced and inadequate for cancer staging.

If malignant lesions extend to the fundus or gastric cardia, or if intra-esophageal cancers are small; conventional radial or linear EUS may not accurately evaluate the depth of the lesion due to the technical difficulty in reaching or locating the lesion by the echoendoscopes. In those cases, a high frequency EUS mini-probe may be employed under endoscopic guidance to most accurately stage the tumor. For example, in distinguishing T1a *vs* T1b intramucosal lesions, high frequency mini-probes have been shown to more accurately assess depth of invasion in comparison to radial or linear EUS. The disadvantage of using an EUS mini-probe is the limited sonographic width and depth, which precludes a comprehensive survey of regional lymph nodes. Furthermore, if the lesion is large (*i.e.*, 5 cm), EUS mini-probes cannot expediently assess penetration depth of the entire lesion.

EUS FOR EC STAGING

When assessed by EUS, malignant lymph nodes classically originate near the intraluminal cancer, and appear as round, hypoechoic nodes with smooth borders that may be enlarged (> 10 mm)[27]. Per 2016 guidelines published by the National Comprehensive Cancer Network, once distant metastases from EC have been excluded, EUS should be employed for evaluation with possible FNA cytologic sampling[28]. At the time of diagnosis, a contrast-enhanced CT scan of the chest and abdomen is recommended to assess for distant metastases (*i.e.*, to liver, lung, bone or adrenals), thereby distinguishing M0 *vs* M1 stages. Following EUS, the optimal treatment regimen changes significantly based on the presence of tumor invasion into the submucosa, detection of regional lymph node malignant spread or distant malignancy. EUS is the most sensitive test for locoregional staging of EC,
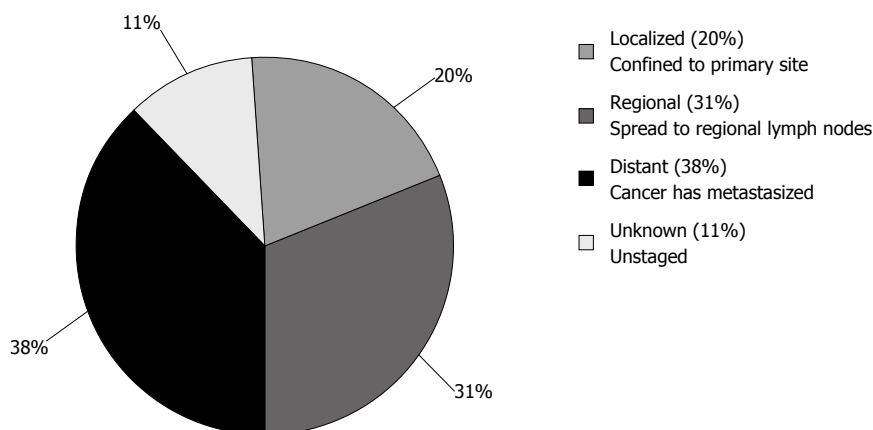
Figure 2 Esophageal cancer stages at diagnosis. Surveillance, Epidemiology, and End Results Cancer Statistics Factsheets: Esophageal Cancer. National Cancer Institute. Bethesda, MD[9].
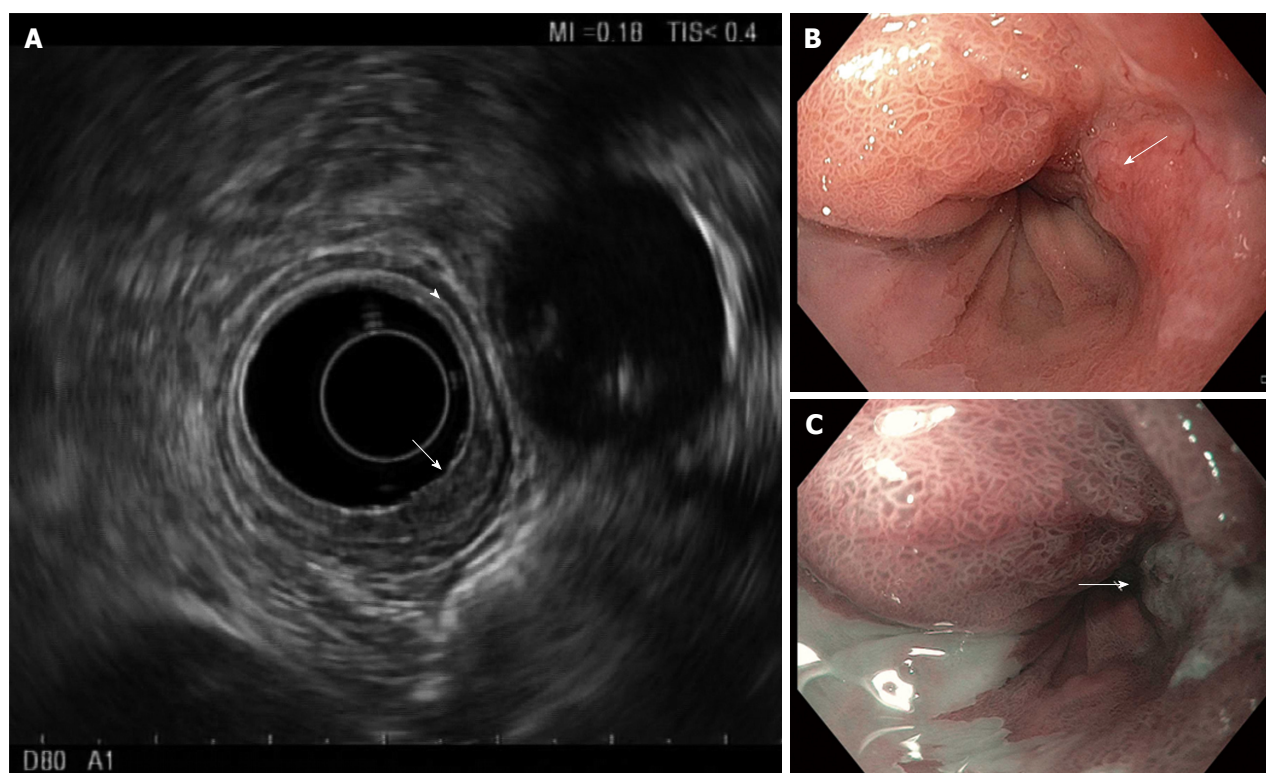

Figure 3 Endosonography of distal esophageal adenocarcinoma. A: Five layers of the esophagus are visible with standard frequency (7.5 MHz) endoscopic ultrasound. From innermost to outermost: the hyperechoic (bright) superficial mucosa, hypoechoic (dark) deep mucosa, the submucosa (arrowhead), followed by the muscularis propria (hypoechoic, very dark), and adventitia (outer echogenic layer). The T1b adenocarcinoma (arrow) causes thickening and distortion of the mucosal layers and submucosa, without invasion of the muscularis propria; B: White-light; and C: Narrow band images are presented for comparison, with arrows to mark the cancer.

and maintains a critical role in developing an accurate therapy plan[27,29-35]. EUS influences the treatment of a significant, although small portion of patients with early disease, as particular attention may be given to the depth of esophageal invasion and celiac lymph node axis, which is thought to act as a gateway for distant metastatic spread[36-38]. Current data confirm the number of malignancy-involved lymph nodes is more important for prognosis than regional anatomic location, which further substantiates EUS-FNA use[39-42].

The results of meta-analyses focused on EUS are summarized in Tables 1 and 2.

DISTANT METASTATIC EC STAGING

Detection of distant metastases is improved with the use of positron emission tomography (PET), when compared to CT and EUS[29,43,44]. Use of PET and/or CT may spare the need of performing EUS when distant metastases are detected, as evaluation of the regional

Table 1 Baseline characteristics of meta-analyses on endoscopic ultrasound in esophageal carcinoma

Ref.	Timeframe	Patients (No. studies; P/R)	EUS types (MHz)	Study criteria
Puli *et al*[52], 2008	1986-2005	2020 (25; 10/15)	NR	EUS accuracy confirmed by surgery in distal and celiac axis lymph node metastasis
van Vliet *et al*[29], 2008	1985-2005	4713 (84; NA[1])	NR	Comparison of diagnostic staging performance of EUS, CT and PET
Puli *et al*[32], 2008	1986-2005	2558 (49; 16/33)	NR	EUS studies on T and N staging confirmed by surgery
Thosani *et al*[30], 2012	1988-2008	1019 (19; 12/7)	Radial and/or mini-probe (7.5-30)	EUS in T1a *vs* T1b lesions compared to histology by EMR or surgery/excluded studies on < 15 patients, or with suspicious lymph nodes (> 1 cm)
Sun *et al*[76], 2015	1992-2013	724 (16; 10/6)	Radial, linear and/or mini-probe (5-20)	EUS staging accuracy after neoadjuvant chemotherapy. Surgery was confirmatory test in all included studies.
Qumseya *et al*[36], 2015	1994-2012	656 (11; 4/7)	Radial, linear and/or mini-probe (NR)	EUS in BE and HGD, or esophageal adenocarcinoma (EAC)/excluded studies on advanced esophageal cancer

[1]Did not report retrospective or prospective nature of studies. References[29,30,32,36,52,76]. P/R: Prospective to retrospective ratio; NR: Not reported; BE: Barrett's esophagus; HGD: High-grade dysplasia; EAC: Esophageal adenocarcinoma; EUS: Endoscopic ultrasonography; CT: Computed tomography; PET: Positron emission tomography; NA: Not applicable.

Table 2 Outcomes of meta-analyses on endoscopic ultrasound in esophageal carcinoma

Ref.	Sensitivity (95%CI)	Specificity (95%CI)	Heterogeneity	Conclusion/interpretation
Puli *et al*[52], 2008	Celiac N = 66% (62-71); M = 67% (63-72)	Celiac N = 98% (97-99); M = 98% (97-99)	Insignificant: $P > 0.10$ for all estimates	EUS has low sensitivity and utility for staging metastases to celiac lymph nodes and distant sites.
van Vliet *et al*[29], 2008	N staging: EUS = 80% (75-84); CT = 50% (41-60); PET 57% (43-70)	N staging: EUS = 70% (65-75); CT = 83% (77-89); PET = 85% (76-95)	NR	EUS, CT, and PET have distinctive roles in staging. For distant metastases, PET probably has higher sensitivity than CT. No evidence of publication bias in CT *vs* EUS studies; other analyses too small to test.
Puli *et al*[32], 2008	T1 = 82% (78-85); T4 = 92% (89-95); w/o FNA N = 85% (83-86); w/ FNA N = 97% (92-99)	T1 = 99.4% (99-100); T4 = 97% (97-98); w/o FNA N = 85% (83-86); w/ FNA N = 96% (91-98)	Insignificant: $P > 0.10$ for all estimates	EUS has excellent accuracy, with better performance in T4 over T1 disease (AUC 0.94-0.98). N staging is improved with FNA use (AUC 0.99 *vs* 0.89).
Thosani *et al*[30], 2012	T1a = 85% (82-88); T1b = 86% (82-89)	T1a = 87% (84-90); T1b = 86% (83-89)	Significant; $P < 0.05$ by χ^2	EUS has good accuracy for T1a and T1b lesions; AUC $\geq$ 0.93. Technical factors can affect the diagnostic accuracy of EUS.
Sun *et al*[76], 2015	T1 = 23% (16-32); T2 = 29% (19-41); T3 = 81% (72-88); T4 = 43% (31-56); N = 69% (58-79)	T1 = 95% (93-97); T2 = 84% (77-88); T3 = 42% (33-52); T4 = 96% (94-97); N = 52% (42-62)	Significant; I^2 = 0%-75% depending on stage (table presented in article)	EUS has modest accuracy after neoadjuvant therapy; AUC for T staging ranges from 0.64 to 0.84, while AUC for N-staging was 0.64.
Qumseya *et al*[36], 2015	$\geq$ T1sm = 56% (47-65)	>/-T1sm = 89% (85-92)	Significant; I^2 = 82%; Q = 56, $P < 0.0001$	Advanced disease detected in 14% (95%CI: 8%-22%; $P < 0.0001$). The NNT (performing EUS) to identify 1 case of advanced disease was 7 (95%CI: 5-13). EUS significantly changes therapeutic approach.

NR: Not reported; EUS: Endoscopic ultrasonography; CT: Computed tomography; PET: Positron emission tomography; AUC: Area under the curve.

lymph nodes is not necessary prior to initiation of palliative chemotherapy or chemoradiotherapy. When indicated, EUS may be used to confirm the presence distant metastases and exclude benign findings. Confirmation or exclusion of nodal involvement by EUS will help calculate the exact radiation field, especially when the lymph node is away from the primary tumor, thus minimizing radiation induced complications.

LOCOREGIONAL EC STAGING

Use of CT or PET is considered inadequate for staging celiac and mediastinal lymphadenopathy[26,29,31]. PET may not be necessary for clinical staging if distant metastatic disease is detected on CT scan. Conversely, in patients with superficial EC (T1 disease) use of PET carries risk of over-staging due to false-positive regional/distant enhancement[21].

For evaluation of regional lymph nodes, the combination of EUS and CT (EUS-CT) has been shown to be more accurate than either modality alone, and EUS-CT outperformed PET, 69% *vs* 48%, respectively. The sensitivity of combined EUS-CT was 83% *vs* 22% for PET[45]. Some data support PET scan consideration for: (1) patients with locally advanced (T2 or greater) cancers following EUS (with or without ER); (2) those with positive regional lymph nodes (N1 or greater) detected by EUS-FNA; and (3) patients in whom
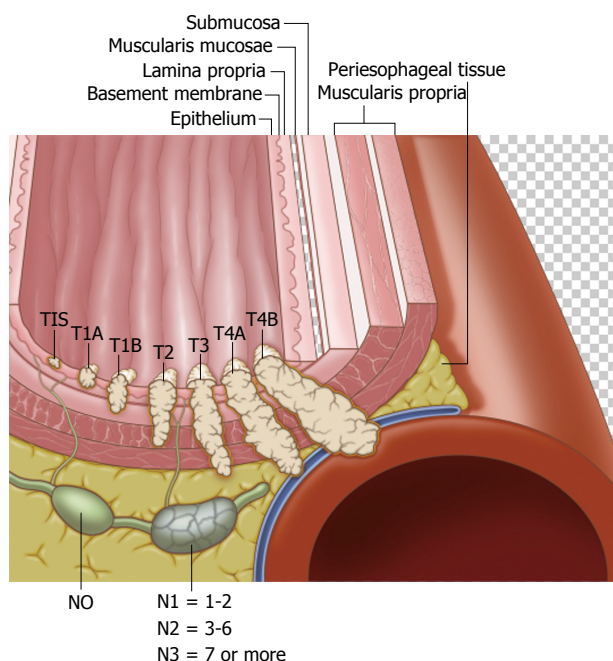
Visual Art: ©2016 The University of Texas MD Anderson Cancer Center

Figure 4 Locoregional esophageal cancer staging.

complete EUS examination was not possible (*i.e.*, due to severe malignant stenoses)[29,46].

When PET scan is performed before EUS, it can provide a road map to potentially positive lymph nodes and decrease or obviate the need for stricture dilation, thus lessening the risk of esophageal perforation. One in three malignant stenoses may initially be too narrow for the EUS scope to traverse[47,48]. Incremental dilation of severe malignant strictures often is not necessary, as completion of EUS may not change treatment[49].

SUPERFICIAL EC STAGING

Intramucosal cancers (T1a) have a 6%-10% risk of metastasis, while invasion into the submucosa (T1b) increases the risk of metastasis to 19%-23%[50]. In a meta-analysis including 1019 patients with T1 (superficial) esophageal cancers, Thosani et al[30] evaluated the diagnostic accuracy of EUS in differentiating mucosal (T1a) *vs* submucosal invasion (T1b) by EC. Nineteen international studies (12 prospective, 7 retrospective) conducted between 1988 and 2008 were included. Studies using mini-probe EUS dominated (14 mini-probe, 9 radial scopes; five studies used both) in comparing findings to the gold-standard, surgical resections of SCC and/or EAC (with or without endoscopic mucosal resection). The area under the curve for pooled sensitivity and specificity was at least 0.93 for both T1a mucosal and T1b submucosal lesions. The pooled sensitivity, specificity of EUS for T1a staging were 0.85 (95%CI: 0.82-0.88), 0.87 (95%CI: 0.84-0.90); and for T1b staging a sensitivity 0.86 (95%CI: 0.82-0.89) and specificity of 0.86 (95%CI:

0.83-0.89) were estimated. Heterogeneity was present among the studies, as the χ^2 P value for heterogeneity was < 0.05 for all pooled estimates.

MULTIMODAL STAGING OF LOCAL ESOPHAGEAL CANCERS

ER should be considered with EUS for staging superficial EC (T1 lesions, generally < 2 cm), which provides locoregional staging and histologic assessment of primary tumor depth and lymphovascular invasion. Due to lack of a singular near perfect test, combining EUS with ER functions as a "double check" to prevent staging errors by sonographic or histologic evaluation[51,52]. Superficial tumor invasion, which may be difficult to visualize by standard radial EUS (7.5-12 MHz) due to lower resolution, can be more accurately assessed by histology of ER specimens[51-53]. The addition of EUS to ER confers the benefit of nodal assessment with possible FNA sampling. Furthermore, EUS excludes deeper invasive cancer (T2 or deeper lesions) that would make ER unsafe and unnecessary[32,54].

For confirmed T1a cancers, ER followed by ablation of high-risk residual tissue *via* radiofrequency ablation or photodynamic therapy, offers survival rates similar to surgery[55-63]. EUS prior to ER is especially important in patients with large intraluminal tumors[64]. When EUS is combined with cross-sectional imaging, patients are considered to have completed clinical staging, thereby identifying stage T2 or T3 patients who may benefit from radical esophagectomy with extended lymphadenectomy[58,61,65,66].

ENDOSONOGRAPHY FOR ESOPHAGOGASTRIC JUNCTION CANCERS

Data regarding the utility of EUS in cancers of the EGJ is limited, and liberal use of ER has been suggested[53]. In a study by Dhupar et al[53] 181 patients with EGJ cancers (98% adenocarcinomas) were included that underwent EUS staging and resection (surgical or endoscopic) without neoadjuvant therapy from 1995 to 2014. The authors found that EUS accuracy at the EGJ was inferior to that of other regions of the esophagus when compared to resected specimens; with 23% under-staged and 29% over-staged by EUS. The negative effect was particularly pronounced with smaller, early EGJ cancers being more frequently over-staged.

NEOADJUVANT THERAPY PRIOR TO SURGERY

Neoadjuvant (induction) therapy may be given pre-operatively to patients with locally advanced or locoregional disease, due to improvement in survival
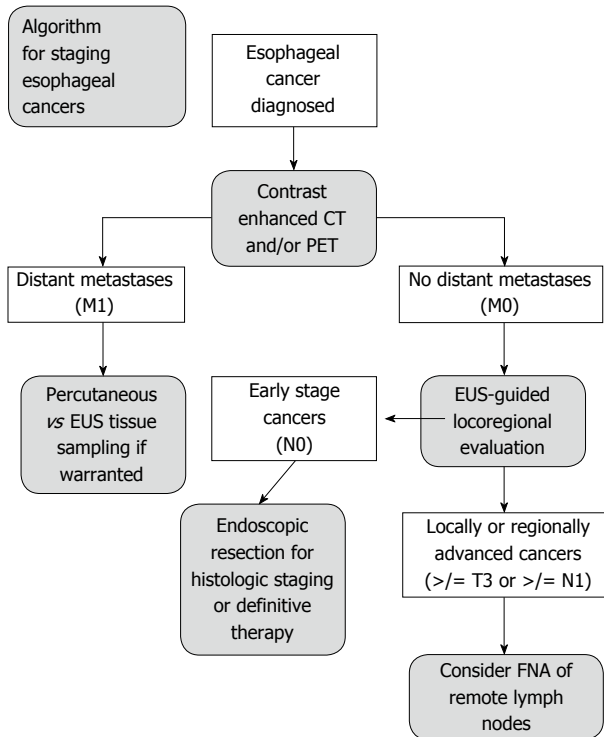
Figure 5 Algorithm for staging esophageal cancers proposed by DaVee and Lee. Esophagogastric junction cancers excluded. EUS: Endoscopic ultrasound with selective fine-needle aspiration; T, N, M: Tumor, node, and metastasis stages; CT: Computed tomography; PET: Positron emission tomography; FNA: Fine-needle aspiration.

compared to surgery alone for cancers of the esophagus and EGJ[67-73]. Data suggest the accuracy of EUS after neoadjuvant chemotherapy for locoregional cancers is subpar[35,74-76]. The reasons for lower accuracy of EUS after induction therapy are due to regional changes in response to healing and inflammation.

A meta-analysis by Sun *et al*[76] evaluated the staging accuracy of EUS for EC after preoperative chemotherapy. The authors included 724 patients (69% with adenocarcinoma) from sixteen studies (ten prospective, six retrospective) conducted between 1992 and 2013. Most procedures were performed with 7.5 and 12 MHz echoendoscopes. Pooled estimates of EUS test characteristics were used in either fixed-effects or a random-effects model, depending on study heterogeneity. EUS was most sensitive in localized staging of T3 lesions at 81% (95%CI: 72%-88%) with 42% specificity (95%CI: 33%-52%). EUS sensitivity in stages T1, T2, and T4 was poor, with T1 lesions estimated at 23% (95%CI: 16%-32%) and 95% specificity (95%CI: 93%-97%); T2 lesions at 29% (95%CI: 19%-41%) and specificity 84% (95%CI: 77%-88%), and finally T4 lesions at 43% (95%CI: 31%-56%) with specificity 96% (95%CI: 94%-97%). When assessing for regional lymph node spread, EUS had sensitivity 69% (95%CI: 58%-79%) and specificity 52% (95%CI: 42%-62%). Overall, EUS was found to be moderately accurate after neoadjuvant therapy; AUC for T staging ranged from 0.64 to 0.84, while the

AUC for N-staging was 0.64. EUS accuracy did not improve with time following neoadjuvant chemotherapy in a subgroup analysis. Therefore, EUS should only be performed in specific cases after neoadjuvant therapy, such as FNA of a suspicious lymph node that would change management.

ADJUVANT THERAPY AFTER SURGERY

Postoperative (adjuvant) therapy has been shown to improve survival and reduce the risk of local recurrence, in patients with positive resection margins, or with positive lymph nodes in cancers of the esophagus or EGJ[77-81]. However, an intensified adjuvant chemo-radiation regimen found no improvement in disease-free or overall survival in patients with EGJ and gastric adenocarcinomas[82]. A recent review concluded there are no validated adjuvant treatment strategies for SCC[82]. PET may be used to evaluate for cancer response and recurrence after multimodal therapy[83]. Data regarding the utility of EUS following surgery and adjuvant chemoradiation are limited.

RADIATION THERAPY FIELD DELINEATION

Precise EC tumor measurements are important for accurate radiation targeting and treatment. PET has been found to be accurate for evaluation of tumor length in esophageal cancers[84-86]. In a retrospective study of 53 patients by Rollins *et al*[84] PET and EUS were compared to surgical pathology for measurement of tumor length. Both PET and EUS correlated significantly with resection specimen tumor length; PET (Pearson R = 0.5977, 95%CI: 0.390-0.747, *P* < 0.0001) *vs* EUS (Pearson R = 0.5365, 95%CI: 0.311-0.705, *P* < 0.0001). In a subgroup analysis, after excluding tumors with significant response to neoadjuvant chemotherapy, both PET and EUS again correlated significantly with tumor length; PET (R = 0.5651, *P* = 0.0005) *vs* EUS (R = 0.4637, *P* = 0.0057). These data suggest EUS or PET may reliably be used in evaluation of tumor length for radiotherapy field definition, and the addition of EUS to PET imaging in these cases is low-yield. However, in patients with suspicious (but not-diagnostic) lymphadenopathy EUS-FNA may further define the radiation field (Figure 5).

COST ANALYSIS

EUS has been shown to be economical in multiple studies. For initial staging, EUS was found to be the least costly strategy by Hadzijahic *et al*[87] as EUS found T4 and/or M1 disease more frequently than CT (44% *vs* 13%, *P* < 0.0001). Furthermore, in patients without metastatic disease, EUS was found to be the most cost effective EC staging modality at $13811, *vs* CT-guided FNA $14350 and surgery $13992[88]. Pretreatment EC

staging by EUS was found to save an average of $3443 per patient, by identification of stage I and stage IV tumors, which prevented unnecessary neoadjuvant chemoradiotherapy or surgery, respectively[89]. Furthermore, selective use of FNA for suspicious lymph nodes during EUS, resulted in reduced costs compared to routine FNA[34], however the effect on patient-outcomes remains to be determined.

EMERGING ADJUNCTS TO SONOMORPHOLOGIC EVALUATION

Generally, healthy tissue is softer and more elastic than cancerous tissues. Elastography, or elasticity imaging, may be combined with ultrasound or magnetic resonance modalities and is a non-invasive method to measure the flexibility of tissues. There are many elastography techniques under investigation, such as quasistatic/strain imaging and shear wave elasticity imaging; however, all techniques rely on measuring the degree of distortion within the tissue. Much like Doppler ultrasound, which uses color to highlight flow in vessels, EUS elastography provides the operator with a colorized image displaying the variation of elasticity of tissues. Typically, when using EUS elastography, firm tissues appear blue to violet, while softer tissues appear red, yellow or green. Elastography-enhanced EUS has been shown in small studies to improve the diagnostic accuracy of regional lymph node staging in EC patients when compared to standard EUS sonomorphologic evaluation[90-92]. Currently, the role and clinical efficacy are undefined for EUS elastography in EC, although the we speculate the technique could replace FNA cytology, as it is noninvasive and possibly lower risk for the patient.

When unique contrast agents are parenterally administered, contrast-enhanced harmonic EUS (CEH-EUS) may be used to further characterize the microvascular pattern of lesions identified by standard imaging modalities[93]. In 2016, the United States Food and Drug Administration approved the use of sulfur hexafluoride lipid-type A microspheres (Lumason®) for ultrasonographic characterization of focal liver lesions. CEH-EUS has not been rigorously studied in esophageal carcinomas, but preliminary data suggest contrast-enhanced images are of limited value due to the relative avascularity of common esophageal malignancies[93,94].

Tridimensional (3D) EUS may be used alone, or with ultrasonographic contrast, to evaluate the invasion depth of tumors. The 3D images are thought to more accurately convey the relationship of cancers to nearby organs and vessels, and may reduce the operator-dependent error that is inherent to standard EUS[95].

LIMITATIONS

Studies on EUS techniques are often limited by several factors, such as changes in practice patterns, radiographic or pathologic techniques, and sonography equipment; which has considerably evolved from 1980 to the current era. Testing characteristics for EUS vary widely depending on the type of equipment used (frequency of ultrasound probe, FNA *vs* fine needle biopsy, gauge of needles, and expertise of the endosonographer, cytotechnician, and/or pathologist).

Squamous cell esophageal cancers are more common in Japan, which may contribute to variation in EUS diagnostic accuracy and practice patterns in comparison to the United States[96]. Japan Esophageal Society guidelines suggest *sm1* lesions (T1b cancers with less than 200 micrometers invasion into submucosa) may be resected endoscopically, in contrast to EC invading the middle or deep submucosa (*sm2* or *sm3* lesions)[22,96].

In interpreting meta-analyses, the biostatistical model chosen (fixed-effects *vs* random effects models) and heterogeneity (variation) among studies may confound analysis and interpretation[97]. Higher levels of heterogeneity in meta-analyses decrease confidence in drawing conclusions about the studied relationship[98,99]. Cochran's Q test and the χ^2 heterogeneity statistic may be used to assess for the presence of heterogeneity within a meta-analysis[100], however the I^2 quantitatively describes the degree of heterogeneity[98,99]. In example, an I^2 index of 25%, 50%, or 75% express a numerical value that may be interpreted as low, moderate, or high levels of heterogeneity among selected studies, respectively[97].

CONCLUSION

Despite modern improvements in diagnosis and treatment, EC continues to carry a high risk of morbidity and mortality, as most cases are diagnosed at advanced stages. EUS, the most sensitive test for locoregional assessment of EC, should be considered in patients without distant metastases prior to neoadjuvant (induction) chemoradiotherapy. EUS may not add additional information in some cases of locally advanced esophageal cancers, and is not routinely recommended. When suspicious lymph nodes are identified remote to the primary tumor, EUS-FNA can obtain cytology specimens to more accurately define the radiotherapy field. Aggressive efforts at early diagnosis and innovative treatments for EC are desperately needed.

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