ENDOSCOPIC ULTRASOUND

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Conventional endoscopy has allowed examination and sampling of the mucosal layer of the gastrointestinal tract. Conventional ultrasonography allows transcutaneous examination of abdominal viscera. Endoscopic ultrasonography (EUS), or endosonography, is a combination of endoscopic and ultrasound technology, where the union is greater than the sum of its parts. As a result, EUS allows imaging and intervention beyond the mucosal layer of the gastrointestinal tract and its reach extends to the mediastinum, liver, adrenals, pancreatobiliary system, intra-abdominal lymphatic system, and peri-rectal tissues. EUS is at the forefront of advances in endoscopic innovation and has become a particularly indispensable tool in the staging of gastrointestinal and pulmonary malignancies.

Equipment

The endoscopes used to perform EUS are called echoendoscopes. There are two types of echoendoscopes, radial and linear echoendoscopes. The endoscopes attach both to conventional endoscopic light sources and processors and also to an EUS ultrasound processor. Radial echoendoscopes provide circumferential views that are perpendicular to the shaft of the scope. The radial echoendoscope is a diagnostic scope that does not allow fine needle aspiration (FNA) or therapeutic interventions. The linear echoendoscopes provide a single plane view that is parallel to the shaft of the scope. This scope is similar to an ERCP scope in that, endoscopically, it is a side-viewing scope and has an elevator. A biopsy channel allows the passage of an FNA needle and the configuration of the scope allows "real-time" imaging while passing the needle and performing fine needle aspiration. Finally, the echoendoscopes have a Doppler ultrasound feature allowing demarcation of significant vascular structures in the plane of view and their relationship with lesions of interest to the examiner. This is particularly important and allows FNA of lesions in close proximity to large vascular structures. There are also EUS miniprobes that are catheter probes that can be passed through the large caliber biopsy channel of an endoscope. They have a shallow depth of view and are particularly useful for inspecting small mucosal or subepthileial lesions. They can also be passed into the common bile duct for the evaluation of biliary or peri-biliary lesions.

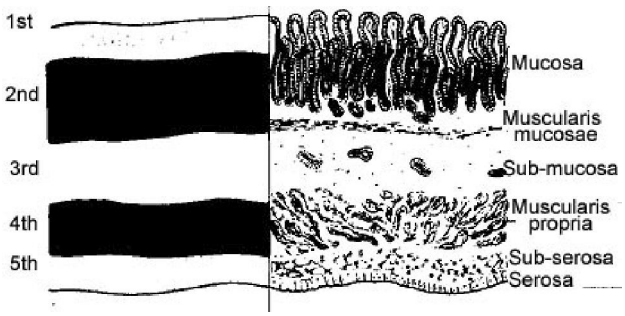

Figure 1: Layers of the gastrointestinal wall as seen by EUS. (adapted from www.eusimaging.com)

On EUS, the gastrointestinal wall appears in five layers (Fig.1). These wall layers appear as alternating hyperechoic and hypoechoic layers (figure & image). Seven standard positions are described for EUS examination and include (1) horizontal duodenum,(2) duodenum near the papilla,(3) duodenal bulb,(4) gastric antrum,(5) body of stomach,(6) fundus of stomach, and (7) distal esophagus (Tab.1). The normal anatomy of the esophagus, stomach, duodenum, liver, pancreas, mediastinum, and hepatobiliary system, as seen on EUS, have been clearly defined in the literature (Fig.2&3).

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Esophagus – Spine – Aorta – Left Atrium – Carina Fundus of the Stomach – Tail of the pancreas – Left kidney – Aorta – Diaphragm – Splenic artery & vein Body of the Stomach – Body & tail of pancreas – Liver – Spleen – Splenic artery & vein – Celiac artety – Aorta Stomach Antrum – Head and neck of pancreas – Superior mesenteric artery – Portal confluence – Inferior vena cava	Duodenal Bulb – Head of pancreas – Bile duct – Gallbladder – Portal vein – Hepatic artery Descending duodenum – Portal confluence – Common bile duct – Ampulla of Vater – Head and uncinate process of pancreas – Inferior vena cava Horizontal duodenum – Aorta – Inferior Vena Cava

Table 1:

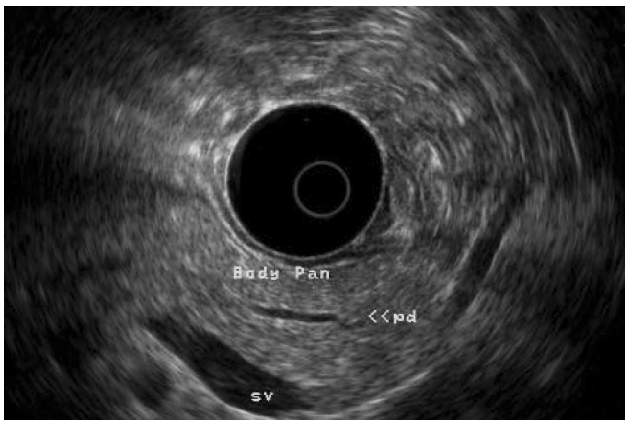

Figure 2: Normal anatomy. Transgastric view of body of pancreas (Body Pan), pancreatic duct (pd) and splenic vein (SV).

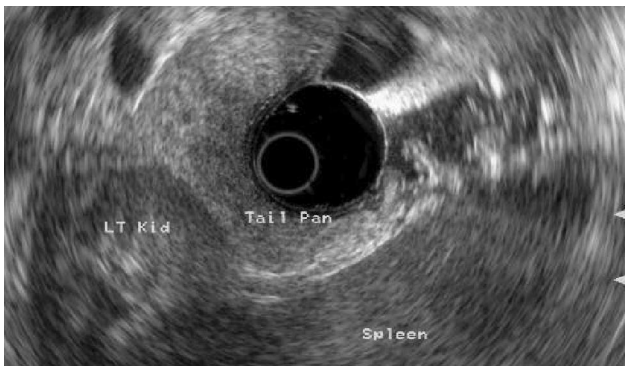

Figure 3: Normal anatomy. Transgastric view of tail of pancreas (Tail Pan), left kidney (LT Kid), and spleen.

Adhering to these seven standard positions when performing an EUS examination ensures a complete examination and reduces the likelihood that a significant finding will be missed. Similarly, anatomical landmarks for rectal EUS are also defined.

EUS FNA

EUS-guided fine needle aspiration (FNA) provides some of the most clinically useful information obtained from endosonography. EUS FNA allows confirmation of the diagnosis in a primary lesion, associated lymphadenopathy, and metastatic locations.

The first step in performing EUS FNA is localization of the lesion and positioning the echoendoscope so that, optimally, the scope is as straight as possible so that the FNA needle, when passed through the scope's biopsy channel, will as remain as straight as possible. The EUS FNA needle is then advanced through the biopsy channel of the echoendoscope and the elevator can be used to assist in needle tip deflection, if needed. Before actually inserting the needle into the desired lesion, it should be re-inspected to identify vascular structures in close proximity and identify the straightest path into the lesion which avoids the vascular structures. When advancing the FNA needle into the lesion, it should be done under constant "real-time" ultrasound guidance (Fig.4). Repetitive thrusting movements in a controlled fashion are employed to shear off cells and collect them within the lumen of the needle.

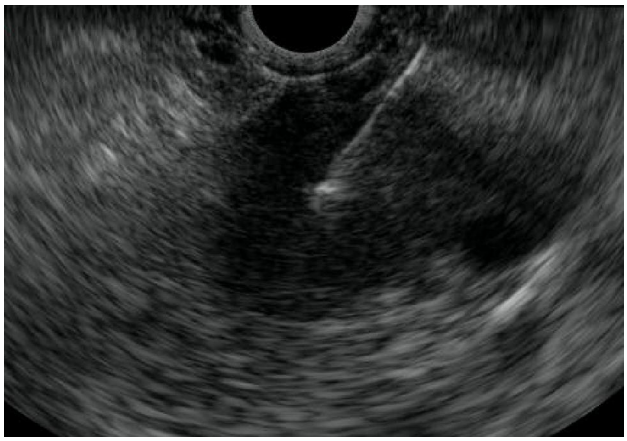

Figure 4: EUS image of fine needle aspiration. The bright echogenic white line is the needle.

The needle is then withdrawn from the scope and the sample is used to make slides and a portion is collected

in formalin to make a cell block. Ideally seven to ten passes of the needle are made to ensure a diagnostic sample. Optimally, a cytopathologist is present for the FNA part of the procedure who can provide immediate and on-site confirmation when a diagnostic sample has been achieved.

Cancer Staging

EUS and FNA are now an integral part of the staging algorithm of many gastrointestinal cancers and non-small cell lung cancer. EUS provides complimentary information to than gleaned from conventional CT and MR imaging. EUS is used most importantly for tumor (T) and nodal (N) staging. Nodal staging is especially useful in the evaluation of lung, esophageal, and rectal cancers where the presence of malignant lymphadenopathy may alter therapy by determining the need for preoperative neoadjuvant chemotherapy or radiotherapy, or in some cases, determining inoperability. On EUS imaging, malignant lymph nodes typically appears round, hypoechoic, are greater than 1cm in diameter, and have smooth borders (Fig.5). The role of EUS in determining the presence of distant metastases is limited. Occasionally, unsuspected distant metastases are detected when performing EUS for local staging.

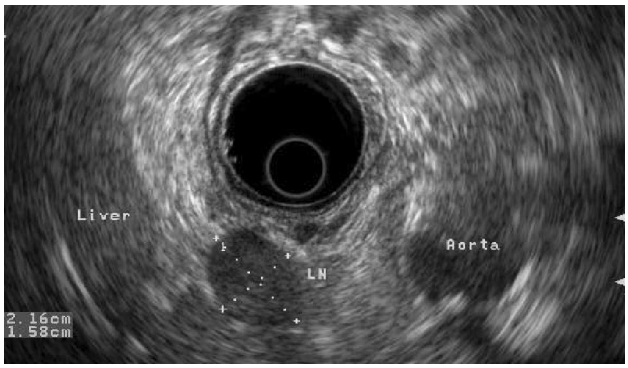

Figure 5: EUS appearance of a malignant lymph node: hypoechoic, homogenous appearance, round shape, greater than 1cm diameter, and smooth outline.

Esophagus

Histological diagnosis of esophageal cancer is usually accomplished by standard endoscopy and biopsy. EUS allows accurate T staging in esophageal carcinoma by assessing the depth of tumor invasion. Lymph node staging is another advantage of EUS examination in this setting. Differentiation between a benign and malignant lymph node can often be made based on endosonographic appearance alone and the confirmation of metastasis to a given lymph node can be achieved by EUS FNA. Finally, occasionally EUS examination will determine inoperability by visualizing T4 or metastatic disease, for example tumor invasion into adjacent structure including the aorta, carina, or pleura. In a study by Harewood and Kumar, the outcome of patients with esophageal cancer in the pre- and post-EUS eras was compared.[1] Tumor recurrence and survival were better in the EUS-staged group and EUS was shown to be more accurate in the identification of patients who would benefit from preoperative neoadjuvant therapy.

One limitation of EUS in staging esophageal neoplasms has been the inability to completely assess a lesion when a malignant stricture is present. A miniproble may be helpful in this situation. Alternatively, careful sequential dilation of the malignant stricture can also be done.

There is a growing body of evidence demonstrating the utility of EUS in benign esophageal disorders including achalasia, indeterminate esophageal strictures, subepithelial lesions, and possibly Barrett's esophagus.

Stomach

When doing standard endoscopy, one may find a subepithelial lesion, meaning a prominence or mass with normal overlying epithelium. The diagnostic test of choice in this scenario is EUS. The ability of EUS to clearly delineate the histological layers of the gastrointestinal tract wall allows the endosonographer to identify which layer or layers of the GI wall are giving rise to the particular lesion and thus narrow the differential. EUS FNA further allows confirmation of the diagnosis by image guided sampling of the lesion. A lipoma which commonly arises from the submucosa has a very characteristic bright hyperechoic appearance that is usually diagnostic and may obviate the need for histological confirmation (Fig.6).

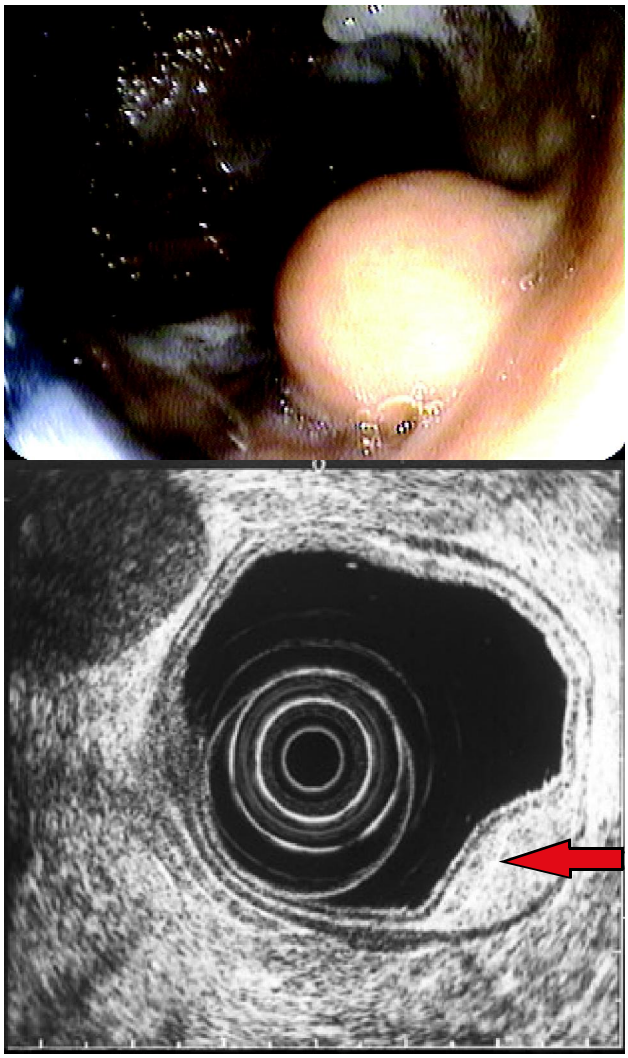

Figure 6: Above is an endoscopic view of a subepithelial lesion in the stomach. Below is an EUS view of the same lesion demonstrating the class appearance of a lipoma, a bright hyperechoic lesion arising from the submucosa.

The role of EUS in gastric adenocarcinoma is limited because of less accurate tumor (T) staging, due to large tumor sizes and associated inflammation and ulceration.

The association between Helicobacter pylori infection and gastric MALT lymphomas has been clearly established.[2] EUS has a vital role in the accurate staging of these lesions and in developing the optimal treatment regimen. Patients with early gastric MALT lymphomas, confined to the mucosa and submuocsa and no lymph nodes, may be initially treated with Heilocobacter eradication treatment alone and have a 75% chance of a complete response. EUS allows accurate assessment of the depth of the lesion for this purpose. Those patients with more locally advanced lymphomas as determined by EUS, with deeper gastric wall involvement and associated lymph nodes, will not be cured by Helicobacter pylori eradication alone and need to be treated with standard lymphoma chemotherapy protocols (CHOP) and surgery and radiotherapy. EUS imaging is also critical for determining response to therapy and detecting early relapses.

Liver

Generally the left lobe of the liver can be seen best on EUS transgastrically and the inferior part of the right lobe transduodenally. An examination of the liver should always be done when performing an EUS for cancer staging purposes. Metastatic liver lesions, which appear as round hypoechoic lesions, may be seen on EUS, having been missed on CT imaging. EUS may detect small lesions not visible on transabdominal imaging because of the proximity of the EUS ultrasound transducer to the liver. EUS-guided FNA can be performed of liver lesions to confirm metastatic involvement. It is important to remember that a limitation of EUS examination of the liver is that one can never be sure that the entire liver has been imaged endosonographically. The superior aspect of the right lobe is the portion of the liver that has the greatest chance of not being seen on EUS.

Adrenal Gland

The left adrenal gland can be visualized by EUS and should be examined for metastatic involvement during cancer staging. Conventional imaging alone is not able to distinguish between benign and malignant adrenal lesions. Furthermore, left adrenal masses seen on conventional imaging can be evaluated and sampled by EUS. The right adrenal is often impossible to visualized by EUS because of its more distant anatomical relation to the stomach and proximal duodenum.

Pancreas

With the new widespread use of CT imaging, incidental findings are commonly identified. A frequent incidental

finding is a cystic lesion in the pancreas. Pancreatic cysts range from those that are completely benign (pancreatic psuedocysts), to those that are frankly malignant (pancreatic adenocarcinoma with cystic degeneration), with those with a intermediate pre-malignant potential (serous and mucinous cysta-denomas, intraductal papillary mucinous neoplasms) in between. One of the commonest indications for performing an EUS examination is to evaluate pancreatic cysts, to determine the pathologic nature and malignant potential of the cyst and to determine if there is overt malignancy in the cyst. Theses cysts can develop in the head, body, and tail of the cyst and information regarding the nature can be obtained from the sonographic appearance of the cyst. A cystic lesion without solid components or septations, especially with a history of an episode of acute pancreatitis, is a psuedocyst. Serous cystadenomas have multiple, small (<3mm) compartments while a mucinous cystadenoma does not have this appearance and may instead have peripheral calcifications. If a mass is associated with a cyst, one should think of pancreatic adenocarcinoma. An intraductal papillary mucinous neoplasm (IPMN) usually appears as a dilated main pancreatic duct or side branches and may also appear as a septated cyst with or without a solid component. Although these endosonographic features may be helpful, they may not be diagnostic and performing an FNA is preferred both to look for malignant cells on cytology and to note the appearance of the aspirate. Fluid aspirated from mucinous cysts tends to have a thick, mucoid, stringy appearance. Furthermore, The Cooperative Pancreatic Cyst study showed that testing for cyst fluid CEA levels is an accurate way to identify mucinous cystic lesions.[3] This distinction is important because the malignant potential of a mucinous cyst is greater than that of a serous one.

Studies have shown that EUS is more accurate than other modalities, including transabdominal ultrasound, CT, and MRI for detecting and staging pancreatic tumors. EUS is also very accurate for predicting respectability of pancreatic tumors. The strength of EUS is its ability to evaluate mucosal, vascular, and ductal involvement of a pancreatic lesion. For pancreatic tumors less than 3 cm, EUS has a much higher detection rate than other modalities, and EUS is, therefore, the best test to screen patients suspected of having a pancreatic tumor, for examples a neuroendocrine tumor, especially if conventional imaging is negative. EUS is less likely to provide additional information in patients with large pancreatic tumors. EUS FNA is able to provide histological confirmation of a suspected pancreatic tumor before surgery in operable cases and in inoperable patients, prior to palliative chemotherapy or radiation. In a study by Chang and colleagues, EUS FNA had a sensitivity of 92%, specificity of 100%, and diagnostic accuracy of 95% for the diagnosis and staging of pancreatic cancer.[4]

Patients with unexplained, especially recurrent, acute pancreatitis should undergo EUS where the following causes may be found: early pancreatic tumors, IPMN, CBD stones or sludge, pancreas divisum, or previously unsuspected chronic pancreatitis.

Traditionally, tests to diagnose chronic pancreatitis are divided into functional (stool fecal fat staining, 72 hour fecal fat, stool elastase, stool chymotrypsin, bicarbonate secretion) and structural or morphological (abdominal x-ray, CT, ERCP, MRCP) tests. However, early chronic pancreatitis can remain undiagnosed by these modalities. EUS is very useful for the diagnosis of chronic pancreatitis. On EUS imaging, a normal pancreas has a homogenous, granular, echogenic pattern with a smooth outer border. The normal pancreatic duct is smooth, without prominent side branches or echogenic filling defects, and is less than 3mm in diameter. Studied have identified several EUS findings, changes in both the appearance of the pancreatic parenchyma and the pancreatic duct, that are highly diagnostic for chronic pancreatitis (Tab.2). The area where EUS and other modalities continue to have difficulty, is the diagnosis of pancreatic cancers arising in the background of chronic pancreatitis.

Pancreatic ductal changes	Pancreatic parenchymal changes
– Ductal dilation	– Lobular pancreatic parenchyma
– Hyperechoic margins	– Hyperechoic foci or stranding Cysts
– Visible side branches	
– Calcifications(Ductal stones)	
– Ductal irregularity	

Table 2: EUS criteria for diagnosing chronic pancreatitis

Bilde Duct, Gall bladder, Ampulla

EUS provides excellent sonographic visualization of the extrahepatic duct biliary tree, transduodenally. Common bile duct (CBD) stones appear as hyperechoic mobile lesions often with posterior acoustic shadowing (Fig.7).

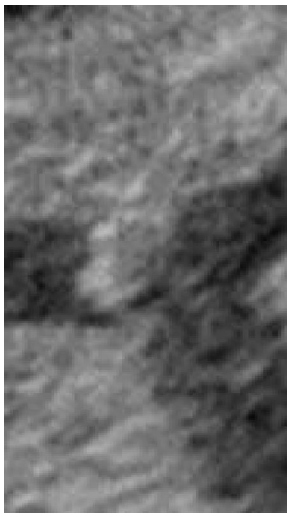

Figure 7: EUS image of a CBD stone which appears hyperechoic and is casting a posterior acoustic shadow.

EUS is indicated in patients with a low or moderate probability of CBD stones, especially those who are at high risk for post-ERCP complications. EUS can help identify those patients with a CBD stone who would benefit from an ERCP and those patients who do not have a stone can, therefore, avoid an ERCP and its associated complications. In patients with an indeterminate CBD stricture, EUS can help identify if there is an associated mass and then guide FNA. In a study evaluating the utility of EUS in the evaluation of indeterminate biliary strictures, of 24 patients with negative or nondiagnostic cytology on ERCP, EUS FNA was able to obtain the diagnosis in 71 (17/24) of patients.[5] Intraductal ultrasound is also useful in the evaluation of indeterminate bile duct strictures. It has been suggested that gallbladder polyps greater than 5mm can be investigated with EUS to assess the risk of malignancy. Given that Pakistan is in an area of high prevalence for gallbladder adenocarcinoma, this is an indication that can be further assessed here. Finally, EUS has a role in the staging of ampullary tumors and can help differentiate between early (T1) and more advanced (T2-4) lesions. The presence of gallbladder microlithiasis (which has a "starry sky" appearance) can also be determined by EUS.

Mediastinum

Mediastinal lymphadenopathy can be detected by chest x-ray of CT imaging and may be due to either benign or malignant processes. Benign causes include tuberculosis, sarcoidosis and fungal infections like histoplasmosis. Malignant causes included lymphoma and metastases. EUS can visualize lymph in the subcarinal, subarotic locations and also paraesophageal and pre- and para-tracheal lymph nodes (Fig.8).

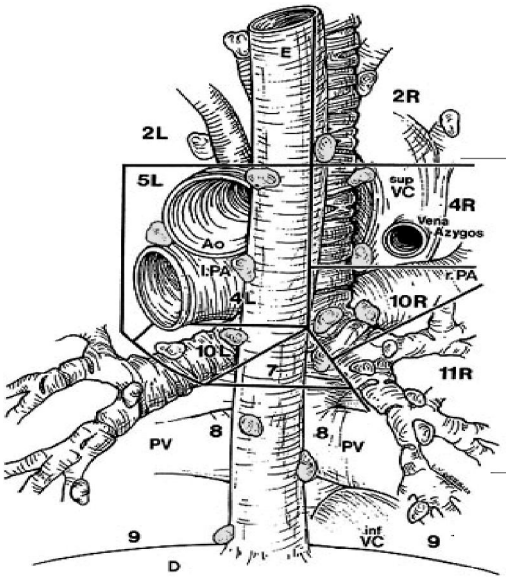

Figure 8: American Thoracic Society classification of mediastinal lymph nodes.
(adapted from www.eusimaging.com)

Furthermore, EUS-guided FNA can sample the nodes and provide histological confirmation of malignancy, if present. The role of EUS in the evaluation of lymphadenopathy associated with esophageal and non-small cell lung cancer has been addressed in other parts of this article. Samples can also be obtained for AFB smear and culture to facilitate the diagnosis of tuberculosis. Given the prevalence of tuberculosis in Pakistan, perhaps the greatest impact of EUS here will be in the evaluation of suspected tuberculous mediastinal lymphadenopathy. There are several Indian studies on EUS for this indication. In one study, 60 patients with mediastinal lymph nodes greater than

1 cm on CT (80% had fever, 68% were PPD positive, all had negative sputum AFM smears or cultures), underwent EUS FNA.[6] EUS FNA was able to make a diagnosis in 93 56/60 patients, of which 82% (46/56) had tuberculosis.

Posterior mediastinal masses can also be evaluated by EUS FNA. EUS FNA is a less invasive way ti evaluate mediastinal nodes and masses as compared to mediastonoscopy.

Lung

When staging a patient with non-small cell lung cancer (NSCLC), in the absence of distant metastases, regional lymph node status is crucial for determining treatment options. CT imaging is unable to differentiate between benign and malignant mediastinal lymph nodes. Histological confirmation, which can be provided by EUS FNA, is required for accurate nodal staging. Routine EUS FNA reduces the need for surgical staging procedures in approximately half of patients. The limitation of EUS FNA is its negative predictive value of approximately 75%, and thus a negative EUS FNA does not preclude a mediastinoscopy as the next step in nodal staging before making a final decision regarding whether to proceed with surgery.

Rectum

As with most malignancies, the prognosis and treatment of rectal adenocarcinoma is stage dependent. EUS allows more accurate staging than conventional imaging modalities alone. The benefits of EUS are in the accurate T and N staging compared with CT scan. This allows identification of the patients with more locally advanced malignancy who would benefit from pre-operative chemo-radiation. A study examining the clinical impact of EUS on rectal cancer compared the outcome of those patients staged in the pre-EUS era with those staged when EUS had become standard of care for the staging of rectal cancer.[7] Patients who underwent EUS were more likely to receive pre-operative chemo-radiation, had a lower recurrence rate (21.9% vs. 47.1&, p=0.03) and had a lower five-year mortality rate (6.9% vs. 19.1%, p=0.75). In another study, EUS changed the management of 38% of patients, primarily by detecting lymph nodes that were not seen on CT.[8] Finally, EUS can be helpful in some patients in whom there is concern for recurrence after initial treatment but this role is limited by radiation-induced inflammation and fibrosis of the wall of the rectum.

As has been already discussed, EUS provides detailed and accurate imaging of the gastrointestinal wall. This ability is used in the evaluation of patients with fecal incontinence in whom EUS is able to provide a structural assessment of the internal and external anal sphincters. In normal examinations, after introducing the echo-endoscope into the rectum and gradually withdrawing it through the anal canal, the internal and external sphincters will appear as two concentric, hypoechoic uninterrupted rings. EUS can identify disruptions in these muscles which could be due to surgical or traumatic injuries, or other causes.

Transrectal ultrasound can also be used in the evaluation of patients with perianal Crohn's disease by detecting and mapping fistulas and abscesses.

Interventional EUS

EUS is the preferred method for endoscopic pancreatic psuedocyst drainage in patients in whom there is concern about the presence of blood vessels between or in the vicinity of the gut wall and the pseudocyst. EUS with color Doppler can identify those vessels and assist in choosing a safe puncture site.

The ability of EUS to visualize the extrahepatic bile ducts can be used to puncture and access the CBD, thereby assisting in ERCP in difficult cannulation cases. EUS guided injection of botulinum toxin has been described for achalasia.

Celiac Plexus Blockade & Neurolysis

One of the landmarks during any EUS examination is the identification of the take-off of the celiac artery from the abdominal aorta. This is also the location of the celiac plexus and a celiac lymph node (if present). The ability to visualize the location of the celiac plexus in the retroperitoneal space posterior to the stomach and pancreas, has allowed EUS-guided celiac plexus blockade and neurolysis for chronic pain arising from the pancreas. In celiac plexus neurolysis (CPN), performed in patients with pain due to pancreatic cancer, a neurolytic agent (absolute alcohol), is injected into and around the celiac plexus under "real-time"

ultrasound imaging and guidance. Celiac plexus blockade (CPB) is performed in patient with chronic pain due to chronic pancreatitis and triamcinolone is injected into the celiac plexus. Common side effects of these procedures include back or abdominal pain, diarrhea, and transient postural hypotension. Serious complications are rare. CPN and CPB are best used as a part of a comprehensive and multidisciplinary pain management program and have been shown to reduce oral opioid usage.[9,10]

Complications

Complications due to EUS procedures can be divided into sedation-related complications, complications associated with all endoscopic procedures, and those unique to EUS.[11] Sedation-related complications are similar to those of standard endoscopy. Complications associated with all endoscopic procedures include bleeding, infection, and perforation. The risk of perforation and bleeding with EUS are similar to that of standard endoscopy. The risk of bacteremia with EUS is low. EUS differs from standard endoscopy in the ability to perform FNA. Prophylactic antibiotics are indicated in two settings: transrectal FNA and FNA of cystic lesions. Pancreatic FNA carries a 1-2% risk of pancreatitis. EUS-guided CPB and CPN are also associated with a low risk of transient diarrhea, transient hypotension, and abscess formation.

The ability of EUS to provide high resolution imaging and the ability to pass needles into lesions under "real time" ultrasound guidance has led to research into multiple novel therapeutic possibilities. EUS-guided radiofrequency application, delivery of radiation seeds, and injection of anticancer agents into tumors are all being investigated. Finally, a role for EUS may develop in the emerging field of NOTES (Natural Orifice TransEndoscopic Surgery) by helping to guide, for example, the creation of anastomoses between various luminal organs (choledochoduodenostomy, hepaticogastrotomy).

In summary, endoscopic ultrasound and FNA is a powerful tool in the hands of trained gastroenterologists and is invaluable in the evaluation of pancreatic diseases, the evaluation of mediastinal lymphadenopathy and masses, and the staging of many gastrointestinal malignancies. EUS FNA is now the standard procedure for sampling pancreatic masses, lymph nodes, and subepithelial lesions.

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