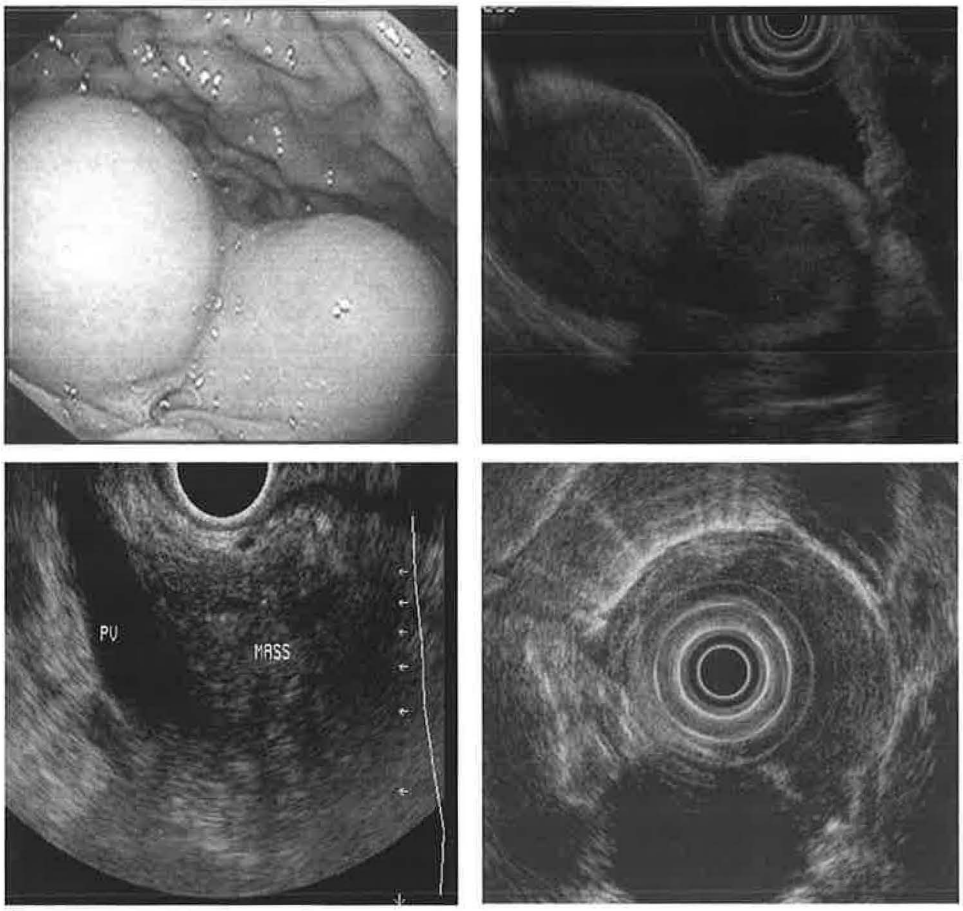
THE EMERGING ROLE OF ENDOSCOPIC ULTRASONOGRAPHY IN CANCER STAGING



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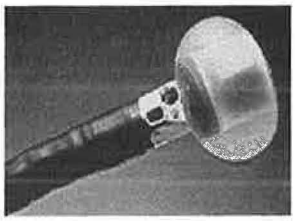
This is to acknowledge that Dr. Jayaprakash Sreenarasimhaiah has disclosed no financial interests or other relationships with commercial concerns related directly or indirectly to this program. Dr. Sreenarasimhaiah will not be discussing off-label uses in his presentation.

Over the past two decades, major advances in radiographic imaging have had an enormous impact upon the diagnosis and staging of solid organ cancers. The evaluation of these tumors must be expedient and highly accurate to ensure appropriate management. Computerized axial tomography (CT) and magnetic resonance imaging (MRI) have been able to provide significant detailed views of the extent of tumors and their potential spread to adjacent or distant sites. Positron emission tomography (PET) scans have also been able to identify tumor presence based on fluorodeoxyglucose (FDG) activity of cancer cells. Nevertheless, all of these imaging tests have their limitations. The extent of tumor spread particularly into adjacent structures such as lymph nodes and vasculature is often underestimated or unclear by these techniques. However, over the last two decades the evolution of a technology known as endoscopic ultrasonography has given promise to improved staging of many solid organ tumors.

TECHNOLOGIC ASPECTS

Endoscopic ultrasonography (EUS) was first developed in 1980 as a prototype technology to evaluate pancreatic cancer.[1] Its arrival into clinical practice was in 1989 following a long period of evolution and research applications. This unique imaging technique combines fiberoptic endoscopic visualization of the gastrointestinal tract with ultrasonography. An ultrasound transducer is mounted to the tip of the endoscope and enables imaging outside of the gastrointestinal tract to adjacent structures. Imaging can be acquired of nearby structures and local or adjacent infiltration of tumors. Distant spread of tumors should be initially excluded by CT imaging.

Curvilinear array



Radial scanner

US catheter probe

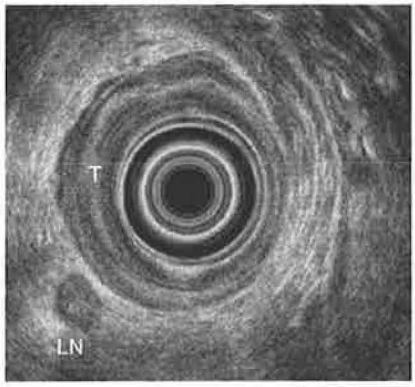
Generally, two types of echoendoscope are utilized clinically, the radial scanner scope and the curvilinear array scanner. The radial scanner scope provides a detailed 360º view from within the gastrointestinal lumen. Scanning is achieved with either 7.5 or 12 MHz frequency. Higher frequency scanning provides better visualization of details at close range such as the multiple layers of the gastrointestinal mucosal and muscular walls. Lower frequency scanning enables deeper penetration into surrounding structures. The second type of scanner, curvilinear array imaging, has a limited sector of 100º of scanning area and is equipped with color-flow and Doppler capabilities. The scanner is parallel to the shaft of the endoscope and thus allows direct visualization of a needle up to 8cm. This echoendoscope is therefore essential in fine needle aspiration (FNA). In contrast, the needle is perpendicular to the image on the radial scanning scope and so visualization during FNA is not possible.

Recently, catheter-based ultrasonic probes have become available for use with standard videoendoscopes. These probes are passed through the accessory channel to image small mucosal and submucosal lesions at a high frequency of 20 MHz. The focal zone for ultrasound penetration is typically within 1 to 2cm due to the small size of the transducer.

APPLICATIONS OF EUS

Esophageal cancer

The incidence of esophageal cancer has been increasing steadily over the past decade, particularly adenocarcinoma which now exceeds squamous cell carcinoma since 1990.[2] Approximately, 13,200 people are annually diagnosed with esophageal cancer in the U.S. with curative success remaining below 10%. In certain parts of the world, particularly northern China and northern Iran, the incidence is 100 per 100,000, or 20-fold the incidence in the U.S.[3]



T3 N1 Esophageal cancer

EUS is the single most effective modality in staging of depth of esophageal tumor infiltration with regard to tumor (T) and nodal (N) classification. Unlike CT, MRI, and PET scanning, tumor growth into the various layers of the esophageal wall can be assessed. Also, subtle infiltration into the adjacent mediastinal structures can be seen best with EUS such as pericardial or pleural involvement. FNA biopsy of suspicious lymph nodes, particularly in the celiac axis can determine whether a tumor is advanced beyond operative management with curative intent.

Tumor (T) staging is based upon infiltration of the layers of the esophagus. Mucosal-based tumors are T1 and may be amenable to minimally invasive therapy such as endoscopic mucosal resection or ablative photodynamic therapy. Penetration of the tumor through the submucosa and into but not entirely through the muscularis propria is rendered a T2 lesion. Infiltration through the muscularis propria but still contained within the esophageal adventitia is characteristic of a T3 lesion. Advanced T4 tumors are seen to grow beyond the outer esophageal layer and into surrounding structures such as the aorta, pericardium, or pleura.

Lymph nodes can be examined for suspicious sonographic features. Nodes that are larger than 1cm, hypoechoic, and round instead of elliptical may suggest tumor involvement and are labeled as N1 lesions. FNA can be used to confirm this if access to the lymph node by needle biopsy does not need to enter through the primary esophageal tumor. Positive lymph nodes in the celiac axis suggest distal involvement and are equivalent to metastatic (M1) disease. In the setting of a distal esophageal tumor, suspicious proximal periesophageal or cervical lymph nodes visualized by EUS also suggests M1 disease.[4]

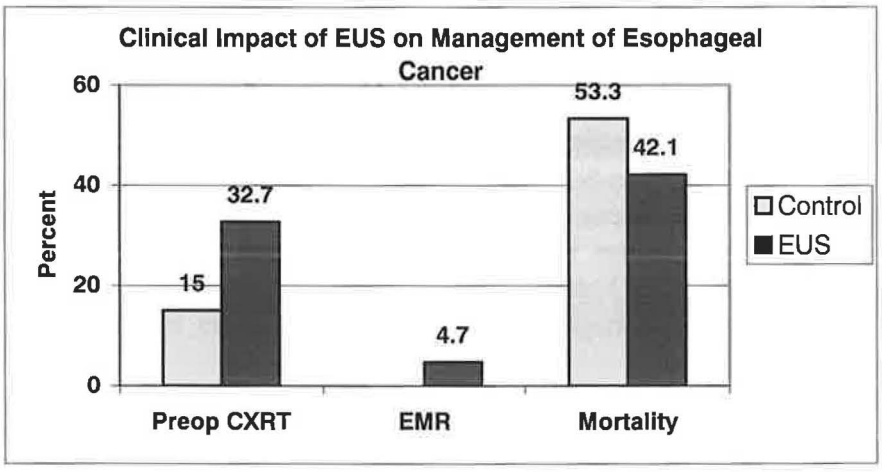
Such staging is not readily distinguished by any other imaging modality. The accuracy of T stage ranges between 85 to 90% while nodal staging is approximately 80%. EUS-guided FNA of lymph nodes increases nodal staging to the range of 86 – 95%.[4-7] EUS imaging enables the identification of locally advanced tumor (T3, T4, or TxN1) in which preoperative neoadjuvant chemoradiation provides the best outcome.[8]

Staging of esophageal cancer by EUS

T1	Limited to lamina propria or submucosa
T2	Invades muscularis propria but not entirely through
T3	Invades through entire muscularis propria into adventitia
T4	Invades adjacent structures
Tx	Cannot be assessed
N0	No regional lymph nodes
N1	Regional lymph nodes excluding celiac nodes
Nx	Cannot be assessed
M0	No distant metastatic disease or celiac lymph nodes
M1	Distant metastatic disease or positive celiac lymph node

Stage 0	Tis, N0, M0
Stage I	T1, N0, M0
Stage IIA	T2 or T3, N0, M0
Stage IIB	T1 or T2, N1, M0
Stage III	T3, N1, M0
	T4, N0 or N1, M0
Stage IV	Any T, any N, M1

The clinical impact of EUS on outcomes of esophageal cancer has been studied extensively. Harewood, et al., evaluated a group of 60 patients with de novo nonmetastatic esophageal cancer who did not undergo EUS. This group was compared to another comprised of 107 similar patients with non-metastatic disease who underwent EUS with or without FNA prior to treatment decisions.



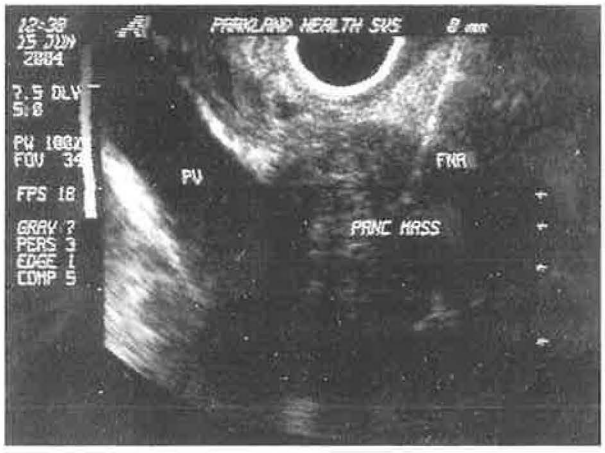
Chemoradiation therapy (CXRT); Endoscopic mucosal resection (EMR)

Of the patients in the EUS group, 58 of 107 underwent FNA of suspicious appearing lymph nodes. Overall, a higher proportion of the EUS group (32.7%) received preoperative chemoradiation. Additionally, 4.7% were found to have T1 lesions that

were removed by endoscopic mucosal resection (EMR) rather than esophagectomy. In the control group, 53.3% of patients died in a 24-month follow-up. The use of EUS in the second group, however, showed a reduction of mortality to 42.1% in the same follow-up period. This study demonstrates that EUS staging of non-metastatic esophageal adenocarcinoma is associated with a recurrence-free survival advantage and overall reduction in mortality.[9]

Pancreatic cancer

Currently, pancreatic cancer is the fourth leading cause of cancer death in the U.S. with approximately 28,000 new cases per year.[10] Unfortunately, the majority of cancers are detected when they reach a size greater than 3cm. Additionally, 80% have regional or distant spread by the time of diagnosis.[11] Surgical therapy for the majority of cases has traditionally been the Whipple resection, particularly for lesions in the head of the pancreas. Despite advancements in operative techniques, the 5-year survival of 5% has remained unchanged over the last few decades.[12] It is for this reason that preoperative staging of pancreatic cancer be performed as accurately as possible to avoid unnecessary surgical intervention, which may have a high morbidity and mortality with a low benefit.



Resectable pancreatic cancer

EUS depicts fine detail of the pancreatic parenchyma many of which are not seen by any other available imaging modality. Early fibrosis, calcifications and pancreatic ductal changes are easily detected. Most tumors appear irregular and hypoechoic or as inhomogeneous regions within normal echogenic areas of the pancreas. Involvement of tumor into the portal vein, splenic vein, superior mesenteric vein and artery, common bile duct, and duodenum can readily be identified. Additionally, ascites, subtle liver lesions, and regional or celiac lymph nodes can also be examined and sampled. In most cases, the determination by EUS of a tumor invading the portal vein, superior mesenteric vessels or celiac trunk precludes surgical resection.[13] Determination of T and N stage by EUS in pancreatic cancer had been previously reported to be highly accurate at approximately 80% and 72% respectively.[14]

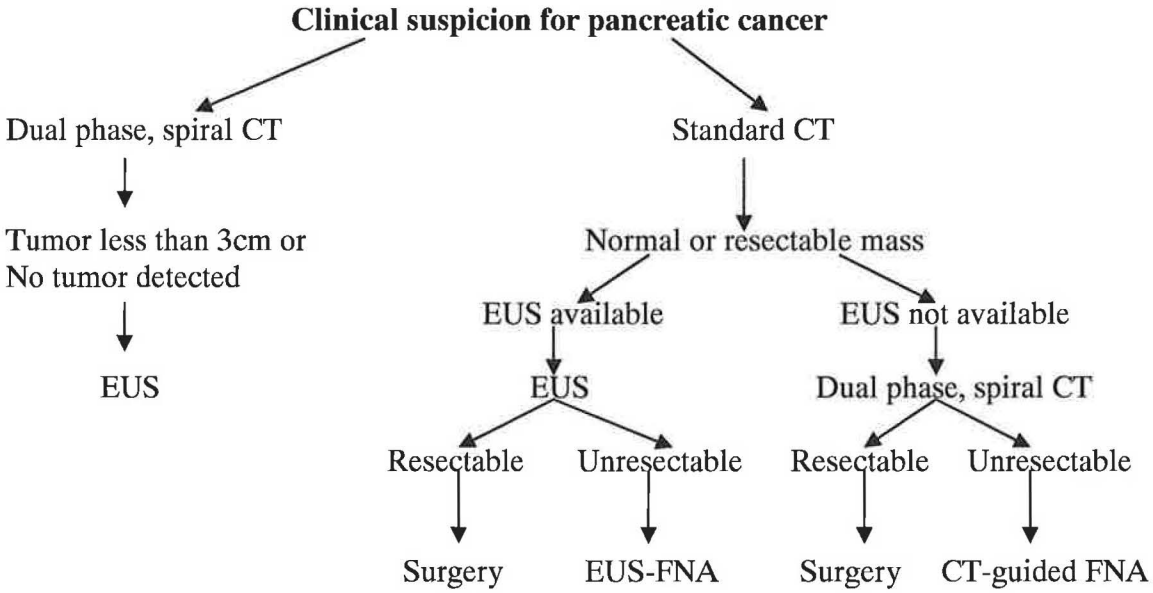
Recently, a study compared EUS-guided FNA with multidetector spiral CT in the diagnosis of pancreatic cancer. In 81 consecutive patients with suspicion of a pancreatic neoplasm, both EUS and CT with multiphasic pancreas protocol were used. Mean tumor size was 3cm and the majority were located in the head of the pancreas. Overall accuracy in diagnosis of pancreatic cancer using spiral CT, EUS and EUS-FNA were 74%, 94%, and 88% respectively. In those cases that a mass was suspected but CT could not readily identify, EUS and EUS-FNA had accuracy in diagnosis of 92%. The absence of a mass on EUS excluded pancreatic neoplasm (negative predictive value) in 100%. Cytologic analysis of suspicious lesions seen on EUS-FNA had an 89% accuracy of diagnosis.[15]

Standard percutaneous FNA of pancreatic lesions such as by CT or transabdominal ultrasound have an overall accuracy of 80% while EUS-FNA has sensitivity of 88 – 92%.[16,17] Interestingly, FNA by percutaneous methods has been shown to result in tumor seeding along the needle track. A four-fold increase in tumor cells has been noted in intraperitoneal lavage cytology following percutaneous FNA. However, such a concern is not present in EUS-FNA. Pancreatic tumors are usually biopsied by a transduodenal approach and therefore the needle tract is typically resected at surgery.[18]

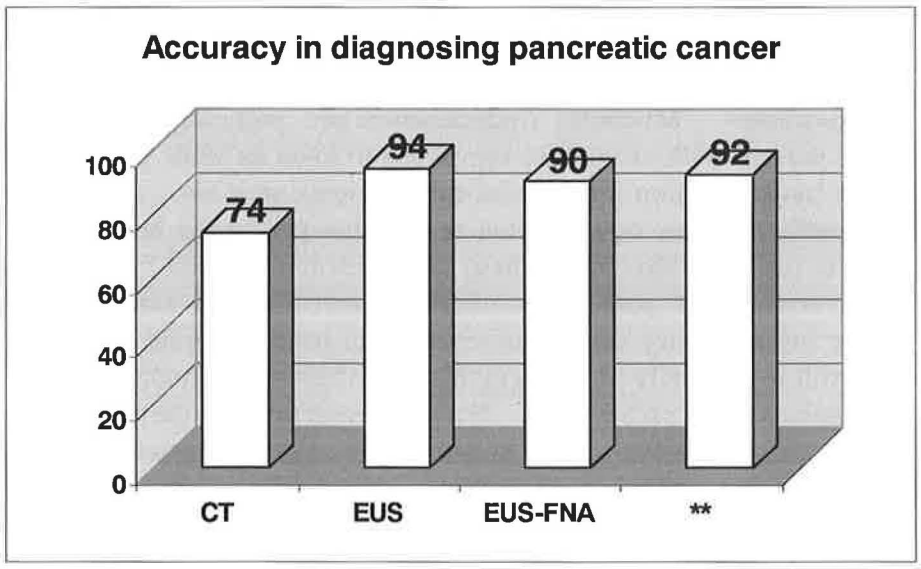
Staging of pancreatic tumors by EUS

T1	Limited to pancreas but less than 2cm
T2	Limited to pancreas but exceeding 2cm
T3	Invades duodenum, bile duct, or peripancreatic tissue
T4	Invades adjacent large vessels, stomach, spleen, or colon
Tx	Cannot be assessed
N0	No regional lymph nodes
N1	Regional lymph nodes
	Primary head tumor – celiac and pyloric nodes
	Body or tail tumor – splenic hilum or peripancreatic tail nodes
Nx	Cannot be assessed
M0	No distant metastatic disease
M1	Distant metastatic disease
Mx	Cannot be assessed
Stage I	1 or T2, N0, M0
Stage II	T3, N0, M0
Stage III	Any T, N1, M0
Stage IVa	T4, any N, M0
Stage IVb	Any T, any N, M1

The importance of EUS staging in pancreatic cancer is to determine the most appropriate management. The surgical management for cancers in the pancreatic head traditionally remains the Whipple procedure which is a large operation with potential complications, particularly depending on the experience of the surgeon and the volume of such cases in a particular hospital. Overall inpatient mortality across the U.S. between 1988 and 1998 was shown to be 9.5% ranging between 4.7 to 14.6%.[19] Additionally, many cancers are found to be inoperable at the time of surgical exploration. Therefore, the following algorithm can help result in the most appropriate diagnostic workup and care:



One of the distinct advantages of EUS is the ability to perform FNA at the same time as staging. A histologic diagnosis is often a prerequisite to start chemoradiation in those individuals with advanced inoperable tumors. In the usual setting, the index CT is not set up for FNA sampling and thus would require a second CT procedure. During EUS-FNA, the presence of the cytopathologist at the bedside to provide preliminary biopsy analysis has been shown to increase yield.[20]



**Accuracy of EUS-FNA in diagnosis of pancreatic cancer in patients without identifiable mass on CT scan. (Aggarwal, et.al. *Am J Gastroenterol*, 2004)

The use of EUS also has an impact on the economic burden of pancreatic cancer. In the US, direct medical costs of pancreatic cancer have been estimated to be $881 million dollars annually including hospitalization, outpatient visits, medications, and medical procedures.[21] Patients that undergo laparoscopic exploration of a pancreatic tumor incurred a total cost of $21,046 including operative and pathologic fees. In those that underwent EUS staging with FNA diagnosis, total costs including hospital and technical costs and professional fees of both the endoscopist and the pathologist was $2,440. Therefore, the economic savings of EUS staging are obvious in a patient with unresectable pancreatic cancer.[22]

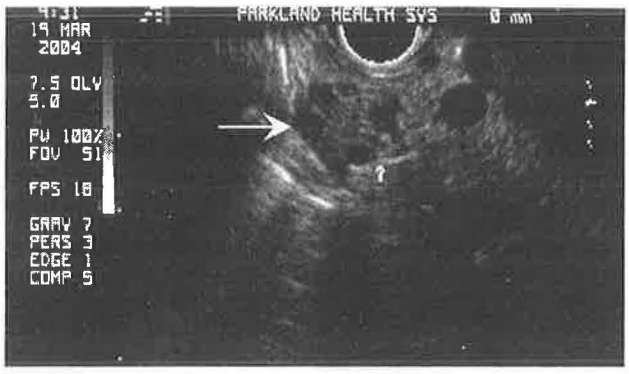
Additionally, EUS has a therapeutic role in the management of pancreatic cancer. Palliation of pain is an important concern. Celiac plexus blocks have long been used in pain management traditionally by CT-guidance or surgical approach with fluoroscopy. EUS-guided celiac plexus block can be achieved using a 22-guage needle advanced through the gastric wall and injected into the plexus with real-time imaging. A combination of bupivacaine and ethanol is often used. Weirsema and colleagues showed a successful initial response to pain of 82% - 91% by this method. An anterior approach from EUS may result in fewer theoretical spinal cord injuries. However, the need for repeat injections and tolerance is unclear.[23] Additionally, EUS-guide injection of anti-neoplastic agents has been examined in pancreatic cancer. Studies of injection of local immunotherapy are currently in phase II/III trials to determine if there is a clinical benefit and may open avenues for future therapy.[22, 24] Furthermore, studies in animal models have used radiofrequency ablation by EUS guidance to treat small pancreatic lesions without complications giving rise to the potential of treating unresectable adenocarcinoma or small neuroendocrine tumors in humans.[25]

Cystic neoplasms of the pancreas

Cystic neoplasms of the pancreas consist of early malignancy, benign lesions, or inflammatory processes. Mucinous cystadenomas are premalignant or malignant in nature and may present with or without symptoms or even as acute pancreatitis. Due to its potential for transformation into mucinous cystadenocarcinoma, surgical resection is advised.[26] In contrast, serous cystadenoma is a benign pancreatic lesion accounting for 25% of all cystic lesions. Most often these are incidentally found but may grow into a size causing symptoms of pain or duodenal obstruction and rarely are malignant. Pseudocysts are inflammatory walled-off collections resulting from pancreatitis. Very often, it is difficult to clinically or radiographically differentiate mucinous cystadenomas, serous cystadenomas, and pseudocysts. Surgical resection is often performed due to diagnostic uncertainty. However, EUS can sometimes aid in characterizing these lesions.

Endosonographic imaging of serous cystadenomas shows multiple small compartments separated by thin-walled septations. Larger serous cystadenomas may have a focus of fibrosis or calcification. Aspiration of fluid is easy due to its thin nature and can be sent for cytologic analysis. Mucinous cystadenomas have mucin or debris floating within and aspiration is often difficult due to the viscous nature of the contents. Differentiating mucinous cystadenoma from cystadenocarcinoma is unreliable even by EUS-FNA and if suspected should prompt surgical resection.[27] Pseudocysts can be of varying sizes and often contain debris, blood, or necrotic tissue floating within the cyst

fluid. Aspiration yields fluid that demonstrates inflammatory cells and is often rich in amylase.[28] Despite cyst fluid analysis, a diagnosis of the benign serous cystadenoma is found only 50% of the time that it is suspected. Therefore, if diagnostic uncertainty remains or symptoms develop, surgical resection is usually advocated.[27]



Serous cystadenoma of pancreas

Intraductal papillary mucinous tumors (IPMT) of the pancreas are often difficult to diagnose but can be aided by EUS examination. The identification of this rare condition is important because of its premalignant nature with almost virtual transformation into a malignancy through a very indolent course. Findings can be variable and include a diffusely dilated pancreatic duct, cysts of varying sizes that mimic microcystic or serous cystadenomas, and focal hypoechoic masses. Aspiration of fluid from large unilocular cysts can be performed and demonstrate similar cytologic findings as mucinous cystadenomas.[29-31] Several cyst fluid tumor markers are currently being studied to help differentiate the type of pancreatic cyst. High concentrations of the carbohydrate antigens CEA and CA72-4 have been found in fluid of mucinous cystadenomas and mucinous cystadenocarcinomas, while it is low in serous cystadenomas and pseudocysts.[32] The diagnosis of cystic neoplasms of the pancreas can be difficult. It is generally agreed that imaging by CT, MRI, or EUS alone is insufficient and cyst fluid aspiration and analysis may assist in the recognition of mucinous or malignant lesions.

Gastric neoplasms

Gastric carcinomas are rare and usually present in late stages in Western countries. However, due to its frequency, it is found often in early stages in parts of the world such as Japan. EUS has a useful role in staging early cancers. Early adenocarcinoma is confined to the mucosa (T1m) or submucosa (T1sm) and has a 95% five-year survival following resection.[33] High-frequency (20mHz) ultrasonic miniprobes can be used with a standard endoscope to stage such small lesions with 92% accuracy. However, lesions larger than 2cm are evaluated by standard echoendoscopes and often are overstaged resulting in a accuracy of 50%.[34]

The role of EUS in advanced gastric carcinoma depends upon the treatment options. In patients who are being considered for operative resection, T-staging by EUS is fairly accurate at 80% for T1 lesions and 90% for T3 or T4 tumors. The diagnosis of T2 lesions is only at 62% accuracy due to difficulty in assessing invasion beyond the gastric muscularis propria.[35,36] The use of EUS in preoperative staging for advanced gastric carcinoma has been shown to alter therapy in 30% of cases, usually resulting in more limited resections, particularly for stage T1-T3 tumors.[37]

Staging of gastric adenocarcinoma by EUS

T1	Confined to mucosa or submucosa
T2	Infiltration into muscularis propria or subserosa
T3	Infiltration into serosa
T4	Tumor involvement of adjacent structures
Tx	Cannot be assessed
N0	No lymph node metastasis
N1	Involvement of perigastric lymph nodes within 3cm of tumor edge
N2	Involvement of perigastric lymph nodes greater than 3cm from tumor edge Or along the left gastric, common hepatic, mesenteric, or splenic arteries
Nx	Cannot be assessed
M0	No distant metastasis
M1	Distant metastasis
Stage I	T1N0M0, T1N1M0, T2N0M0
Stage II	T1N2M0, T2N1M0, T3N0M0
Stage III	T2N2M0, T3N1M0, T4N0M0
Stage IV	T3N2M0, T4N1M0, any T/any N/M1

Endoscopic mucosal resection is a minimally invasive method that has been shown to be effective for early gastric cancers. Submucosal elevation by endoscopic injection combined with a cap-suction technique can resect gastric tissue containing the mucosa and muscularis mucosal layers. This method has been shown extensively to be an appropriate therapeutic alternative to surgical resection for well and moderately differentiated adenocarcinoma measuring less than 2cm in size. Specifically, those lesions identified by EUS to not invade into the third (submucosal) echogenic layer or have lymphadenopathy are amenable to this therapy. This therapy is not indicated in undifferentiated or signet-ring cell carcinoma due to increased risk for lymph-node involvement.[38,39]

Gastric mucosa-associated lymphoid tissue lymphoma (MALT) is a tumor that arises from chronic gastritis with formation of lymphoid follicles due to an immunologic response against Helicobacter pylori infection. This tumor contains B cells that initiate clonal expansion of centrocyte-like cells and subsequently develops into lymphoma. Endoscopically, a variety of presentations are possible including patchy or diffuse erythema, superficial or deep ulcerations, and exophytic or infiltrating mass lesions. CT scan is useful to determine if there are enlarged lymph nodes within the abdomen or perigastric region. However, EUS is much more accurate than CT at determining the presence of perigastric lymph nodes as well as the depth of tumor into the various layers of the gastric wall.[40]

Staging of MALT lymphoma by EUS

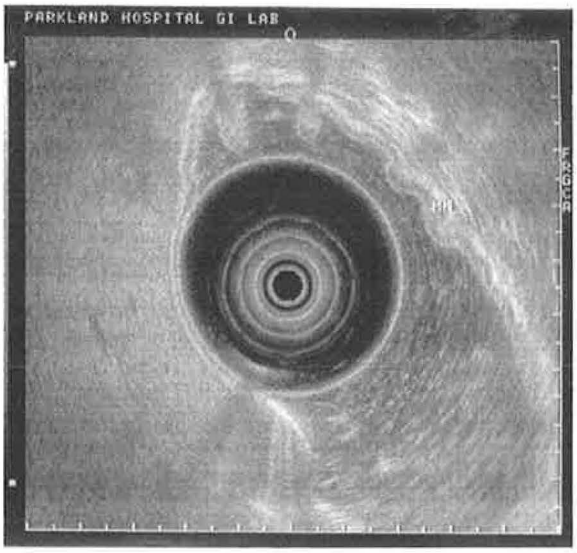
T1a: Superficial mucosa: first (hyperechoic) layer
T1b: Deeper mucosa to muscularis mucosa: up to second (hypoechoic) layer
T2: Submucosa: third (hyperechoic) layer
T3: Beyond submucosa into muscularis propria, fourth (hypoechoic) layer and the serosa, fifth layer

Ann Arbor Modified Classification for MALT lymphoma

EI: Lymphoma restricted to GI tract on one side of diaphragm
- EI1: Limited to mucosa and submucosa
- EI2: Extending beyond submucosa

EII: Lymphoma infiltrating lymph nodes on same side of tumor
- EII1: Infiltration of regional lymph nodes
- EII2: Infiltration beyond regional lymph nodes

EIII: Lymphoma infiltrating GI tract/lymph nodes on both sides of diaphragm
EIV: Diffuse or disseminated involvement of extra-GI organs



Stage I Gastric MALT lymphoma

Tumors shown by EUS to be confined to the mucosa or submucosa are usually dependent upon *H. pylori* stimulation and therefore may be potentially cured by eradication of *H. pylori* alone.[41] Deeper penetration into muscular layers may necessitate chemotherapy, radiation and possibly surgical resection. For those with early tumors considered to be cured by *H. pylori* eradication, close follow-up with endoscopic biopsies and even endoscopic ultrasound can detect recurrence in a timely manner.[40,42]

Submucosal tumors

Many lesions are often found in a submucosal location during routine endoscopy. The majority are benign lesions. However, certain neoplasms are sometimes discovered. One important lesion that is well visualized by EUS is carcinoid tumor of the stomach. Carcinoid tumors are neuroendocrine in origin with a less aggressive course than typical adenocarcinoma. These tumors have potential to produce a variety of functionally active substances such as serotonin, histamine, gastrin, somatostatin, kinins, and prostaglandin.

However, the majority of gastrointestinal carcinoids are inactive. EUS can be used to evaluate carcinoid tumors found in the upper GI tract and rectum. Sonographic appearance suggests a hypoechoic, homogeneous lesion with distinct smooth margins that most often arises from one of the first three echogenic layers, i.e. mucosa, muscularis mucosa and submucosa. Unlike other submucosal lesions, diagnosis of gastrointestinal carcinoids can be made by standard endoscopic biopsies rather than fine needle aspiration. The location of the tumor dictates management. Duodenal or rectal carcinoids are very indolent and have no risk of metastasis until they penetrate into the muscularis propria (fourth echogenic layer) or exceed 2cm in size.[43] Gastric carcinoids can be multicentric and have a higher risk of metastasis particularly in Japan. Lesions less than 1cm and located within the mucosa or muscularis mucosa are easily removed endoscopically. However, gastric carcinoids exceeding 2cm in size or are visualized on EUS to invade the submucosa or muscularis propria should be considered for surgical resection.

Etiology of gastric submucosal lesions or extrinsic compression visualized by EUS

Arising from submucosal layer
- Lipoma, rarely liposarcoma
- Carcinoid
- Granular cell tumor
- Varices
- Pancreatic rests (aberrant pancreas tissue)
- Histiocytoma, fibroma
- Duplication cysts
- Splenic remnant or implant

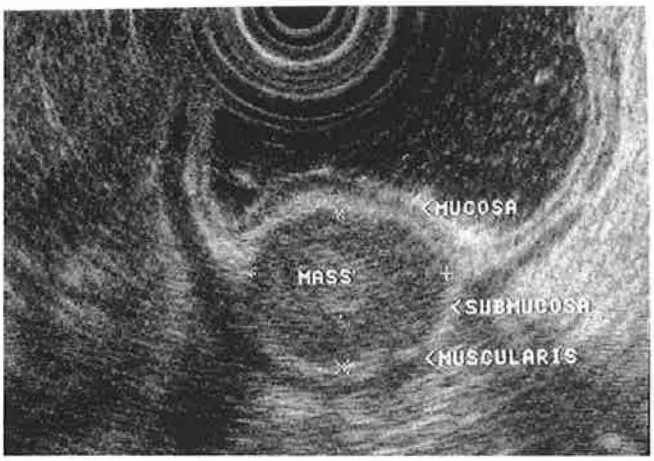
Arising from muscularis propria
- Gastrointestinal stromal cell tumors (leiomyoma and leiomyosarcoma)

Extrinsic compression
- Spleen
- Liver
- Pancreatic pseudocyst
- Enlarged lymph nodes, metastases

Another submucosal gastrointestinal tumor seen infrequently is the granular cell tumor which arises from Schwann cells or smooth muscle. These lesions can be found anywhere in the body including most often the skin, tongue, oropharynx and breast. In the gastrointestinal tract, they are usually discovered incidentally in the esophagus, stomach or colon.[44] EUS demonstrates hypoechoic lesions arising from the muscularis mucosa or submucosa. Tumors greater than 2cm in diameter, increasing in size on serial exams or infiltrating through the intestinal wall should be removed due to potential for rare malignant transformation. Otherwise, observation is warranted unless symptoms are present.[45]

Gastrointestinal stromal tumors (GIST) are mesenchymal tumors that express the c-kit proto-oncogene protein (also known as CD117) and arise from the gastrointestinal

wall, mesentery, omentum, or retroperitoneum. The expression of c-kit distinguishes GISTs from true leiomyomas, leiomyosarcomas, and other mesenchymal tumors of the GI tract. GISTs comprise the vast majority of mesenchymal tumors.[46] Symptoms range from asymptomatic to abdominal pain, bowel obstruction, or gastrointestinal bleeding. The majority are found in the stomach (60 – 70%) and small bowel (20 – 30%) with the remainder found within and outside of the gastrointestinal tract. Many are found incidentally at the time of routine endoscopy. It has been estimated that up to 25% of GISTs are malignant.[47]



Gastrointestinal stromal tumor

Endoscopically, stromal tumors appear as a submucosal lesion or bulge with either overlying normal mucosa or a central umbilication with ulceration. Endosonographically, GISTs are classically visualized as hypoechoic masses arising from the fourth sonographic layer corresponding to the muscularis propria. Occasionally, they may arise from the second or muscularis mucosa layer as well.[48] Certain features of GISTs seen on EUS may suggest malignancy or malignant potential. These include tumor size exceeding 4cm, irregular border, echogenic foci and cystic spaces.[49] When features such as this are found or if diagnostic uncertainty remains, EUS-FNA can be accomplished. Immunohistochemical staining and analysis for CD117 expression can confirm GISTs. Routine endoscopic forceps biopsies are usually unrevealing due to the deeper submucosal location of these tumors. EUS can aid in determining whether surgical resection is warranted or if observation with surveillance endoscopy is indicated. There are no established consensus guidelines regarding surveillance intervals and methods for those tumors that are not surgically removed. Furthermore, guidelines for postoperative surveillance of tumor recurrence are yet to be defined.

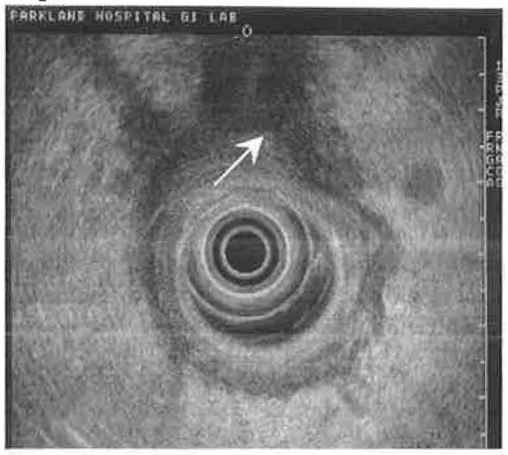
Rectal cancer

Rectal cancer may be detected in a variety of stages. Local recurrence after resection is a significant cause of morbidity and mortality in these individuals. Transrectal EUS has been able to provide extensive details regarding depth of tumor invasion, sphincter involvement and lymph node infiltration. EUS may help determine the extent of surgical resection required while still preserving sphincter function.
Multiple studies have shown that EUS has an accuracy exceeding 90% for T1, T2, and T4 tumors. Accuracy is only 73% for T2 lesions because of difficulty in assessing invasion though the muscularis propria. Accuracy of nodal staging is reported to be 72%.[37] However, EUS-FNA increases the accuracy of nodal staging above 80%, which is superior to CT scan staging.[50]

Staging of rectal cancer by EUS

T1	Extending into mucosa and submucosa
T2	Extending into but not through the muscularis propria
T3	Extending through muscularis propria into perirectal fat
T4	Infiltration into adjacent organs
N0	No regional lymph nodes
N1	Metastatic disease in 1 to 3 regional lymph nodes
N2	Metastatic disease in 4 or more regional lymph nodes
M0	No distant metastasis
M1	Distant metastasis
Stage I	T1/2, N0, M0
Stage II	T3/4, N0, M0
Stage III	Any T, N1/2, M0
Stage IV	Any T, any N, M1

Initial staging of rectal carcinoma should begin with a CT scan to determine distant metastatic disease such as hepatic involvement. Following this, rectal EUS can help determine the most beneficial therapeutic approach. Neoadjuvant chemoradiation therapy has been shown to offer the most benefit for those with T3 or T4 rectal cancer prior to surgical resection.[51] In a recent study, outcomes of rectal cancer were compared between a group of 68 patients (non-EUS control group) and another group of 73 patients (EUS group) who had nonmetastatic disease. In the control group, 14.9% underwent preoperative adjuvant therapy and 63.8% received this postoperatively. In the EUS group, 58.5% of patients received preoperative adjuvant therapy and 26.4% postoperatively. Both groups were of similar demographics and underwent similar surgical resections. Tumor recurrence rates were 47.1% and 21.9% in the control and EUS groups respectively. Mortality rates, however, did not differ when adjusted for age, gender, timing of adjuvant therapy and tumor stage. This study suggests that routine staging of locally advanced rectal cancer by EUS can help determine which patients should be offered preoperative chemoradiation therapy. This demonstrates that the use of



T4 N1 Rectal cancer

EUS is associated with a recurrence-free survival advantage.[52] In a study of restaging rectal cancer following neoadjuvant chemoradiation therapy, the accuracy of EUS was considerably reduced to 48% for T-stage and 77% for N-stage. This is due to radiation and chemotherapy-induced inflammation, edema, and immature fibrosis of the rectal wall making identification of the individual layers of bowel wall difficult.[53]

Comparison of accuracy of EUS and CT in staging of gastrointestinal malignancies

		T stage		*N stage*	
Tumor	***N***	***EUS***	***CT***	***EUS***	***CT***
Esophagus	367	85%	58%	75%	54%
Stomach	326	85%	30%	79%	39%
Pancreas	82	82%	44%	68%	48%
Rectum	419	84%	68%	84%	60%

Sial et al. *Medscape General Medicine*, 2001;3(3)

Lung and mediastinal tumors

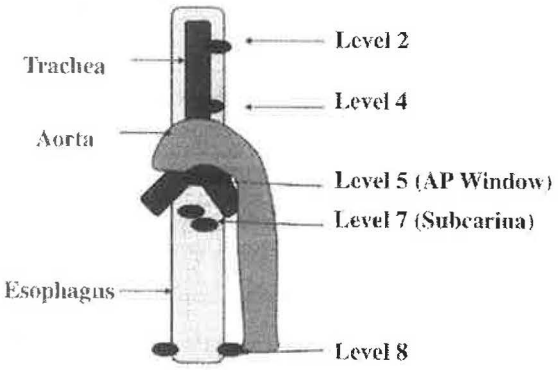
In recent years, the role of the gastroenterologist-endosonographer has extended into areas outside of the gastrointestinal tract and abdominal organs. EUS is rapidly becoming involved in the staging of lung cancer, the most common cause of cancer death worldwide. In the US, lung cancer is diagnosed annually in 177,000 individuals, accounts for 28% of annual cancer deaths and has an economic burden exceeding $35 billion dollars.[54] In the setting of non-small cell lung cancer (NSCLC), only 25% of cases are amenable to surgical resection. Furthermore, 5-year survival of this group is only 41.4%.[55] Therefore, the selection of appropriate candidates for surgical therapy depends on accurate staging.

CT scanning of the chest is the initial test to evaluate lung cancer. While it is very useful at detecting the extent of tumor involvement within the lung parenchyma and the presence of pleural effusions, it is still not a reliable method for mediastinal lymph node staging in NSCLC. Only lymph nodes exceeding 1cm in size are identified consistently. Using surgical findings as the gold standard, there still remains a poor sensitivity (45.5 to 84.4%) and specificity (57 to 84.1%) for detecting mediastinal lymph node metastasis by CT imaging.[54,56] CT-guided FNA of middle mediastinum lymph nodes can be achieved through the right paratracheal space or suprasternal area. However, this is operator-dependent and not widely available in most hospital radiology departments. Multiple studies have shown that CT-guided FNA in the mediastinum carries substantial risks such as pneumothorax in up to 22% of cases.[57]

The use of PET in staging of NSCLC has been prospectively shown to be more accurate than CT imaging in detecting metastatic disease in the mediastinum. While the false-negative rate is low, up to 24% of PET scans in this setting are falsely positive resulting in unnecessary neoadjuvant chemotherapy. This is due to the lack of tissue

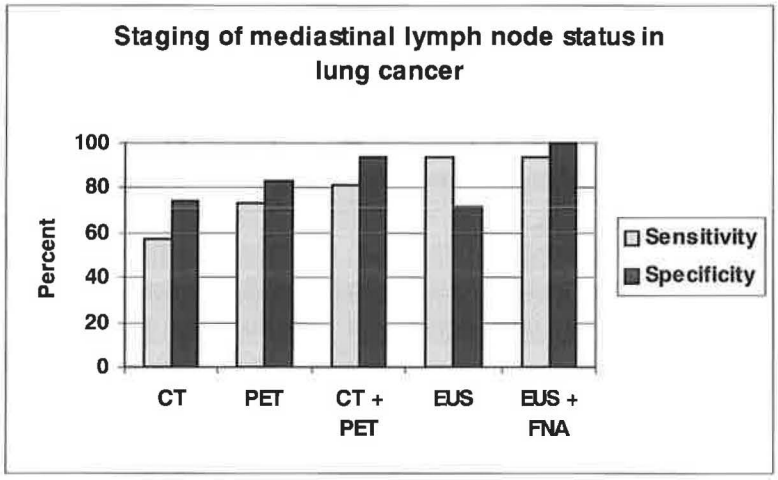
confirmation as any active inflammatory or infectious process can be misinterpreted as mediastinal lymphadenopathy.[54,58,59]

Mediastinoscopy is frequently performed when suspicious or enlarged lymph nodes are seen on CT or other radiographic imaging. Some surgeons will routinely perform mediastinoscopy to achieve more accurate staging even when imaging of the mediastinum is negative. Complications occur at a rate of 1.7% and include most commonly pneumothorax, left recurrent laryngeal nerve injury, esophageal tear, avulsion of large blood vessels, wound infections, and risks of general anesthesia.[60] The sensitivity of detecting metastatic disease in accessible lymph nodes ranges from 79 to 93% with specificity close to 100%.[61] Due to its invasive nature, however, the use of mediastinoscopy is declining in favor of less invasive modalities such as PET and EUS.



EUS is a unique noninvasive modality to stage NSCLC as it can both image and sample lymph nodes or potentially metastatic lesions in the posterior mediastinum, retroperitoneum, celiac region, left adrenal gland, and left lobe of the liver. Imaging with FNA biopsy can be safely accomplished by a transesophageal or transgastric approach with almost no complications. Most lymph nodes identified by EUS are within the subcarinal space (station 7), subaortic or aortopulmonary window (station 5), paraesophageal area (station 8), inferior pulmonary ligament region (station 9), and main bronchial area (station 10). Limitations to EUS imaging include lymph nodes far away from the esophagus such as lobar (station 12) and interlobar (station 11) nodes. Also, air interference from the trachea makes nodes anterior and lateral to the trachea (stations 3 and 6) difficult to evaluate by EUS.[54,62]

EUS-FNA of mediastinal lymph nodes has a reported specificity for malignancy of nearly 100% and a sensitivity ranging from 88% to 96%.[61,62] CT staging of the mediastinum may often be falsely negative. In a recent study of patients with NSCLC, a normal mediastinum as determined by CT imaging was followed by EUS in 69 patients. EUS-FNA was able to detect positive tumor invasion into mediastinal lymph nodes in 14 of the 69 patients, direct mediastinal invasion by the tumor in 2 patients, and 1 patient with left adrenal gland metastatic disease. This study among others supports the practice that potentially operable patients with nonmetastatic NSCLC by CT criteria may benefit from EUS staging.[65]



A comparison of CT, PET and EUS has been prospectively examined in the mediastinal staging of potentially resectable lung cancer. In a recent study, 33 consecutive patients with lung cancer suggested by radiographic imaging or bronchoscopy with biopsy/cytology were examined prior to operation. Using surgical histology as the gold standard, prediction of mediastinal lymph node stage by CT, PET, and EUS had sensitivities of 57%, 73%, and 94% respectively. Specificities were 74%, 83%, and 71%. Accuracies were 67%, 79% and 82%. When PET was combined with CT imaging, the sensitivity improved to 81% and specificity to 94%. When EUS-FNA was performed, specificity improved to 100% with no complications. This study demonstrated that EUS is superior to the other two modalities in mediastinal staging with the added advantage of lymph node sampling. However, CT is essential for evaluation of the pretracheal region and the remainder of the thorax. PET scanning has a useful role in determination of distant metastatic disease.[66]

A relatively new technology known as endobronchial ultrasound (EBUS) has become available for the past few years. Its use has been examined in the setting of intrathoracic malignancies with the question of whether the airway is infiltrated with tumor or whether it is merely compressed. In a study of 131 consecutive patients, EBUS was used following standard chest CT imaging and was subsequently evaluated surgically. In determination of involvement of the bronchi by lung malignancy, CT had a poor specificity of 25%, sensitivity of 75%, and accuracy of 51%. EBUS had 100% specificity, 89% sensitivity, and 94% accuracy when using surgical histology as the standard. Thus, EBUS may become a promising technology in this setting.[67]

FUTURE DIRECTIONS

Beyond diagnosis and staging of a variety of neoplasms, EUS has potential to develop into a therapeutic tool as well. Remarkable advances have been made and are continuing to evolve in therapeutic EUS, particularly with its ability to directly target tumor tissue with a needle advanced under real time imaging. High intensity focused ultrasound (HIFU) delivered to tumor cells has been shown in animal models to result in temperature elevation of tumor cells, which are more thermosensitive than normal cells.

This results in mechanical push-pull forces and subsequent cellular damage.[68] Endoscopically, HIFU has been investigated in a canine model to ablate rectal tumors and more recently as a transesophageal thermal therapy. In a rabbit model, the same concept was used to target liver lesions of the left lobe after endoscopically creating a gastrostomy and placing the ultrasound transducer within 10 to 20mm of the liver surface from the gastric side. In these animal models, small transducers were easily placed on the tip of an endoscope suggesting the possibilities of endoscopic therapy.[69-70]

Similar to the percutaneous therapy of hepatic metastases or hepatoma, radiofrequency ablation performed by EUS guidance has been investigated in a swine model. Trans-gastrointestinal insertion of a needle into a pancreatic mass with application of radiofrequency current resulted in histologically proven coagulation necrosis of 8 to 12mm diameter sections.[71]This finding suggests potential clinical applications for small neuroendocrine tumors or possibly palliation of unresectable pancreatic adenocarcinoma. Furthermore, other ablative therapies such as laser, microwave or cryotherapy may also be possible.

As EUS provides minimally invasive access to tumors, there is potential for delivery of targeted therapeutic agents. In phase I and II clinical trials, Chang and associates injected local activated T-lymphocyte and cytokine immunotherapy (Cytoimplant) into advanced pancreatic adenocarcinoma. Median survival was 13.2 months with no procedure-related complications which was longer than the control group. However, in comparison to gemcitabine, a survival advantage was not detected.[71,73] The injection of modified adenoviruses (ONYX-015) into pancreatic tumors has been examined as well and when combined with gemcitabine resulted in reduction of tumor burden in a small subset of patients.[74] Injection of alcohol by EUS guidance has been tried in a few case reports with partial response for solitary hepatic metastasis and gastric stromal cell submucosal tumors.[71,75]

SUMMARY

Endoscopic ultrasound is rapidly progressing into a vital part of the diagnosis and staging of many cancers within and outside of the gastrointestinal tract. Staging of locally advanced tumors by EUS can determine the most appropriate management regarding surgery, chemotherapy and radiation. Furthermore, the addition of FNA to EUS has provided increased accuracy in the histologic diagnosis of tumors and their spread to lymph nodes in order to provide optimal therapy. This technology provides a unique intraluminal access and close proximity to tumors of the pancreas, stomach, esophagus, rectum, and mediastinum. Multiple studies have shown the superiority of EUS over other conventional imaging modalities in staging local and regional involvement of these neoplasms. EUS can assist in targeting complex surgical and medical therapies to those individuals who would most likely benefit. In addition to diagnosis, EUS has incredible potential as a therapeutic modality. Current investigations suggest the possibility of EUS-guided ablation and immunotherapy for the treatment or palliation of a variety of tumors. Since its inception two decades ago, EUS has come on a long journey that is certainly to continue for an even longer time.

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