

## Endoscopic ultrasound: Current roles and future directions

Scott R Friedberg, Jesse Lachter

Scott R Friedberg, Department of Internal Medicine, University of Pittsburgh Medical Center, Pittsburgh, PA 15213, United States

Jesse Lachter, Rambam Healthcare Campus, Technion Israel Institute of Technology, Haifa 3109601, Israel

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Correspondence to: Scott R Friedberg, MD, Department of Internal Medicine, University of Pittsburgh Medical Center, 200 Lothrop St., Pittsburgh, PA 15213, United States. [friedbergsr@upmc.edu](mailto:friedbergsr@upmc.edu)  
Telephone: +1-305-6324895

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### Abstract

Endoscopic ultrasound (EUS), developed in the 1980s, was initially predominantly used for guidance of fine needle aspiration; the last 25 years, however, have witnessed a major expansion of EUS to various applications, both diagnostic and therapeutic. EUS has become much more than a tool to differentiate different tissue densities;

tissue can now be characterized in great detail using modalities such as elastography; the extent of tissue vascularity can now be learned with increasing precision. Using these various techniques, targets for biopsy can be precisely pinpointed. Upon reaching the target, tissue can then be examined microscopically in real-time, ensuring optimal targeting and diagnosis. This article provides a comprehensive review of the various current roles of EUS, including drainage of lesions, visualization and characterization of lesions, injection, surgery, and vascular intervention. With EUS technology continuing to develop exponentially, the article emphasizes the future directions of each modality.

**Key words:** Endoscopic ultrasound; Future; Trends; Roles

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**Core tip:** In recent years, endoscopic ultrasound (EUS) has evolved and is now used in various applications, both diagnostic and therapeutic. Classically used to differentiate different tissue densities, EUS is now used to characterize and localize tissue with much more precision. Upon reaching the target, tissue can then be examined microscopically in real-time, ensuring optimal targeting and diagnosis. This article provides a comprehensive review of the various current roles of EUS, including drainage of lesions, visualization and characterization of lesions, injection, surgery, and vascular intervention. With EUS technology continuing to develop exponentially, the article emphasizes the future directions of each modality.

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### INTRODUCTION

Flexible endoscopy was first developed in 1911 and

ultrasound later arrived in 1956. In the 1980s, these modalities were merged to form the endoscopic ultrasound (EUS). EUS allowed the visualization of structures near the gastrointestinal tract. It did not have much of a role in gastroenterology, however, until the advent of the fine needle aspiration (FNA) in 1991. FNA was a major step for EUS; it was the first time structures outside the lumen could be interacted with and explored. It was the first time the vast length of the gastrointestinal tract could truly be exploited as a potential inlet to the rest of the body.

For the last 25 years, EUS has increasingly been used in the field of gastroenterology. This trend is likely to continue as novel technology is developed and the demand for minimally invasive techniques continues to grow. Procedures that utilize EUS-FNA have specifically spearheaded this growth, but EUS itself has also evolved to be useful for many other procedures, both diagnostic and therapeutic.

Certain EUS advances have caught on faster than others, and in this review several of such modalities will be discussed. The focus will be on the current status of each modality and the direction to which each is heading. Each EUS modality will be categorized in terms of its main function, that is, drainage, visualization, injection, surgery, and vascular interventions.

## CHARACTERIZATION OF LESIONS

EUS-guided biopsy is the modality of choice to characterize and stage lesions in the GI tract, with the most commonly targeted organs being the pancreas, submucosal lesions, and lymph nodes<sup>[1]</sup>.

Because of its success thus far, much of the EUS research has been focused on improving characterization of lesions. This has led to advancements which have improved the ability to characterize lesions both from afar (ultrasound) and up close (*via* biopsy). Ultrasound imaging is no longer limited to the conventional B mode imaging, and now includes newer, more advanced modalities such as contrast-enhanced ultrasound and elastography. Forward-viewing EUS (FV-EUS) has improved the ability to access lesions, and modern microscopy advancements now enable real-time optical biopsy.

### Elastography

EUS elastography is a major recent advancement in EUS characterization of lesions. The underlying principle of elastography is that compression of a target tissue by a probe produces a smaller strain in hard (usually malignant) tissue than in soft (usually benign) tissue; therefore, elastography can indicate which areas are likely to be malignant vs benign.

Because elastography can be used in real-time, elastography serves as an important marker that can direct EUS-FNA. The sensitivity in identifying metastatic lymph nodes is at least 85%<sup>[2]</sup>. Another advantage of

elastography is that it is relatively inexpensive and does not require extensive training, though it is operator-dependent and is therefore inherently subjective. In addition, elastography can be used in the diagnosis of other conditions, such as prostate cancer, and rectal cancer<sup>[3]</sup>. Elastography can potentially also be used for adrenal tumors and biliary duct cancers because of their proximity to the gastrointestinal tract, but this research is still in its very early stages<sup>[2]</sup>.

Shear wave elastography is a special type of elastography that requires no manual compression of tissue as applied in conventional elastography, and is therefore less operator-dependent. Measurements of shear wave velocity yield additional information on the tissue's elasticity and therefore can help in diagnosis. Thus far shear wave elastography has been used mostly to characterize breast lesions, liver fibrosis, and thyroid lesions<sup>[2]</sup>. It has also been used in transrectal ultrasonography for prostate cancer<sup>[4]</sup>. It is anticipated that shear wave elastography will soon be used with EUS procedures.

Despite the promise that elastography has shown thus far, it is currently only used if EUS-FNA results are negative or inconclusive<sup>[3]</sup>. In the future, elastography may be able to be merged with other imaging techniques, such as fusion imaging, contrast-enhanced EUS, or 3D elastography to increase accuracy even further<sup>[2]</sup>. Another notable advancement in elastography is the automated histogram, which allows more quantitative, less subjective elastography, thereby increasing accuracy and reducing operator bias<sup>[2]</sup>.

### Tissue harmonic echo

Tissue harmonic echo (THE) imaging is a new technology that provides yet another modality of imaging pancreatic cystic lesions. THE mode imaging provides better characterization of lesions than conventional B mode images. The principle behind THE is that the sonogram is produced by higher harmonic frequencies as ultrasonic beams propagate through tissues. It has thus far only been used in abdominal ultrasound, but there is potential for EUS as well. More studies need to be done to determine whether THE significantly improves EUS diagnostics<sup>[5]</sup>.

### Contrast enhanced EUS

Contrast enhanced EUS (CE-EUS) is yet another advanced ultrasound modality. Its advantage is that it allows vascularity to be depicted, thereby improving accuracy, sensitivity, and specificity for diagnosing pancreatic masses and lymphadenopathy<sup>[3]</sup>. CE-EUS can also be used during EUS-FNA to help avoid vessels. Contrast enhanced color and power Color-Doppler sonography (CD-EUS) enable detection of intratumor vasculature, by producing pseudo Doppler signals from microbubbles. Contrast enhanced harmonic EUS (CH-EUS) was more recently developed to overcome the limitations of CD-EUS. CH-EUS can depict the microbubbles themselves rather than the entire flow

through the vessels thus allowing visualization of both microvessels and parenchymal perfusion<sup>[6]</sup>.

CE-EUS is an emerging technique with promise, but it has been scrutinized for being qualitative in nature, and therefore research is underway to develop more quantitative techniques<sup>[3]</sup>.

### **Needle-based confocal laser endomicroscopy**

Needle-based confocal laser endomicroscopy (n-CLE) is a technique allowing *in-vivo* "optical" histology using fluorescent contrast. N-CLE therefore can show which areas are most suspicious for malignancy and require biopsy. Preliminary results of n-CLE studies have been very promising, and in the future n-CLE may stand as the second option for diagnosing pancreatic cysts when EUS-FNA is inconclusive<sup>[7]</sup>. In the near future, n-CLE may become routinely used after EUS-FNA of solid pancreatic masses returns inconclusive<sup>[7,8]</sup>. Despite how accurate n-CLE proves to be, it will likely catch on slowly due to high cost and the difficulty of predicting pathology based on surface characteristics<sup>[9]</sup>. N-CLE can theoretically one day deem classical tissue acquisition obsolete, although tissue acquisition will continue to provide diagnostic benefits, such as the ability to perform molecular testing, flow cytometry, and PCR<sup>[8]</sup>. Ideally, pancreatic cystic neoplasms will eventually be diagnosed in a personalized fashion, implementing the techniques of cytology, nCLE, and molecular markers differently for each patient<sup>[9]</sup>. With this arsenal, one may be able to accurately predict which lesions will progress quickly, and therefore require urgent treatment such as endoscopic ablation or surgery. At the same time, improved diagnostic techniques may also reveal those lesions that progress slowly and therefore can be followed less closely.

In summary, recent years have brought on many advances in the ability to characterize lesions, most notably pancreatic lesions. This boom has been spearheaded by the improvement of ultrasound technology, the most important currently being CH-EUS and elastography. For now, to obtain the most accurate characterization, a combination of the two are used in clinical practice<sup>[3]</sup>. In the future, ideally all techniques will be in the armamentarium, so that each patient can receive personalized treatment.

## **DRAINAGE**

### **Pancreatic fluid collection**

Pancreatic fluid collection (PFC) is a common complication of pancreatitis. The decision whether or not to drain depends on multiple factors, namely, clinical presentation, duration, size, and location. If drainage is indicated, it must be decided whether to intervene surgically, endoscopically, or radiologically (percutaneously). Currently, surgery is performed when a wall has not yet formed around the collection. Alternatively, if a wall has already formed, endoscopic drainage is considered<sup>[10]</sup>. Walled-off collections include both pseudocysts (fluid) and walled off

necrosis (WON; solid). Studies have shown endoscopic drainage to have higher rates of treatment success than percutaneous drainage, as well as lower rates of re-interventions<sup>[11]</sup>. ERCP is considered if the collection communicates with the pancreatic duct.

Endoscopic drainage is aided by EUS guidance specifically when there is either no intraluminal bulge, portal hypertension, nearby collateral vessels, necrosis, or calcification in the wall<sup>[12,13]</sup>. EUS drainage is performed *via* either a transgastric or transduodenal approach, and therefore requires the collection to be near ( $\leq 1$  cm) the GI lumen<sup>[14]</sup>. EUS provides precise localization of the collection as well as precise measurement of the thickness of the wall and distance from the GI lumen.

EUS-guided drainage can be enhanced in many instances with the use of a self-expanding metallic stent (SEMS). This stent provides a wider diameter for drainage, thus leading to a quicker resolution of symptoms<sup>[15]</sup>. SEMS is most useful in WON, as it allows for repeated access for necrosectomy<sup>[16]</sup>. SEMS has greatly improved EUS-guided drainage, though additional research is needed on SEMS, as it is still a relatively new tool.

Alongside the current recommendations and considerations listed above, the decision how to drain ultimately depends not only on the actual collection but also the institution, local expertise, and the patient preference.

### **Pancreatic duct**

EUS guidance may be helpful in decompression of the pancreatic duct during an obstruction. Currently, EUS is only used when ERCP-guided cannulation fails or when the papilla is inaccessible (*e.g.*, gastric or duodenal obstruction or surgically altered anatomy)<sup>[16]</sup>. The pancreatic duct can be drained either by the rendezvous procedure or translumenally, through the stomach or duodenum<sup>[16]</sup>.

### **Biliary**

Similar to pancreatic duct drainage, biliary drainage may be done endoscopically with EUS guidance when ERCP cannulation has failed, the papilla is inaccessible, or anatomy is surgically altered. Classically, the alternatives to ERCP have been percutaneous or surgical methods, but EUS provides a safer alternative<sup>[17]</sup>, and internal drainage is considerably preferable from a patient perspective.

Like pancreatic duct drainage, EUS-guided biliary drainage can be done in three different ways<sup>[18]</sup>: Transpapillary rendezvous, or translumenally *via* either choledochoduodenostomy or hepaticogastrostomy. The data is still limited at this point, but many believe that the results are promising for EUS-guided biliary drainage, with the overall success rate around 90%<sup>[19]</sup> with a minimal complication rate. EUS-guided biliary drainage results have been so promising that experts increasingly argue that EUS should become the first-

line treatment, ahead of percutaneous drainage<sup>[16]</sup>. It is argued that EUS-guided drainage is superior because it both reduces adverse event rates and the need for re-interventions, thereby reducing costs of therapy<sup>[20]</sup>.

As in PFC drainage, SEMS is also being used more often for biliary drainage. Forward viewing-EUS, a new tool discussed below, combined with a SEMS, has been shown to be the best method when performing EUS guided choledochoduodenostomy for malignant distal biliary obstruction<sup>[21]</sup>. Preliminary results suggest that, in the future, gastroenterologists may assume the responsibility of biliary drainage from surgeons, whether it be for ERCP or EUS.

### **Gallbladder**

The gallbladder needs to be drained in cholecystitis if the patient is unfit for surgery or has an unresectable pancreatic cancer, or if the cholecystitis is refractory to antibiotics. Classically, drainage has been performed percutaneously, although studies have shown that EUS-guided endoscopic drainage is equally as successful as percutaneous drainage<sup>[22]</sup>. Drainage by EUS can be performed either with a plastic stent, metal stent, or naso-gallbladder/nasobiliary drain.

### **Abscesses**

EUS has developed into a favorable alternative to traditional percutaneous drainage of abscesses<sup>[16]</sup>. Accessible abscesses include those in the mediastinum, lesser sac, perihepatic and subphrenic spaces, and pelvic and perirectal regions.

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## **INJECTION**

### **Nerve block**

Nerve blocks are administered to reduce transmission through a nerve, thereby reducing chronic pain and the resulting need for opioids and analgesics. Nerve blocks are often conducted using neurolysis, in which cytolytic agents, commonly alcohol or phenol, are injected to damage the nerves. The nerves most commonly targeted are in the celiac plexus for pancreatic cancers and, less commonly, chronic pancreatitis. Neurolysis can be performed percutaneously or endoscopically by EUS. The percutaneous approach has been the more widely used approach, though studies have shown that endoscopic approach may provide more lasting results<sup>[16,23]</sup>, as the injection is delivered under greater control.

### **Tattooing**

EUS-guided fine-needle tattooing (EUS-FNT) is a technique in which carbon particle labels are injected into pancreatic lesions *via* EUS guidance. These labels then serve as markers during laparoscopic distal pancreatectomy, which ultimately reduces operating time, cost, and amount of healthy pancreas that is inadvertently resected<sup>[24]</sup>.

### **Targeted destruction of lesions**

**Alcohol ablation:** Alcohol can be injected using EUS guidance in order to ablate pancreatic lesions, neuroendocrine tumors, or metastases from the abdomen. Alcohol ablation has proven very effective, especially for certain pancreatic lesions, particularly when combined with taxols or other agents. Currently, alcohol ablation of neuroendocrine tumors is only indicated if the patient is unfit for surgery. It is uncertain how effective alcohol ablation has been for neuroendocrine tumors because there is not yet sufficient data for predicting prognoses.

**Radiotherapy:** Fiducials, which are small 3-5 mm radiopaque metal markers, may be placed in tumors or lymph nodes using EUS guidance and a 19-gauge FNA needle<sup>[17]</sup>. These fiducials act as points of reference for targeted external beam radiation therapy<sup>[25]</sup>. Alternatively, EUS can guide injection of seeds through 19-gauge needles for brachytherapy (internal radiotherapy, various plasmids).

**Chemotherapy:** Chemotherapeutic agents, commonly paclitaxel, have been injected using precise EUS guidance. Chemotherapy injection can be combined with other therapeutic methods such as alcohol ablation. EUS-guided chemotherapy has been used for pancreatic cysts and tumors and esophageal cancers, but much more research is needed to understand the long-term results<sup>[18]</sup>.

**Photodynamic therapy:** Photosensitizing drugs can also be injected using EUS guidance. Exposure to the specific wavelength of light leads to cytotoxic effects, vascular effects, and inflammatory reactions, thereby leading to necrosis of the targeted site.

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## **SURGERY**

### **Natural orifice transluminal endoscopic surgery**

Natural orifice transluminal endoscopic surgery (NOTES) is a surgical technique that uses the body's natural orifices as inlets to reach various organs *via* EUS guidance. Pioneered by Dr. Anthony Kalloo, NOTES procedures have a number of potential benefits. Without external incisions, there are no scars or risks of skin infection, and thus the NOTES approach offers a potentially quicker recovery and therefore shorter hospital stay. Furthermore, less anesthesia may be required. NOTES procedures are currently being developed to: Create anastomoses - Gastroduodenal anastomosis by NOTES has succeeded as a minimally invasive approach for certain gastrointestinal bypass procedures. These bypass procedures include treatment of obstructions, such as duodenal stenosis or gastric outlet obstruction. NOTES can also be used for gastrojejunal bypass, as a malabsorptive-type bariatric procedure. Studies are needed, however, to compare these NOTES procedures

directly with conventional surgical approaches<sup>[26]</sup>.

Remove and biopsy organs-NOTES also has the potential to become a minimally invasive alternative to routine laparoscopic procedures. NOTES can be used for liver biopsy, cholecystectomy, appendectomy, thyroidectomy, and procedures involving mediastinal and spinal tissues. The transgastric approach has been the most studied inlet to date. So far, however, the majority of human NOTES procedures have been transvaginal cholecystectomy and appendectomy. More human research is needed on the transgastric and transrectal approaches.

NOTES has many advantages and therefore much potential, although it has undoubtedly been slow to catch on. Devices designed specifically to facilitate NOTES are needed. Despite NOTES being an endoscopic procedure and therefore inherently within a gastroenterologist's "jurisdiction", its ultimate procedural goal is often that of a surgeon. Techniques such as NOTES obscure the distinct borders of each specialist, and the medical community must come together and decide who is best trained to perform each procedure. To do so, it must first be decided how to base the decision; should the decision be based on the approach or the ultimate goal of the procedure? If based on the approach, it must then be asked if NOTES should be considered a surgical approach? How do we even define surgery today? Should a NOTES cholecystectomy be considered surgery even though EUS-FNA is not? If a consensus is reached among the medical community, NOTES may, like the arrival of laparoscopy in 1901, lead to a momentous step forward in medicine.

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## VASCULAR

### **Angiography**

Angiography is another novel application of EUS. EUS can guide access into small vessels, such as the celiac branches and hepatic vein. Although thus far only conducted in animals, EUS can also be used to measure portal vein pressure and therefore guide portal hypertension therapy<sup>[25]</sup>.

### **Bleeding control**

EUS can also be applied to control gastrointestinal bleeding, such as treatment of varices, insertion of porto-systemic shunts, pseudoaneurysm control, embolization, and coil application. Studies have shown notable success, concluding that EUS should be considered when managing patients who have failed with conventional therapy<sup>[27]</sup>. Studies are still in their early stages, however, and much research on EUS and vascular interventions is on the horizon<sup>[18]</sup>.

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## NOVEL TOOLS

### **Forward viewing EUS**

Forward viewing EUS (FV-EUS), a relatively novel tool,

is believed by some experts to be an upgrade to the conventional curved linear array EUS (CL-EUS)<sup>[21]</sup>. FV-EUS gives the endoscopist better and more stable access into cysts. It also is easier to maneuver because of its short, hard tip, thereby allowing for more dexterity during interventional procedures. This allows the endoscopist to reach more difficult locations within the GI tract; this is especially true in the lower GI tract, as FV-EUS has been shown to allow for easier cecal intubation<sup>[21]</sup>. FV-EUS also enables a shorter training time, which may lead to a more widespread usage than the conventional curved linear array EUS. In addition to its technical advantages over CL-EUS, some studies have also shown that FV-EUS can detect additional gastrointestinal lesions<sup>[28]</sup>.

Disadvantages do exist though; the EUS view is reduced from 180 to 90 degrees; this however, reportedly, does not pose difficulty for experienced endosonographers. It is also more difficult with FV-EUS to intubate the cervical esophagus. It may also be more difficult to aspirate pancreatic pseudocysts because of the lack of fixation of the guide-wire without an elevator. Also regarding NOTES procedures, it is unclear if FV-EUS or CL-EUS is superior; a multicenter randomized trial, comparing the two endoscopes, found the same success rates, mean procedure times, and ease of access and complication rates<sup>[29]</sup>. FV-EUS and CL-EUS shared the same diagnostic yield of upper GI subepithelial lesions, though FV-EUS led to a shorter procedure time and a larger tissue sample area<sup>[30]</sup>. Clearly, more studies are needed on FV-EUS to determine when it provides significant advantage over the CL-EUS.

### **3D reconstruction**

Three-dimensional imaging has been found useful in gynecologic ultrasound, and may also find a place in gastrointestinal EUS if proven advantageous.

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## CONCLUSION

EUS has come a long way in the last 25 years. Ultrasound has become much more than a tool to differentiate different tissue densities; tissue can now be characterized in great detail; the extent of vascularity within a tissue and how malignant the tissue appears can now be learned with increasing precision, all in real-time and without radiation. Using these techniques, targets for biopsy can be precisely pinpointed. Upon reaching the target, tissue can then be examined microscopically in real-time, to ensure optimal targeting and diagnosis.

EUS and its associated advancements have begun to take advantage of the fact that the gastrointestinal tract runs medially throughout the majority of the body and is very accessible; the gastrointestinal tract is now beginning to be used as an inlet to the rest of the body. After having brought ultrasound technology inside the gastrointestinal tract in the 1980s, EUS is

now being used as a guide outside the lumen. Many of these recent technologic advancements are in early stages and have not yet been studied extensively. The years ahead are therefore expected to be bright for EUS, as more research concludes and as these various technologies begin being implemented into clinical practice.

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