ENDOSCOPIC ULTRASONOGRAPHY (EUS): CURRENT APPLICATIONS AND FUTURE POTENTIAL

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INTRODUCTION

Endoscopic ultrasonography (EUS) is not a new procedure - it was first reported as far back as 1980. With refinements in technology it has found diverse clinical applications and has become widely adopted into clinical practice in the USA, Japan and mainland Europe. In stark contrast, EUS has been slow to develop in the UK and other countries such as Australia where, with the exception of a few centres, EUS remains in its infancy. This article is intended to provide a broad overview of EUS, its current indications and potential future applications.

WHAT IS EUS?

For many years clinicians have been frustrated by the frequency with which the pancreas cannot be adequately visualised by transabdominal ultrasound because of a patient's body habitus or overlying bowel gas. This provided the impetus to the development of EUS by mounting an ultrasonic transducer on a modified endoscope, which could then be placed in the stomach or duodenum in closer proximity to the pancreas.[1]

Technology has advanced hugely since then and there are now several different methods of performing EUS. The variation most commonly used is a 360-degree radial scanning instrument (Olympus [Figure 1]) which provides a cross-sectional image perpendicular to the long axis of the endoscope (Figures 2-4). Alternatively, curved linear array echoendoscopes (Pentax-Hitachi [Figure 5]) provide a 110-degree sector scan in the same plane as the long axis of the endoscope (Figure 6).

Although images provided by the radial echoendoscope are intuitively easier to interpret, the plane of imaging does not permit a visualisation of the path of a biopsy needle in 'real time'. The linear array system achieves this and is therefore the instrument of choice for EUS-guided fine needle aspiration biopsy.

Both types of scanners operate at frequencies of 7.5 and/or 12 MHz. Recently, slim catheter probes that can pass down the biopsy channel of a regular endoscope have also been developed; these high frequency (20 or 30 MHz) 'miniprobes' allow very detailed examination of small superficial lesions and increasingly roles are being found for them in pancreatic and biliary imaging as they can be passed into the biliary and pancreatic ducts. EUS is usually performed on an outpatient basis under conscious sedation similar to routine endoscopy.

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WHAT ARE THE CURRENT INDICATIONS FOR EUS?

These are outlined in Table 1. EUS is most firmly established in the locoregional staging of several malignancies, but also has evolving roles in benign diseases.

TABLE 1
Current uses and developing roles of endoscopic ultrasound.

Current applications
- Staging oesophageal and gastric cancer.
- Gastrointestinal submucosal tumours.
- Staging mediastinal lymph nodes in potentially resectable lung cancer.
- Analysis of large gastric folds.
- Staging pancreatic cancer.
- Localisation of pancreatic neuroendocrine tumours.
- Chronic pancreatitis.
- Choledocholithiasis.
- Diagnosis of ampullary tumours.
- Staging rectal carcinoma.
- Anal sphincter defects.

Developing roles of interventional EUS[47-49,55-58]
- Coeliac plexus neurolysis for pain of pancreatic origin.
- Direct drainage of pancreatic pseudocysts.
- EUS-directed tumour injection therapy e.g. pancreatic cancer.
- EUS-guided cholangiopancreatography in cases of failed ERCP.
- EUS directed botulinum toxin injection in achalasia.
- Assessment of portal and/or azygos vein blood flow in portal hypertension.

Cancer staging

Endosonography provides high resolution imaging of the intestinal wall layers and adjacent extraintestinal tissues. As such it is ideally suited to the TNM cancer staging classification[2] but, because it cannot provide information about distant metastatic (M) disease, EUS is complementary to other staging modalities, including helical CT or MRI. EUS has greatest clinical impact when stage-dependent cancer treatment protocols exist, and where it can have an important influence on treatment decisions and clinical management.

Oesophagogastric cancer. The incidence of oesophageal cancer (mostly adenocarcinoma) continues to rise at an alarming rate, especially in Scotland where the crude incidence may be as high as 14 per 100,000.[3] Overall five-year survival rates remain dismal at 5-10% with approximately 70% of patients presenting with unresectable disease.[4] Treatment strategies and prognosis are determined by tumour staging, the importance of which is highlighted by increasing evidence supporting the use of neoadjuvant therapy which

may offer improved survival in selected patients.[5] In most UK and Australian centres CT is the primary staging investigation but commonly this can both understage and overstage the disease.[6,7] In recent years, however, many studies have consistently demonstrated the superiority of EUS over CT for both T and N staging[6-9] (Table 2).

TABLE 2
Accuracy (%) of endoscopic ultrasound (EUS) and computed tomography (CT) in T and N staging of oesophageal cancer (adapted from reference 7).

Author	n	EUS T%	CT T%	EUS N%	CT N%
Tio *et al.*	74	89	59	80	51
Botet *et al.*	42	95	60	88	74
Ziegler *et al.*	37	89	51	67	51
Grimm *et al.*	23	—	—	82	47
Vilgrain *et al.*	51	73	—	50	48

In patients undergoing surgical resection, EUS staging has been shown to correlate more precisely with surgical pathology than CT scanning (92% versus 60% for T stage, 88% versus 74% for N stage).[7] EUS can also better define patients with T4 disease (Figure 2), such as invasion of the mediastinal pleura, aorta or other great vessels.[8,9] Identification of coeliac nodal metastasis, which it can show, is crucial as this upstages the disease (M1), usually contraindicates surgery and provides important prognostic information. EUS is superior to CT for detecting involvement of these nodes, and when combined with fine needle aspiration (FNA) biopsy can readily provide cytopathological diagnosis (Figure 3).

These clear advantages have established EUS as the primary staging modality for oesophageal cancer in the USA, Europe and Japan but there are limitations. Problems remain in differentiating disease limited to the submucosa (T1) from disease extending into the muscularis propria (T2), nor is EUS good at distinguishing early disease limited to the mucosa from disease involving the submucosa, both of which are staged as T1 but which carry a vastly different prognosis.[4] Lastly, EUS has not yet proven accurate enough at re-staging patients following neoadjuvant therapy as the sonographic appearances of inflammation, oedema and fibrosis are essentially similar to those of residual tumour.[10,11] This is an area of current interest and importance as there is clearly a need for better methods of documenting tumour responses and 'downstaging' after neoadjuvant therapy, and thus establishing better selection criteria for candidates suitable for surgery.[12,13]

EUS is more accurate than CT in the locoregional staging of gastric carcinoma and in making a reliable assessment of resectability.[14,15] As with oesophageal tumours, similar problems exist with the staging of early gastric cancers but high frequency probes may improve this in the future. Restaging after chemoradiotherapy and detection of anastomotic recurrence are also problems which this method is still to solve. In patients with thickened gastric folds but negative mucosal biopsies, EUS can accurately image the different gastric wall layers, document which layer(s) are involved and distinguish conditions such as *linitis plastica*, lymphoma and Ménétrier's disease.[16]

Non small-cell lung cancer (NSCLC). Mediastinal nodal staging of NSCLC is crucial in determining treatment strategies and prognosis. The presence of ipsilateral or subcarinal nodal disease (N2) carries a 20% five-year survival rate and identifies a subset of patients that may benefit from neoadjuvant therapy.[17] In contrast, contralateral nodal disease (N3) is surgically incurable and has a 5% five-year survival rate. CT has limited sensitivity and specificity for detecting mediastinal nodal metastases,[18] while mediastinoscopy is invasive, requires general anaesthesia and provides only limited access to the subcarina and posterior mediastinum.

In contrast EUS provides excellent views of these regions, especially the subcarina (Figure 4) and aortopulmonary window (nodal levels VII and V); numerous studies have demonstrated the superiority of EUS over CT for detection of mediastinal nodal involvement.[19,20] EUS alone, however, cannot reliably distinguish malignant from benign nodes: sonographic criteria for malignancy have an accuracy of no greater than 80%.[19,21]

To further complicate the issue, up to one third of NSCLC patients have enlarged but benign mediastinal lymph nodes and, conversely, cancer may reside in nodes of normal size.[22] EUS-guided transoesophageal FNA biopsy is safe, simple and enhances diagnostic accuracy for malignancy to 90-95%.[19,20,28,29] EUS with FNA thus offers an excellent staging tool which may be simpler, safer and more cost-effective at documenting mediastinal involvement by lung cancer. In turn this may allow better selection of patients for surgery, neoadjuvant therapy or palliative management but well-designed outcomes studies are needed to confirm such an approach.

Pancreatic cancer. The role of EUS in diagnosis and staging of pancreatic cancer is more controversial. Pancreatic cancers of less than 2 cm in diameter (Figure 6) are difficult to detect by CT and several studies have shown EUS to be more accurate than CT in both the detection and staging of pancreatic cancer.[23-25,30] However, EUS imaging of the pancreas and surrounding vasculature is difficult and highly operator-dependent, and these studies have generally reported the results obtained by leading experts, often in comparison to outdated or suboptimal CT scanning techniques. Improvements in CT, particularly the use of dual-phase, contrast-enhanced, helical CT, need to be considered along with local expertise (for example, laparoscopic ultrasound) before deciding on the best strategy for diagnosing and staging pancreatic masses.[26,27]

EUS is accurate for assessing portal vein invasion, but assessing involvement of the mesenteric vessels is more challenging. Like CT, EUS cannot reliably distinguish benign from malignant masses, and although EUS-guided FNA is a relatively straightforward procedure, there is a significant false negative rate as these tumours are often tough, fibrotic and hypocellular and the yield of malignant cells on aspiration cytology is small.[28,29] The negative predictive value of EUS-FNA for pancreatic masses is only around 50% and it is not clear whether the use of FNA significantly alters management of these patients.[30,31] Improvements in needle design[32] and the possible development of accurate molecular markers of malignancy

may change the situation. EUS is, however, the most accurate imaging method for pre-operative localisation of pancreatic endocrine tumours although intraduodenal gastrinomas may be difficult to detect and somatostatin receptor scintigraphy may be a better alternative to consider for these lesions.[33,34]

Rectal cancer. Again EUS is superior to CT in the T and N staging of rectal tumours[35,36] with reported accuracies of 75-95% for both T and N staging. In this location the clinical utility of EUS is significant as it aids in treatment selection - local resection (T1), surgery only (T2-3) or pre-operative radiotherapy (T4). EUS is not currently of use in staging more proximal colonic tumours for technical reasons.

Other tumours. Experienced operators reported excellent results of EUS in staging ampullary tumours[37,24] where documentation of pancreatic invasion can be obtained, and also in assessing uncommon intraductal pancreatic tumours with mini probes.[38,39] Reports from Japan also suggest that bile duct catheter mini-probe studies are useful in documenting hepatic artery and portal vein invasion by cholangiocarcinoma.[40] In all of these situations more data are awaited.

EUS in benign conditions

Submucosal lesions. Gastroenterologists are not uncommonly faced with the dilemma of a patient with a submucosal or intramural lesion in the oesophagus, stomach or colon where mucosal biopsies do not provide a diagnosis. It is often unclear what the underlying nature of the lesion is, and whether or not it should be surgically resected, further investigated or simply observed. Lesions such as submucosal vessels, lipomas, benign (or malignant) stromal tumours and carcinoid tumours all enter into the differential diagnosis. EUS can distinguish extrinsic compression from intramural processes and differentiate the nature of the latter on the basis of wall layer of origin (e.g. lipomas are submucosal, leiomyomas arise from the muscularis) and sonographic characteristics (e.g. lipomas are hyperechoic, carcinoids are hypoechoic).[41] This information enhances diagnostic accuracy, assists in management decisions and can predict whether or not endoscopic removal is possible. For the majority of these patients, EUS can predict the benign nature of their lesion with a high degree of confidence, thereby reducing the need for surgery or repeated endoscopic follow-up.

Pancreatic disease. Controversy persists over the 'gold standard' method for diagnosis of chronic pancreatitis and EUS has added another dimension to this controversy. Unlike endoscopic retrograde cholangiopancreatography (ERCP), which primarily provides information about the pancreatic ducts, EUS can also provide information about the pancreatic parenchyma. A number of sonographic features (hyperechoic strands and foci, parenchymal lobularity and ductal changes such as hyperechoic duct margins, irregularity and dilation) have been described,[43,44] and the presence of four or more of these is claimed to be highly predictive of the presence of chronic pancreatitis. Several studies have demonstrated that EUS correlates well with both ERCP findings and histology,[44-46] but sceptics contest that EUS is perhaps too sensitive and lacks specificity. This is clearly an area that will continue to provoke controversy for some time, with study results weakened by the large functional reserve of the pancreas and the lack of a true gold standard for diagnosing chronic pancreatitis. Endoscopic drainage of pancreatic pseudocysts carries a substantial risk of major haemorrhage and other complications; EUS has become established as an important modality for assessing pseudocysts prior to cystgastrostomy.[47,48] The distance between the gastric or duodenal wall and the cyst can be accurately measured, intervening collateral vessels or varices can be documented and Doppler studies can determine whether a pseudoaneurysm is present. Very recently, EUS-guided cyst drainage in a single procedure under 'real time' guidance has been reported, without the need for ERCP or fluoroscopy.[49]

Biliary tract disease. EUS is both sensitive and specific for detecting common bile duct stones with reported accuracy rates of 93-95%, comparable to those of ERCP.[50-52] Because therapeutic intervention still requires ERCP, however, it is not yet clear whether EUS (or any other less invasive test) can replace ERCP in confirming or excluding choledocholithiasis, particularly in those undergoing laparoscopic cholecystectomy. This is currently an area of great interest to those involved in research into cost-effectiveness and outcomes and who seek to define the optimal strategy for investigating such patients.

Anal disease. Endoanal ultrasound has proven valuable in detecting and accurately defining internal and external sphincter defects in patients with faecal incontinence.[53,54]

WHAT IS THE CLINICAL IMPACT AND UTILITY OF EUS?

EUS has developed in an era of rigorous scientific scrutiny of new technologies and, although far from conclusive, a number of studies addressing the impact, outcomes and cost-effectiveness of EUS have been performed.[59,60] Broadly, these suggest that EUS can be a cost-effective technology with major clinical benefits, including the ability to influence patient management. Examples include avoidance of unnecessary surgery, change to less invasive therapy, fewer investigations and improved tumour staging. Preliminary evidence of cost-savings have also been documented - improved staging accuracy by a less invasive technique can shorten hospital stay, reduce the need for more invasive investigations and reduce the cost per curative resection.[30,59,61]

These outcomes studies are among few performed to date in the field of gastrointestinal endoscopy and further large studies to determine the exact place of EUS in gastroenterology are awaited.

WHAT ARE THE FUTURE DIRECTIONS FOR EUS?

EUS continues to evolve with an increasing interest in interventional EUS (Table 1). As well as EUS-guided FNA biopsy of mediastinal or other peritumoural lymph nodes and tumour masses, coeliac plexus neurolysis for chronic pain of pancreatic origin is a safe and simple procedure.[55] EUS-guided cholangiopancreatography has also been described in cases where ERCP has failed[57] and EUS-directed intratumoural injection therapy, for example in pancreatic cancer, shows early promise.[58] Technological advances in the next few years are likely to see an even

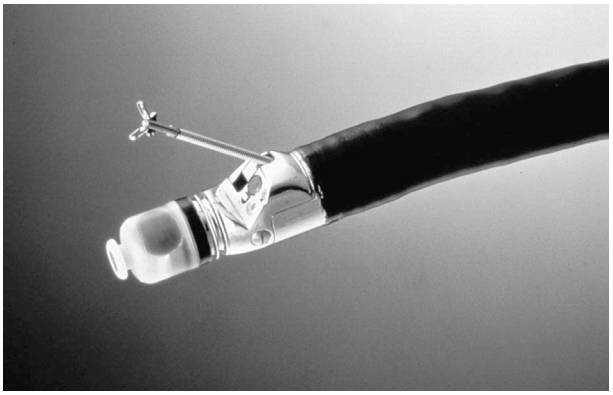

FIGURE 1
360-degree radial echoendoscope (Olympus GF-UM30). The ultrasound transducer is mounted at the tip of a modified endoscope.

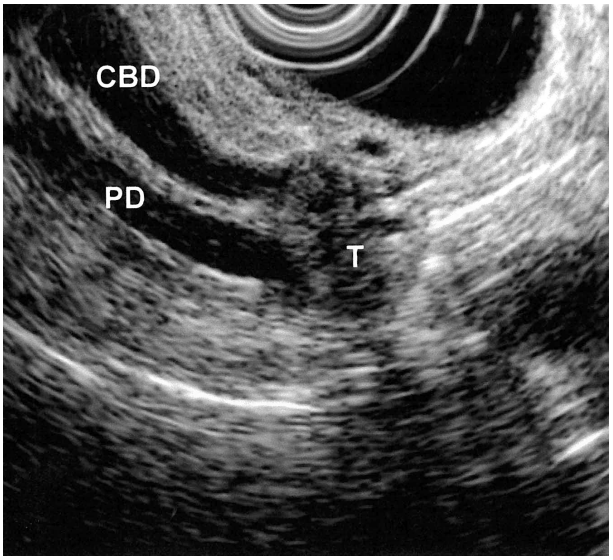

FIGURE 4
Radial image in the duodenal bulb demonstrates a discrete, round pancreatic tumour mass (T) invading the common bile duct (CBD). The pancreatic duct (PD) is also dilated. EUS-FNA confirmed the diagnosis of pancreatic carcinoma.

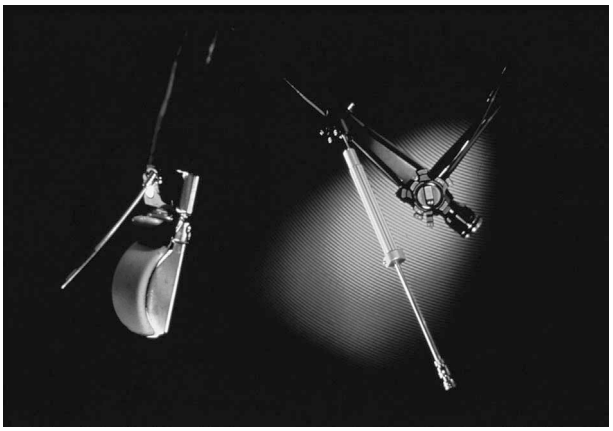

FIGURE 5
Curved linear array echoendoscope (Pentax FG-32UA) with FNA needle. Imaging with this instrument allows EUS-guided FNA biopsy of lesions in real time.

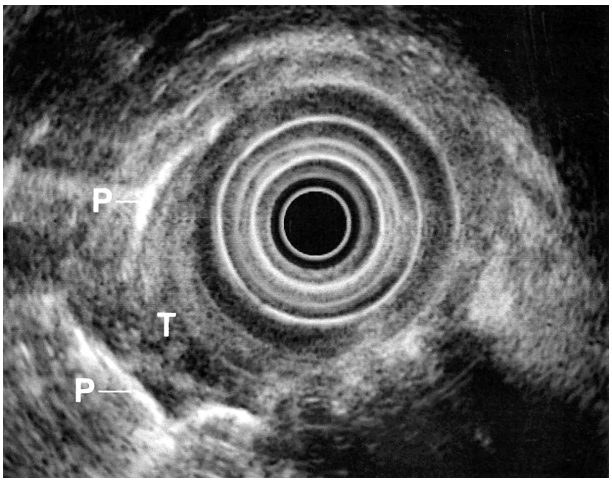

FIGURE 2
Radial image of T4 oesophageal cancer, seen as an irregular hypoechoic mass (T) invading the mediastinal pleura (P).

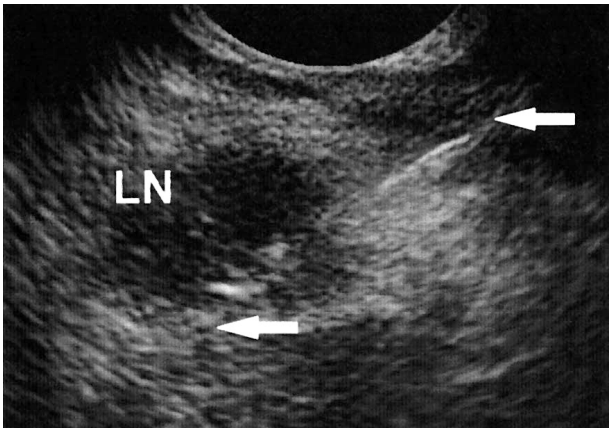

FIGURE 3
Curved linear array image demonstrates a 1cm, round, discrete hypoechoic coeliac lymph node (LN) in a patient with oesophageal cancer. The tip of the biopsy needle is clearly seen within the node (arrows). Cytology confirmed the presence of malignancy (stage M1).

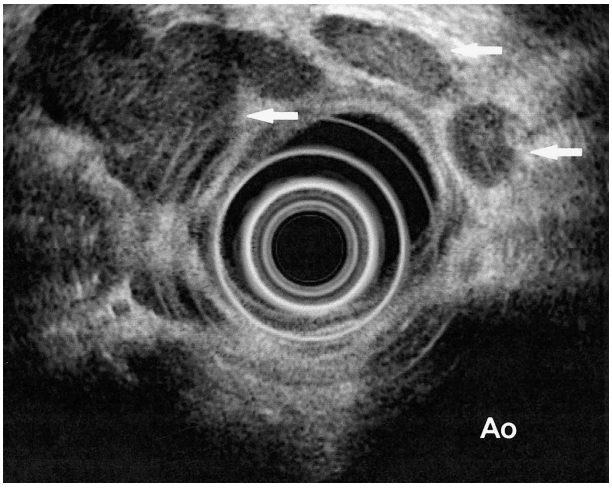

FIGURE 6
Radial imaging in the mediastinum demonstrates discrete, hypoechoic lymph nodes in the subcarina (arrows) in a patient with non-small cell lung cancer (N2, stage IIIA disease). EUS-FNA was positive for malignancy. Ao = aorta.

greater role for interventional and therapeutic EUS, e.g. in pancreatic pseudocyst drainage and tumour therapy.

WHY HAS EUS DEVELOPMENT IN BRITAIN LAGGED BEHIND OTHER COUNTRIES?

Proponents of EUS have already gone some considerable way to answering the questions which are asked about new technologies by the NHS Research and Development Health Technology Programme, namely - does it work?; for whom?; at what cost?; and how does it compare with the alternatives? The feasibility of EUS has been demonstrated as has its efficacy (results obtained by the best operators in ideal circumstances) though more information is needed about its effectiveness - i.e. can the excellent results claimed for EUS be obtained by less experienced doctors performing the procedure in less specialised centres? In addition the acceptability of EUS to patients and all those involved in delivering health care needs to be further analysed. Finally, the potential for cost savings, so far highlighted in the USA, needs to be confirmed in other countries.

Clinical scepticism over technical aspects of EUS hindered its development for many years in the UK resulting in its use here lagging far behind our European, North American and Japanese counterparts. Interest in EUS is increasing but still there are less than 20 sets of equipment in place in the UK, many of which are under-utilised or used only for limited applications, e.g. oesophageal cancer staging. Although becoming cheaper, equipment is expensive, (in the order of £150,000-£200,000) and the learning curve is steep, requiring prolonged intensive training even for experienced endoscopists. The lack of stage dependent protocols to direct management of gastrointestinal malignancies also reduces its clinical value and the inability to provide staging on distant metastases makes it unlikely that EUS can replace other modalities such as CT. On the other hand high quality MRI and helical CT continue to improve and in the future may be able to provide much of the information that EUS can currently deliver.

CONCLUSIONS

This overview has highlighted the major established roles and potential future applications of endoscopic ultrasound. Although EUS technology has been slow to develop in both the UK and Australia, we are gaining ground and can learn from the extensive experience of other countries. For the foreseeable future its main role will continue to be T & N staging of oesphagogastric, lung, pancreatic and rectal cancers. In these conditions EUS is ideally suited to provide valuable information to clinicians and be part of the multidisciplinary management of these serious malignancies which continue to carry a poor prognosis for most patients.

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