Endoscopic ultrasound in cancer staging

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Background: Endoscopic ultrasound (EUS) represents one of the most significant developments in endoscopy over the past 20 years. It allows highly detailed assessment of the gastrointestinal wall layers as well as to visualize extraluminal structures such as the mediastium and retroperitoneum.

Methods: The literature was reviewed to assess the role of EUS in cancer staging.

Results: EUS is an integral part of the staging of many upper gastrointestinal cancers as well as rectal and lung cancer and has been shown to be cost-effective. It can be used to confirm malignancy in suspicious lesions as well as to identify and confirm nodal or metastatic spread. It has been used to re-stage cancers following chemoradiotherapy, but results are disappointing. Future developments are discussed, which may include using EUS-guided delivery of anti-tumour agents directly into tumours.

Keywords: endoscopic ultrasound/EUS/cancer staging

Introduction

Endoscopic ultrasound (EUS) represents one of the most significant developments in endoscopy over the past 20 years. At high frequency, the gastrointestinal (GI) wall appears as five acoustic layers that correlate with histological layers of the luminal GI tract. This allows highly accurate T-staging for GI tumours. At lower frequencies, the depth of penetration increases, allowing visualization of extraluminal structures such as the mediastium and retroperitoneum where nodal metastases may be found. The development of curvilinear array echoendoscopes has expanded the applications of EUS, allowing real time biopsy of suspicious masses or nodes (Table 1).
Instruments

Echoendoscopes are classed as radial or linear depending on the orientation of the ultrasound transducer. Radial endoscopes produce a 360° view in a plane perpendicular to the long axis of the endoscope insertion tube, whereas a linear array endoscope produces sector-shaped images parallel to the long axis of the insertion tube. Although interpretation of linear array imaging is not as intuitive as that of radial images, linear array imaging offers advantages in the ability to perform EUS-guided fine needle aspiration (FNA) biopsy.

High-frequency catheter ultrasound probes are also available. These are small probes which can be advanced through the working channel of a regular endoscope. They have a higher frequency (15–30 MHz) than a regular echoendoscope (5–12 MHz), giving higher quality images of structures close to the probe but decreased depth of penetration for extraluminal structures. Non-endoscopic probes (Olympus MH-908) can also be used for oesophageal or rectal imaging. They have a similar frequency to regular echoendoscopes, allowing good imaging of extraluminal structures for nodal staging, whereas their slim diameter means that they can be passed through most oesophageal or rectal strictures.

Identification of malignant lesions

The aetiology of the majority of endoscopic lesions can be determined by their appearance at endoscopy. However, in some cases endoscopic appearances alone are not diagnostic while biopsies are rarely positive if lesions lie beneath the mucosa. EUS is able to visualize the gut wall as a series of concentric layers of differing echogenicity: the mucosa (layers 1 and 2) is hypoechoic; the submucosa is relatively hyperchoic (layer 3); the muscularis propria is again hypoechoic (layer 4) and the serosa (layer 5) is seen as a bright hyperechoic band.

Subepithelial GI lesions, for example, are relatively common, mostly asymptomatic and usually found incidentally at endoscopy. The

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majority are benign but some are potentially malignant, the most common of which are GI stromal tumours (GIST). These arise in the second or fourth (muscularis propria) EUS layer of the gut wall and EUS-FNA or biopsy will provide diagnostic cytology in 75% of cases, with positive tissue staining for tyrosine kinase receptor (KIT). The malignant potential of a GIST cannot be determined by EUS as small lesions have been shown to metastasize; however, lesions which are greater than 3 cm, are of mixed echogenicity, have an irregular edge or are associated with lymph nodes should be considered for surgical excision. Other submucosal lesions with malignant potential include carcinoids, granular cell tumours and lymphoma. Although lymphomas account for only 1% of submucosal lesions, the stomach is the most common site of extranodal non-Hodgkins lymphoma (NHL). Early stage lymphomas appear as a thickening of the second or third wall layers, whereas at a more advanced stage there is diffuse hypoechoic thickening with disruption of all the wall layers.

EUS is useful in linitis plastica, where diffuse hypoechoic infiltration of the submucosa or muscularis propria is seen. The diagnosis can be confirmed by EUS-FNA targeted biopsies of abnormal area under real-time guidance. Similarly, EUS can be used to differentiate normal prominent gastric folds from Menetrier’s disease.

**Confirmation of malignancy**

In recent years, EUS has developed to allow FNA of suspicious lesions, including biopsies of mediastinal lymph nodes, pancreatic, liver or adrenal lesions. To obtain cytology specimens, 19–25 G needles can be used whereas a tissue core biopsy needle (Quick-Core, Wilson-Cook Medical Inc., Winston-Salem, NC, USA) has been developed which allows 18 mm core samples to be obtained. The choice of FNA or core biopsy is a personal choice and is based on clinician experience, the presence of a cytopathologist and the type of lesion present. The exception to this is where sarcoidosis or lymphoma are suspected. In these cases a core biopsy is usually obtained as histology rather than cytology is required to confirm the diagnosis.

EUS-FNA is sensitive. A review of 333 consecutive patients who underwent EUS-FNA in a large centre demonstrated an accuracy of 86% for diagnosing malignancy, with 84% sensitivity and 96% specificity. A review of 876 consecutive EUS-FNA in a single centre revealed a non-diagnostic rate of 9.5%. The procedure is also safe with a complication rate of 1–2%, which is similar to that of computed tomography (CT) or ultrasound-guided needle aspiration.
The risk of tumour seeding along the biopsy tract is very small with only two cases reported in the literature.\textsuperscript{11,12} The overall sensitivities and specificities for malignancy reported in the literature range from 82% to 96% and 94% to 100%, respectively.\textsuperscript{1,13,14}

**Tumour staging**

Correct staging of cancer is essential for patient care. It not only gives a good indication of survival, but also allows for optimum management of the patient. Tumours are staged using the TNM classification which describes the anatomic extent of cancer at the time of diagnosis and before therapy. The definitions of TNM are based on the depth of invasion of the tumour into the wall or beyond (T-stage), the presence or absence of regional lymph node involvement (N-stage) and identification of distant metastasis (M-stage). EUS provides uniquely detailed images of the different wall layers allowing an accurate determination of T stage. Both benign and malignant lymph nodes can be seen by EUS. Endoscopic features suggestive of malignancy include a short axis diameter greater than 5 mm, a round shape, distinct outer border and hypoechoic echo features.\textsuperscript{15,16} Although the presence of all four endoscopic features is highly accurate at predicting malignant involvement, all four criteria are found in only 25% of malignant nodes.\textsuperscript{16} In these cases, EUS-FNA is of value.

**Oesophageal cancer**

Accurate staging in oesophageal cancer is very important as it not only determines prognosis but also the most appropriate therapy. In patients with very early oesophageal cancer (Tis/T1m), local treatment with endoscopic mucosal resection or photodynamic therapy can be considered. For those with more advanced disease (Stages IIB–III), neoadjuvant chemotherapy or chemoradiotherapy is usually undertaken prior to surgery as this may improve survival.\textsuperscript{17,18} For those patients with metastatic disease (Stage IV), palliative treatment is appropriate.

EUS is the most accurate method of determining T-stage (Fig. 1) with an accuracy of 85–90% for T-stage compared with 50–80% for CT in two meta-analyses.\textsuperscript{19,20} The accuracy of EUS for N-staging is 75–79%,\textsuperscript{19,21} which is consistently more accurate than CT.\textsuperscript{19,21–26} The addition of EUS-FNA has been shown to increase accuracy to 87–100%.\textsuperscript{20,22,27,28} The major disadvantage of EUS staging in oesophageal cancer is its inability to traverse a malignant stricture which occurs in 20–30% of patients.\textsuperscript{29–32} Dilatation can be safely
performed, however, allowing complete staging in 87% of patients. Alternatively, a high-frequency ultrasound probe or small non-endoscopic probe can be used. These offer similar T-staging, although N-staging is inferior with the high-frequency ultrasound probe as a result of decreased depth of penetration.

Gastric cancer

EUS is less accurate in staging gastric cancer than in the oesophagus with an accuracy of 57–92% for T-stage and 30–87% for N-stage. There are several reasons for the variation in the results from different studies including different study design, correlation with pathological findings and changes in the TNM classification. Compared with other staging modalities, EUS is superior to conventional CT for T- and N-staging. Since the advent of helical and multidetector row CT the accuracy of CT has improved, although one study demonstrated that EUS is still more accurate for T-staging but less accurate for N-staging, whereas another demonstrated higher accuracy for T-staging (86% versus 76%) and N-staging (90% versus 70%) compared with helical CT. These differences were not, however, statistically significant.

Pancreaticobiliary cancer

EUS allows high-resolution imaging of the pancreatic duct and surrounding parenchyma. Compared with other imaging modalities, EUS is the most sensitive non-operative technique for detecting pancreatic
mass with a sensitivity of 96% (range 85–100%) \(^60-73\) compared with 75% for US, 77–80% for CT and 89% for angiography.\(^{61,64,74,75}\) EUS can identify pancreatic cancer in up to 8% of patients in whom CT has demonstrated a ‘full’ or enlarged pancreas but no mass.\(^{76}\) The specificity of EUS for pancreatic cancer is high with one study demonstrating 100% specificity in 155 patients followed for a mean of 25 months,\(^{77}\) whereas another study found that in patients in whom pancreatic cancer was missed on initial EUS, a repeat EUS procedure 2–3 months later has a 100% detection rate.\(^{78}\) The majority of these comparator studies were performed before the era of high-resolution multidetector row CT and there are few data at present on the relative staging accuracies of EUS and ‘multislice’ CT in this malignancy.

The ability of EUS to provide T- and N-staging information in pancreatic cancer varies across studies with T-staging accuracies of 62–94% and N-staging accuracies of 41–86%. Reasons for these discrepancies include smaller patient numbers in earlier studies, an increase in non-operative management in later studies and finally modification of the TNM tumour staging system for pancreatic cancer. Further well-designed studies are required to clarify these issues.

The greater availability of CT has led to frequent detection of coincidental cystic lesions of the pancreas. The vast majority of these lesions are small and benign, however, up to 10% represent cystic neoplasms. EUS is ideally suited to image these lesions because of its high resolution and ability to sample cystic contents or adjacent lymph nodes. EUS morphology alone has an accuracy of 51–73%. The addition of EUS-FNA with cytology increases the accuracy to between 59% and 100%.\(^{79,80}\) One multi-centre prospective trial found that an elevated fluid CEA concentration (>192 ng/ml) was the most accurate marker (79%) for identifying mucinous lesions.\(^{79}\)

Confirming the diagnosis of cholangiocarcinoma can be difficult with sensitivities for brush cytology at ERCP ranging from 20% to 80%.\(^{81}\) One study in patients with suspected cholangiocarcinoma but non-diagnostic sampling demonstrated a sensitivity of 86% and specificity of 100% with EUS-FNA.\(^{82}\) In patients with suspicious hilar strictures but negative brush cytology EUS-FNA can confirm or refute the presence of cholangiocarcinoma with an accuracy of 91%.\(^{83}\) This, however, is one of the most technically challenging aspects of EUS practice and in most centres such excellent results cannot be reproduced.

### Rectal Cancer

The mean accuracy for EUS T-staging in rectal cancer is approximately 85% with a sensitivity of 87.5% and specificity of 83.5%.\(^{84}\)
compares with an accuracy of 65–75% for CT and 75–85% for MRI. However for nodal staging, EUS is not significantly superior to either CT or MRI with a mean N-staging accuracy of 75%, a sensitivity of 68.1% and specificity of 81.5%. The addition of EUS-FNA does not greatly affect the N-staging accuracy (80%), possibly due to the fact that perirectal lymph nodes are usually too small to be visualized by EUS unless they contain metastatic disease.

Lung cancer

Accurate staging of the mediastinum is an essential part of the management of non-small cell lung cancer. The gold standard up until recently has been mediastinoscopy; however, it is confined to the middle mediastinum and is operator-dependent. CT and [F-18]fluoro-D-glucose (FDG)-positron emission tomography (FDG-PET) are alternatives, with pooled data demonstrating sensitivities of 60% and 81%, and specificities of 84% and 89%, respectively. The low specificity of PET means that patients require confirmatory pathology to insure that overstaging does not occur.

EUS-FNA is able to access the majority of the lymph nodes in the posterior mediastinum (Fig. 2), with a recent meta-analysis demonstrating a sensitivity of 83% and specificity of 97% for EUS-FNA for malignancy. In eight studies examining patients with abnormal mediastinal lymph nodes on CT, the sensitivity was 90% and specificity 97%. In four studies in patients without abnormal lymph nodes on CT, the sensitivity was 58%. When compared with FDG-PET, EUS-FNA detects more mediastinal abnormalities. The main limitation of EUS is its inability to visualize the stations anterior and superior to the trachea or main bronchi. Combining EUS with endobronchial ultrasound (EBUS) allows access to almost all mediastinal lymph node stations and initial studies demonstrate that EUS and EBUS are complementary, with a combined accuracy of between 98% and 100%.

Metastases

Initial assessment for metastases should always be made using non-invasive imaging techniques such as CT, as EUS ultrasound probes do not have the depth of penetration required for imaging distant organs. However, there are some circumstances where EUS is useful in detecting metastases. In oesophageal cancer, true coeliac axis lymph nodes are classified as metastatic (M1a). EUS is the most sensitive technique for detecting coeliac axis lymph nodes with an accuracy of 81–98%.
for detecting malignant involvement. The medial two-third of the liver is also well visualized by EUS with liver metastases found in up to 7% of patients with oesophageal cancer using EUS, with 2.3% of these not detected on CT in one study. In lung cancer, EUS can identify and biopsy metastases in the left adrenal.

**Role of EUS in restaging after chemoradiotherapy**

The accuracy of EUS for staging decreases markedly after either chemotherapy or radiotherapy as EUS is unable to differentiate...
post-radiation oedema, inflammation and fibrosis with recurrent disease. In rectal cancer, T-stage accuracy after radiation is 48–50%, whereas N-stage accuracy is 77%,\textsuperscript{103–106} and is inferior to FDG-PET.\textsuperscript{106} The accuracy of EUS in restaging oesophageal cancer is significantly poorer than initial cancer staging with an accuracy of between 27% and 82% reported.\textsuperscript{107–112} Despite this, the accuracy of EUS is significantly higher than CT and is comparable with FDG-PET.\textsuperscript{113} Measuring maximal tumour cross-sectional area or 3D volume by EUS is potentially more useful at predicting response but further studies are awaited.

**Therapeutic role of EUS in cancer**

The ability of EUS to identify and potentially target cancers has lead to the development of a therapeutic role for EUS. EUS-guided radiofrequency ablation and photodynamic therapy have been successfully performed in animal models,\textsuperscript{114,115} with case reports of EUS-guided brachytherapy in patients with head and neck malignancy, recurrent oesophageal cancer and pancreatic cancer.\textsuperscript{116–119} Phase I trials of EUS-FNA-guided delivery of anti-tumour agents in patients with pancreatic and oesophageal cancer have been shown to be feasible.\textsuperscript{120–122} EUS-guided neurolysis of the coeliac ganglion is often used for pain control in patients with pancreatic cancer which cannot be controlled with oral analgesia. EUS neurolysis is associated with a significant decline in pain scores in 78% of patients which is comparable with percutaneous results. Although both EUS and percutaneous neurolysis are associated with pain (9% versus 96%), self-limiting diarrhoea (4–17% versus 44%) and orthostatic hypotension (1–20% versus 38%) these occur less frequently with EUS-FNA-guided neurolysis\textsuperscript{123–126} compared with the percutaneous approach.\textsuperscript{127}

**Effect of EUS on patient management and cost-effectiveness**

EUS has been shown to affect patient management in oesophageal, lung, pancreatic and rectal cancer.\textsuperscript{128–134} For example in oesophageal cancer, EUS allows more accurate staging which alters treatment decisions in 34% of patients, especially the decision not to operate,\textsuperscript{133} whereas in lung cancer EUS-FNA decreases the need for mediastinoscopy by 70% as a result of upstaging disease.\textsuperscript{135–137}

EUS has been shown to be cost-effective in staging lung, oesophageal, pancreatic and rectal cancer.\textsuperscript{88,92,131,132,138–140} For example in lung cancer staging, the addition of EUS-FNA to conventional lung cancer
staging reduces the staging costs by 40% per patient, mainly as a result of fewer surgical staging procedures.92

Limitations of EUS
The accuracy of EUS has been shown to be operator-dependent.141–144 The number of cases an individual endosonographer has done can affect performance, with endosonographers who have performed more than 50–75 EUS oesophageal cancer examinations have good agreement and high accuracy for N-staging of oesophageal cancer.141–144 The number of procedures a unit performs is also important. One study found that the accuracy in oesophageal cancer staging in a low-volume centre for EUS (each individual endoscopist performed less than 50 EUS oesophageal staging procedures per year) was significantly lower than that reported from high-volume US EUS centres.145 The Joint Advisory Group (JAG) on GI endoscopy recommend that training should be in a unit undertaking regular EUS examinations with at least 200 procedures per year. Trainees should attend regular weekly sessions for at least 6 months but no specific ‘number’ of cases is required to complete training. The American Society for GI Endoscopy (ASGE) recommend a minimum of 150 supervised cases,146 although the evidence base for this is weak.

The future
Endoscopy is becoming increasingly more interventional with the development of NOTES (natural orifice transluminal endoscopic surgery). Endoscopic gastrojejunostomy has been successfully performed in pig models under EUS guidance.147,148 EUS-guided biliary drainage after unsuccessful ERCP has been reported to be safe, feasible and effective149–154 as has EUS-guided pancreaticogastrostomy.155,156 EUS has been used in porcine models to retrieve entire nodes via a transgastric approach without any serious complications, allowing complete pathological assessment.157 It seems likely that the therapeutic possibilities for EUS will increase significantly in the next few years.

Conclusion
EUS has developed greatly during the past 20 years. It is a now established as a key component of the staging of upper GI, rectal and lung cancers, having demonstrated high sensitivity, specificity safety and
cost-effectiveness. It will become increasingly used as a tool for tissue
sampling and for therapeutic interventions in cancer patients in the
next few years.

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