ENDOSCOPIC ULTRASOUND - A NEW WAY OF LOOKING AT THE GASTROINTESTINAL TRACT

INTRODUCTION

Endoscopic ultrasound (EUS) is now an important diagnostic tool in the management of gastrointestinal diseases and, with refinements in technology, it has found diverse clinical applications. Whilst it is now widely adopted into clinical practice in USA, Japan and Europe, EUS is available in only a few centres in Australia. St Vincent's Hospital Campus has been providing an EUS service since 2000 and this article is intended to provide an overview of its current indications.

INSTRUMENTS

EUS is performed with small high frequency ultrasound transducers mounted into the end of an endoscope, thereby producing clear and detailed images of the intestinal wall layer structure and surrounding organs. It is performed as an outpatient procedure under conscious sedation. No other current imaging method can reveal the gut wall from oesophagus to rectum as a series of histological correlates. With standard EUS frequencies of 5-30 MHz, the intestinal wall is imaged as a multi-layered structure, corresponding to mucosa, submucosa, muscularis and serosa respectively. This has tremendous relevance to GI cancer staging and determining the nature of submucosal lesions.

Several echoendoscopes are available, depending on the study required:

1. **Radial scanner:** The most widely used instrument is a mechanical driven radial scanner (7.5–20MHz) that provides a 360° view oriented perpendicular to the tip of the endoscope and allows detailed images of the intestinal wall and surrounding structures.
2. **Linear Array scanner:** This instrument provides 110° scanning in the same plan as the long axis of the endoscope and has colour Doppler capability. Therefore, this instrument allows real time EUS-guided needle biopsy through the intestinal wall of extraluminal lymph nodes and pancreas lesions, and underpins therapeutic applications such as endoscopic pancreatic pseudocyst drainage.
3. **Catheter miniprobes:** These small diameter, high frequency (20-30 MHz) probes can be passed down the channel of an endoscope and provide high resolution imaging of small mucosal lesions of the GI tract and bile duct.

CLINICAL INDICATIONS

Table 1 highlights the conditions in which EUS can make a difference with respect to clinical outcomes, and several of these indications are discussed in detail.

STAGING GI CANCER

EUS is ideally suited to the TNM staging classification system of GI cancer, as it can not only define extent of tumour involvement through the gut wall but can also identify loco-regional nodal metastases and determine tumour vascular invasion. ***(Figure 1)*** Since prognosis of such cancers correlates with stage at diagnosis, accurate pre-treatment staging is essential in treatment selection, avoidance of inappropriate surgery and determination of prognosis.

- **Oesophageal cancer**
  EUS is the best loco-regional staging modality for oesophageal cancer and is most useful where stage dependent treatment protocols are in place. ***(Figures 2 & 3)*** Numerous studies have demonstrated superiority of EUS compared with Computerised Tomography (CT), with reported T(umour) & N(odal) staging accuracy in the order of 90% and 80% respectively. A careful systematic review of the literature has reinforced this advantage.[1] Case series also demonstrate the ability of EUS to detect coeliac nodal and small liver metastases that are missed on CT, with consequent tumour upstaging and significant impact on patient management. EUS can also better define T4 disease (invasion of pleura, aorta, great vessels) that would prove not to be amenable to attempted resection.

Whilst well designed clinical trials have yet to fully establish the effect on clinical outcome, the increasing use of neoadjuvant chemoradiotherapy places a higher value on pre-treatment staging. In patients undergoing surgery, an R0 resection (ie no residual disease in the area of primary tumour at end of operation) is associated with 5yr survival rates of 20-35% as compared with R1/R2 resections (ie. residual microscopic/ macroscopic disease, 0-10% 5yr survival). In a recent study, EUS correctly predicted tumour response to chemoradiation in 87% patients who had tumour regression, with positive predictive value of 80%.[2] As such EUS can be used to select patients who are likely to benefit from surgical resection after neoadjuvant therapy.

- **Superficial GI cancers:** EUS diagnosis of early GI tract malignancy is a recent and important development in endoscopy.

  a. Early oesophageal cancer: Because of screening programs on patients with Barrett's oesophagus, more cases of early oesophageal cancer are being recognised. High frequency catheter US probes can now improve the staging of early cancer over radial scanning instruments and can allow differentiation of tumour penetration to submucosa. Early cancers that do not penetrate into the submucosa can be treated with curative intent by using endoscopic mucosal resection (EMR) or mucosal ablation with argon plasma coagulation. In a large centre, EUS staging results were associated with a change of management plan in 40% patients with Barrett's related early cancer and allowed for curative endoscopic treatments rather than oesophagectomy in selected cases.[3]

  b. Gastric cancer: As with the oesophagus, the evaluation of depth of cancer invasion is important in choosing preferable treatment such as EMR or surgical resection. For lesions that are confined to mucosa, EMR can be an effective treatment modality and if pathology confirms the EUS diagnosis, the patient is spared radical surgery.

  c. MALT lymphoma: Mucosa-associated lymphoid tissue (MALT) lymphoma is related to *Helicobacter pylori* infection. EUS staging can predict response to therapy whereby disease limited to mucosa or submucosa is likely to regress after *H. pylori* eradication. In contrast, disease that penetrates to deeper layers will likely not regress and will require chemoradiation.

- **Pancreatic cancer:** The major challenge in evaluating patients with suspected pancreatic cancer is to best select those patients for potentially curative surgery or to identify those who will not benefit from surgical exploration. Despite advances in cross-sectional imaging (CT, MRI) that can now better define vascular invasion, EUS remains an important diagnostic tool. ***(Figure 4)*** EUS can provide added accuracy in 1) patients with symptoms suggesting pancreatic disease but negative CT findings and in 2) patients with equivocal findings, even after triple phase multi-detector CT. *EUS is very sensitive for the detection of tumours <2cm in size and can reveal local nodal metastases not seen on other modalities*.[4] Cost-effectiveness studies have been uniformly positive when EUS is included in the staging algorithm for pancreas cancer, in that upstaging obviated unnecessary surgery and potential complications.[5]
- **Pancreatic neuroendocrine tumours:** Whilst surgical resection is usually the treatment of choice, it can be very difficult to localise these tumours pre-operatively or to determine disease extent. EUS is now regarded as a primary method of detecting neuroendocrine tumours as its sensitivity (up to 94% in 1 series) is significantly higher than that of other imaging techniques (US, CT, MRI) and limits the need for more invasive investigations.[6] Somatostatin receptor scintigraphy is also a sensitive test for detection of gastrinoma, with the advantage of identifying metastases in the liver or outside the abdomen, but detects insulinoma less sensitively, as only 60% of these tumours display somatostatin receptors. A large series investigating neuroendocrine tumours suggested that the best approach to tumour localisation was scintigraphy followed by EUS if the former was negative.[7]
- **Rectal cancer:** Endorectal EUS is an accurate method for evaluating local invasion of rectal cancer and perirectal lymph nodes, with T staging accuracy in the region of 85-90%. As with oesophageal cancer, EUS is superior to CT in terms of T & N staging, although the main limitation is that tumours tend to be overstaged as it can be difficult to differentiate inflammatory changes from neoplastic tissue. Nonetheless, rectal EUS findings can determine the type of surgery (eg local excision for T1 disease v radical

resection) as well as the use of pre-operative chemoradiation (T3-4, N1). It also has the ability to detect recurrent disease after surgical resection.

EUS-GUIDED FNA BIOPSY – 'Tissue is the issue'

Using the linear array scanner, precision needle placement under real time ultrasound guidance can be achieved. ***(Figure 5)*** This enables the endoscopist to obtain samples from tissues away from the gut lumen, with current indications including sampling pancreas tumours, lymph nodes, submucosal lesions, ascites and liver metastases. It is a remarkably safe procedure with reported complication rates <1%, related to infectious or bleeding events. Similarly the risk of malignant seeding is also exceedingly low.

Mediastinal staging of lung cancer

As per the American Joint Committee Cancer (AJCC) lung cancer staging classification, patients without mediastinal involvement are potential candidates for surgical resection, whereas patients with mediastinal invasion (T4) or contralateral mediastinal nodal disease (N2) are generally offered chemoradiation without surgery. The management of patients with ipsilateral mediastinal or subcarinal disease (N1) is perhaps more controversial but many centres would treat with chemoradiotherapy.

CT scan has sensitivity and specificity only in the order of 70% for detection of mediastinal disease. Bronchoscopy with transbronchial fine needle aspiration (FNA) also has sensitivity of 55-70%, but cannot access the aortopulmonary window or inferior mediastinal nodes. Mediastinoscopy and thoracoscopy are costly and invasive. PET scanning has reported accuracy of 85% but is limited by false negative results in tumours with low metabolic activity or nodes <1cm size.

EUS and EUS-guided FNA biopsy is an excellent modality for the posterior mediastinal staging of lung cancer and potentially may represent its widest use. ***(Figure 6)*** EUS alone can identify malignant nodes readily in the posterior mediastinum based on morphological features but the addition of EUS-guided FNA biopsy improves both sensitivity and specificity for detection of malignant nodes. Several studies have confirmed its superiority to CT scan although there are no published studies comparing PET with EUS.[8] Nonetheless, outpatient EUS FNA is quick, safe and provides tissue for cytological analysis. Micrometastases can result in false negative EUS FNA because of the small number of cancer cells present. However, it is anticipated that developments in real time PCR techniques on nodal aspirates from EUS FNA may allow detection of micrometastases in pathologically benign nodes of patients with non-small cell lung cancer.

SUBMUCOSAL LESIONS

Intramural GI tumours arising below mucosa can present difficult management decisions. However, EUS can discriminate extramural compression from mural disease, has the ability to delineate the origin of tumours from within the wall layer structure and sonographic characteristics can confirm the pathological nature of the lesion. For example, lipomas are bright, echogenic tumours arising from the 3rd (submucosal) layer, whereas stromal tumours (GIST) are hypoechoic and usually emerge from the 4th (muscularis) layer. ***(Figure 7)*** Sonographic features that arouse suspicion of malignant transformation of GIST tumours include size >3cm, irregular margins, internal cystic areas and peritumoural nodes.

COMMON BILE DUCT STONES

EUS has high sensitivity and specificity for the detection of CBD stones, equal to or better than endoscopic retrograde cholangiopancreatography (ERCP), without the risk of ERCP–induced pancreatitis. This accuracy persists even for small stones in non-dilated ducts. ***(Figure 8)*** In blinded comparative studies, ERCP sensitivity for stone detection was 79-90% compared to 88-100% for EUS.[9] False negative results for ERCP were caused by small stones in dilated ducts, a scenario in which EUS has excellent operating characteristics. In a follow-up study of 238 patients who were initially free of stones on EUS, 97% had no biliary events after 12 months.[10] Therefore, when EUS is negative for CBD stones, ERCP or cholangiography can be avoided.

Prior to laparoscopic cholecystectomy for symptomatic cholelithiasis, EUS is best indicated in intermediate risk patients (ie. history of acute cholangitis or biliary pancreatitis; 8-10mm dilatation of CBD; unexplained anomalies in LFT's) where CBD stones are identified in 20-

50% of cases. When stones are confirmed there is the potential of performing ERCP and sphincterotomy at the same procedure. Equally, unsuspected lesions can be identified, such as gallbladder microlithiasis or pancreatoampullary tumours.

THERAPEUTIC AND INTERVENTIONAL EUS

EUS directed needle puncture offers a potentially expanding role for new endoscopic therapies, with reports of EUS-guided cholangiopancreatography and EUS-directed intratumoural injection therapy. Several established endoscopic treatments now incorporate EUS:

- **Drainage of pancreatic pseudocysts:** Endoscopic transgastric or transduodenal drainage can be achieved usually when a bulging lesion is seen at endoscopy, although there is risk of bleeding and perforation. EUS can determine optimal drainage site and prevent early complications by defining presence of intervening vessels, determine that the pseudocyst is not >1cm away from gut lumen (increased risk of perforation) and can characterise cyst contents (exclusion of cystic neoplasm or abscess). Using a dedicated large channel linear scanning echoendoscope cyst puncture and stent insertion can be achieved under direct US guidance.
- **Coeliac plexus neurolysis(CPN):** CPN has been used for many years to manage abdominal pain from advanced malignancy, using a surgical or transcutaneous approach. The coeliac axis is a landmark that is readily imaged by EUS via a transgastric approach. Wiersema reported EUS-guided transgastric CPN using absolute alcohol for patients with pancreatic cancer, showing significant reduction in pain scores that lasted 12 weeks in the absence of significant complications.[11]

EUS AT ST VINCENT'S HOSPITAL CAMPUS

EUS services are not well developed in Australia, hampered by high capital costs, the relative lack of stage dependent treatment protocols and the need for intensive training, even for experienced endoscopists. Nonetheless, St Vincent's Hospital Campus has been providing an endoscopic ultrasound service since 2000, with emphasis on GI cancer staging, evaluation of submucosal lesions, evaluation of pancreas parenchyma and exclusion of CBD stones. Table 2 highlights the EUS studies undertaken at St Vincent's Hospital since the service started to the present.

The technique of EUS-guided FNA biopsy has not been readily available, although has been able to provide cytological diagnoses when attempted (mediastinal nodal metastases in lung cancer, n=4; sarcoidosis, n=1; reactive mediastinal adenopathy, n=2; pancreatic neuroendocrine tumour, n=1; metastases left lobe liver in gastric cancer, n=1; metastatic SCC, n=1). However, a new linear scanner has now been acquired and it is anticipated that EUS-guided FNA biopsy can be more readily incorporated into diagnostic protocols, particularly for mediastinal staging of lung cancer.

SUMMARY

EUS has come of age as an endoscopic diagnostic modality. It allows clear examination of the gut wall for tumour invasion and can visualise and biopsy tissues adjacent to the intestinal tract such as lymph nodes and pancreas. As such, EUS has broad clinical applications and can enhance diagnosis, improve cancer staging and impact clinical decision making. Up until the present time, EUS has limited availability in Australia but the service is well established at St Vincent's Hospital and will continue to expand its utility.

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Table 1. When endoscopic ultrasound can make a difference

Cancer staging	**Determine appropriate treatment (stage dependent protocols)**
Oesophagus	Surgery (Stg I, IIA), neoadjuvant therapy (IIB, III), palliation (IV)
Stomach	Endoscopic mucosal resection (Stg 0,1), surgery (II, III)
Rectum	Local (Stg I) v. wide resection
EUS-guided tissue diagnosis	Mediastinal node cytology can preclude curative surgery in lung cancer
Submucosal lesions	Confirm and characterise endoscopic abnormalities Guide lesion management: excision v. observation
Pancreas	Confirm suspicious lesions on CT or MRI Localise small lesions Characterise cysts Stage pancreatic and ampullary cancer Evaluate for chronic pancreatitis
Biliary tree	Screen for CBD stones Detect cholangiocarcinoma and gallbladder cancer
EUS-guided therapy	Drainage pancreatic pseudocysts, coeliac plexus neurolysis

(Adapted from Lightdale C, Endoscopic ultrasound: when does it make a difference? Clinical Update American Society for GI Endoscopy 1999;6(4);1-4)

Table 2. Clinical application of EUS at St Vincent's Hospital Campus

INDICATION	**No.**
Cancer staging	
Oesophagus	64
Stomach	28
Rectum	14
Pancreas	49
Ampulla	31
Pancreas cyst	38
Pancreatic parenchyma	84
Submucosal lesions	96
CBD/Stone disease	58*
Neuroendocrine tumours	7
EUS-guided FNA	
Mediastinal nodes	7
Neuroendocrine tumour	1
Liver metastases	1
Coeliac axis mass	1

* CBD stones identified in 9 patients with normal transcutaneous US and cholangiography