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Review

Optimal staging of esophageal cancer

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SUMMARY

EUS and EUS-FNA represent the most accurate method for locoregional staging of esophageal carcinoma, and should be performed for local staging in those patients who are good surgical candidates and other imaging techniques (CT, PET) have demonstrated no distant metastases. The presence of EUS as an adjunct for staging is mandatory in buzy thoracic surgery practices.

Key words: Esophageal cancer, staging imaging modalities

INTRODUCTION

The incidence of esophageal adenocarcinoma has been rising in western countries over the past decades.[1,2] Unfortunately, esophageal carcinoma is an aggressive disease associated with a very poor prognosis due to the fact that most patients have an advanced tumor stage at the time of diagnosis.[3-6] Differences in survival between patients with early (stage I-IIA: 5-year survival = 30-50%) and advanced stage tumors (stage IIB or higher: 5-year survival = 5-15%) correlates with tumor extension through the esophageal wall into the adventitia (T3) and/or with the presence of metastatic lymph nodes (N1) (table 1).[5-10] Direct surgical intervention is generally advised for fit patients with stage IIa or lower disease.[8-10] Recent publications have reported that preoperative adjuvant therapy (chemotherapy and radiotherapy) may help increase survival of patients with advanced stage disease.[11-12] Moreover, in those patients with stage IV disease, palliative measures seem to be as effective as more aggressive treatments (e.g. surgery, chemoradiation).[13] These studies reinforce the importance of accurately staging esophageal carcinoma prior to undertaking therapy.

EUS is the most accurate method for assessing the locoregional spread of tumor in these patients. The purpose of this review is to summarize data pertaining to the role of EUS in pre-operative staging of esophageal carcinoma. In addition, the role of EUS-FNA in sampling lymph nodes to improve staging accuracy of EUS is discussed. Finally, the role of EUS to predict treatment response after neoadjuvant therapy is highlighted. We will discuss also the unique role of EUS in sampling obstructing esophageal masses (pseudoachalasia) and recurrences when other methods fail.

Preoperative staging of esophageal carcinoma

Initial evaluation of the patient diagnosed with esophageal carcinoma centers on assessing the patient's operative risk and staging the tumor. Comorbid conditions (severe cardiac or pulmonary diseases) may preclude a patient with a potentially resectable tumor from undergoing surgery. If the patient is a surgical candidate, preoperative tumor staging is warranted. Initial efforts are directed to exclude the presence of distant metastases. CT scan traditionally has been used for this purpose. However, recent reports have shown Positron Emission Tomography (PET) scanning may be more accurate for the diagnosis of stage IV disease than CT scan or EUS (82 per cent vs 64 per cent vs 71 per cent accuracy, respectively), but not for differentiation of pN0 vs pN1 (59 per cent vs 45 per cent vs 74 per cent accuracy, respectively).[14] If distant metastases are not present, a more detailed local-regional staging (T and N stage) should be obtained. Endoscopic ultrasound (EUS) has been proven to be more accurate than transabdominal ultrasound (US),

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CT scan, Magnetic Resonance Imaging (MRI) or PET scanning for locoregional staging of esophageal carcinoma patients.[14-27] (Table 2).

Endoscopic ultrasound image and its correlation with histology

Currently available echoendoscopes operate at different ultrasound frequencies (5, 7.5, 12 and 20 MHz), allowing one to visualize the esophageal wall as a 5 layer structure (first hyperechoic layer: superficial mucosa, second hypoechoic layer: deep mucosa, third hyperechoic layer: submucosa, fourth hypoechoic layer: muscularis propria and fifth hyperechoic layer: adventitia).[28] Based on these special characteristics, EUS allows one to assess the degree of tumor infiltration into the wall layers and subsequently to determine the tumor stage (T stage).[28] However, the muscularis mucosa cannot be visualized with dedicated echoendoscopes.[29,30] High frequency miniprobes (20 MHz) provide a more detailed visualization, allowing one to delineate 9 layers in the esophageal wall (first and second layer: superficial mucosa [hyper and hypoechoic respectively]; third layer: lamina propria [hyperechoic]; fourth layer: muscularis mucosa [hypoechoic]; fifth layer: submucosa [hyperechoic]; sixth, seventh and eighth layer: [hypo, hyper and hypoechoic respectively] inner circular muscle and outer longitudinal muscle of the muscularis propria with intermuscular connective tissue; ninth layer: adventitia [hyperechoic]).[29,30] Visualization of the muscularis mucosa is important when evaluating superficial lesions and nonsurgical alternatives are being considered (endoscopic mucosal resection, photodynamic therapy).

EUS for T staging of superficial tumors

For the evaluation of superficial lesions (T1), EUS accuracy has been shown to be 80 per cent.[27,29] An accurate tumor stage assessment is mandatory for treatment decision in early tumors, mainly when non surgical therapies, such as endoscopic mucosal resection (EMR) or photodynamic therapy (PDT) are considered as an alternative for cure.

If the esophageal tumor does not invade the muscularis mucosa, lymph node metastases are unlikely to be present and EMR may be curative.[31]

However, if the muscularis mucosa is involved by tumor, lymph node metastases may be present in up to 10% of patients and EMR should not be performed with a curative intent.[31,32] High frequency ultrasound catheters (20-30 MHz) allow one to assess if tumor invades the muscularis mucosa with an accuracy of 84 per cent, improving T staging accuracy in superficial carcinomas (T1 vs T2 lesions) from 76 to 92 per cent.[29,30] However, high frequency catheters have some limitations, such as limited depth of penetration into surrounding tissues, therefore precluding one to obtain an adequate lymph node stage assessment.[33] To obtain acoustic coupling with the esophageal wall with high frequency ultrasound catheters may be difficult.[33] One may attach a latex condom at the very distal end of the endoscope or a balloon sheath, and fill it with water to provide a fluid bath through which the catheter can image the infiltration of the tumor into the different layers.[34,35]

Table 1. TNM and Stage Grouping for Esophageal Carcinoma (AJCC Cancer Staging Manual. 1997)[7]

Stage Group:			
Stage 0	Tis	N0	M0
StageI	T1	N0	M0
Stage IIA	T2	N0	M0
	T3	N0	M0
Stage IIB	T1	N1	M0
	T2	N1	M0
Stage III	T3	N1	M0
	T4	Any N	M0
Stage IV	Any T	Any N	M1
Stage IVA	Any T	Any N	M1a
Stage IVB	Any T	Any N	M1b

TNM Clasification

Primary Tumor (T):
Tx: Primary tumor cannot be assessed.
T0: No evidence of primary tumor.
Tis: Carcinoma in situ.
T1: Tumor invades lamina propria or submucosa.
T2: Tumor invades muscularis propria.
T3: Tumor invades adventitia.
T4: Tumor invades adjacent structures.

Regional Lymph Nodes (N):
Nx: Regional lymph nodes cannot be assessed.
N0: No regional lymph node metastases.
N1: Regional lymph node metastases.

Distant Metastases (M):
Mx: Distant metastases cannot be assessed.
M0: No distant metastases.
M1: Distant metastases.

• Tumors of the lower thoracic esophagus:
M1a: Metastases in celiac lymph nodes.
M1b: Other distant metastases.

• Tumors of the midthoracic esophagus:
M1a: Not applicable.
M1b: Non regional lymph nodes and/or other distant metastases.

• Tumors of the upper thoracic esophagus:
M1a: Metastases in cervical nodes.
M1b: Other distant metastases.

Table 2. Preoperative TN staging accuracy of CT and EUS in esophageal carcinoma patients[27]

	Patients (n)	T Stage (range) (%)	N Stage (range) (%)
CT	1154	45 (40-50)	54 (48-71)
EUS	1035	85 (59-92)	77 (50-90)

EUS for T staging of advanced tumors

In patients with advanced tumors of the esophagus, the presence of a tight stenosis may preclude a complete EUS exam (staging) with the dedicated echoendoscopes. This was demonstrated in a study evaluating a total of 113 patients with esophageal carcinoma. In that study, the authors were able to prove that T and N staging accuracy was significantly higher in those patients with a traversable tumor than in those with non traversable tumor (T stage accuracy: 81 per cent versus 28 per cent; N stage accuracy: 86 per cent versus 72 per cent)36. EUS staging mistakes are due to incomplete tumor traversal leading to T, N and M (celiac lymph node) understaging and oblique scanning resulting in T staging errors.[33,36] Several options are possible to enhance tumor staging in the setting of the patient with stenosis precluding passage of the dedicated echoendoscope:

a. Tumor dilatation with a Savary dilator or a pneumatic balloon to a diameter of 14-16mm appears sufficient to allow traversal of stenotic lesions.[36] However, a perforation frequency as high as 24 per cent has been described with this practice using older instruments with more blunt tips.[37,38] In patients with severely stenotic tumors, a progressive dilation strategy over several days rather than a single dilation is advised.

Furthermore, the newer echoendoscopes are built with a smaller tip that allows for easier passage of the echoendoscope through the stenotic tumor.

b. High frequency ultrasound catheters, due to their small size calibre (3mm in diameter), may allow one to traverse tight strictures by in troducing the probe through the biopsy channel of the endoscope. This may assist with tumor staging and subsequently improve the T and N staging accuracy.[39] However, the limited depth of penetration of miniprobes may lead to incomplete assessment of locoregional spread (understaging of lymph node spread).

c. A blind echoendoscope is available for staging stenotic tumors (OlympusR MH-908). This probe measures 7mm in diameter and can be advanced over a guide wire. One series demonstrated 100 per cent traversal of the tumor stenosis versus 60 per cent with the dedicated radial echoendoscope without dilation.[40] However, this dedicated probe is not widely available. In addition, the celiac axis can not be adequately assessed with this probe.

In summary, these techniques allow one to completely examine stenotic tumors in most patients. The additional information that may be obtained from a complete EUS exam must be balanced by the risk of perforation when dilation is undertaken. To date, a direct comparison of these techniques to determine which is the most accurate has not been performed. Based on our clinical practice, we would recommend to start the exam with an upper gastrointestinal endoscopy to assess the degree of stenosis, if present. If the endoscope evidences a severely tight stenosis that cannot be traversed with a slim endoscope, we would advise not to dilate the lesion as the risk of perforation is elevated and we infrequently are able to pass the echoendoscope even with this intervention. In patients with circumferential stenosis permitting passage of a gastroscope but not the echoendoscope, judicious dilation is undertaken.

EUS for preoperative lymph node staging

There are certain EUS features in the lymph nodes (endosonographic criteria) that have been proposed to be suggestive of malignancy (Table 3).[41,42] These malignant lymph node criteria are based on size (lymph node width greater than 10mm), shape (round), echogenicity (echopoor pattern) and lymph node border (smooth).[41,42] Although none of these criteria is diagnostic of malignancy alone, the presence of an echopoor pattern and a width >10mm have been found to be the most specific EUS criteria for malignancy. Furthermore, it has also been reported that when all four features suggestive of malignancy in lymph nodes are present there is an 80-100 per cent chance of lymph node malignancy.[41,42] Unfortunately, only 25 per cent of malignant nodes will present all 4 criteria diagnostic of malignancy.[41,42] These results demonstrate limitations of EUS criteria for preoperative determination of lymph node staging.

Some investigators have suggested that EUS FNA may help improve the accuracy of N staging by providing cy-

Table 3. EUS criteria for lymph node assessment[41, 42]

	Benign	Malignant
Size (width)	< 10mm	> 10mm
Echogenicity	Echorich	Echopoor
Border	Irregular	Smooth
Shape	Elongated	Round

tologic confirmation of malignant disease spread. During the past decade, EUS (FNA) has been introduced into clinical practice.[43] Studies from different institutions have consistently demonstrated EUS-FNA is safe and accurate for lymph node assessment in the setting of patients with gastrointestinal tumors.[43,44] Sensitivity, specificity and accuracy of EUS-FNA in periintestinal lymph nodes has been documented in different prospective, controlled studies to be over 85 per cent.[43,44] Several retrospective studies assessing EUS FNA accuracy for esophageal cancer lymph node staging showed accuracy similar to what has been previously reported for general gastrointestinal malignancies.[45-48]

One of those studies compared lymph node staging accuracy in two cohorts of patients, a historical cohort of 33 patients staged by means of EUS alone and a later cohort of 31 patients with esophageal carcinoma that were staged by means of EUS and EUS-FNA of non peritumoral lymph nodes for preoperative lymph node staging.[47] Results of that study demonstrated a significant improvement in sensitivity (63 versus 93 per cent, $p<0.05$) and accuracy (70 versus 93 per cent, $p<0.05$) in the cohort of patients who underwent EUS-FNA. These promising results were confirmed by a later prospective study conducted at the Mayo Clinic comparing the performance characteristics of helical CT, EUS and EUS FNA for preoperative lymph node staging of esophageal carcinoma.[49] Authors followed a strict algorithm for lymph node selection, starting by sampling celiac lymph nodes (if present), continuing by lymph nodes located in the perigastric space and finally smapling lymph nodes located in the periesophageal space in a non peritumoral location. The endosonographers were blinded to CT findings, and committed to an N stage prior to performing the EUS-FNA part (EUS-FNA was performed with the asistance of an on site cytopathologist/technologist). Table 4 demonstrates the superior accuracy of EUS FNA over EUS and helical CT.

EUS FNA may also be useful to confirm the presence of metastatic spread of the disease to distant lymph nodes (e.g. celiac lymph nodes that when positive for malignancy represent a stage M1a). In one study, authors reported that distant lymph nodes were visualized in 40 of 198 esophageal cancer patients undergoing EUS examination for preoperative staging.[46] From those 40 patients, EUS-FNA was able to prove malignancy in the nodes in 31 patients (78 percent). From the remaining nine patients, 8 had no malignant lymph (correctly assessed by EUS-FNA and confirmed by surgery), and one patient was a false negative by EUS-FNA. These excellent results have been reproduced by other groups.[50] In a review of the extended experience in a tertiary referral hospital, EUS was shown to have a sensitivity for celiac lymph node detection of 77% (95% CI: 67-88%), and a specificity of 85% (95% CI: 74-96%), with an overall accuracy for EUS-FNA of celiac lymph nodes as high as 98% (95% CI: 90-100%).[50]

Interobserver variation and EUS learning curve for esophageal carcinoma staging

One of the major criticisms of EUS and EUS-FNA is that the technique depends on the operator who performs the exam. Several studies have investigated the degree of inter and intraobserver agreement for EUS staging of esophageal carcinoma.[51-53] These studies have found that experienced endosonographers (>50/75 EUS exams in esophageal cancer cases) have good agreement for T and N stage.

However, when inexperienced endosonographers were tested (<20 EUS exams in esophageal cancer), degree of accuracy and consistency in tumor stage assessment was significantly lower than in experienced endosonographers. Tumor stage, degree of experience, as well as technical factors (balloon overinflation, oblique scanning, and inadequate use of higher scanning frequencies) have been postulated as the main causes for errors among inexperienced endosonographers.[51,53,54] Expert endosonographers[55] tend to

Table 4. Prospective lymph node staging of esophageal carcinoma: CT vs EUS vs EUS FNA[49]

n % (95% C.I.)	*Sensitivity*	*Specificity*	*Accuracy*
CT	14/48	25/28	39/76
	29% (17%, 44%)	89% (72%, 98%)	51% (40%, 63%)
EUS	34/48	22/28	56/76
	71% (56%, 83%)	79% (59%, 92%)	74% (62%, 83%)
EUS FNA	40/48	26/28	66/76
	83% (70%, 93%)	93% (77%, 99%)	87% (77%, 94%)
p-value	***sensitivity***	***specificity***	***accuracy***
CT vs EUS	< 0.001*	0.257	0.003*
CT vs EUS FNA	< 0.001*	0.655	< 0.001*
EUS vs EUS FNA	0.058	0.102	0.012*

Table 5. EUS staging accuracy post-chemoradiotherapy in esophageal carcinoma patients

	N	T stage(%)	N stage(%)
Isenberg G, et al[57]	31	43	----
Zuccaro G, et al[58]	59	37	38
Laterza E, et al[59]	87	47	71
Bowrey DJ, et al[60]	17	59	59
OVERALL	**194**	**44**	**58**

overstage esophageal carcinomas (8-14% of cases) more frequently they than underestimate tumor stage.[56] Oversstaging typically occurs in T2 lesions with some peritumoral inflammation leading to EUS overinterpretation.[56] Understaging occurs in 3-15 per cent of esophageal carcinomas and has been associated with microscopic infiltration of the tumor into the deeper layer (muscularis propria, adventitia) that is beyond the resolution capabilities of the echoendoscopes.[21,53]

Re-staging after chemoradiation

Patients with advanced tumor stage may benefit from preoperative chemoradiation therapy. Often, surgeons desire an evaluation of response to treatment prior to advising the patient on tumor resection.

The role of EUS after chemoradiation therapy has been tested, but results have shown EUS accuracy in this setting is poor (44 per cent for T stage and 58 per cent for N stage) when compared to non treated patients (85 per cent for T stage and 80 per cent for N stage) (Table 5).[57-60]

To explain such differences, it has been suggested that EUS may not be able to differentiate between post-treatment inflammation/fibrosis and residual tumor.[57-59] However, despite the low level of accuracy of EUS after chemotherapy and radiotherapy (T stage), it has been reported that a reduction in maximal cross-sectional area of the tumor after adjuvant therapy correlates with tumor response to treatment and signals a better prognosis.[57,61-63]

Recent publications have suggested that the combination PET/CT scan is more accurate than EUS/EUS-FNA and CT for predicting lymph node status and complete response after neoadjuvant therapy in patients with esophageal cancer.[64]

Recurrence detection

In certain clinical situations we may be suspicious that patients with a negative endoscopy and radiographic evaluation, may have local tumor recurrence. In this regard, there have been a few publications investigating the role of EUS and EUS-FNA for the study of these patients.

Several sudies have suggested EUS is very accurate/sensitive (sensitivity and specificity >92 per cent) for detecting tumor relapse.[65-67]

Based on these results, it has been suggested EUS may play a significant role in the follow up of these patients.[65-67]

The Amsterdam Group prospectively studied a series of 45 patients who had undergone surgical resection of their esophageal carcinoma.[66]

Patients underwent surveillance after surgery, with EUS being performed every 6 months for a period of 2 years. EUS showed a 92 per cent sensitivity for tumor recurrence detection (two thirds of patients with tumor relapse on EUS were asymptomatic).[66,67] However, it is unclear if early detection of tumor recurrence may help improve survival in these patients.

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