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**Endoscopic-ultrasound in gastroenterology: from diagnosis to therapeutic implications**

MekkyMA *et al*. EUS from diagnosis to therapy

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**Abstract**

Since its advent in 1980, endoscopic-ultrasound (EUS) has growing to include a wide range of indications and it is now being incorporated as an integral part of everyday practice in the field of gastroenterology. Its use is extending from just an adjuvant imaging aid to be utilized as a therapeutic tool in various gastrointestinal disorders. EUS was first used to visualize the remote organs; such as the pancreas and abdominal lymph nodes. Once the field of fine needle aspiration was introduced, the diagnostic indications expanded to endorse tissue sampling for diagnostic purposes. Through the same device, the needle can carry a potential therapy for internal organs, which further entails an access to remote sites. In this review, we tried to highlight this expanding spectrum of endoscopic-ultrasoundindications and utilities in the field of gastroenterology.

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**Key words:** Endoscopic ultrasound; Endoscopic ultrasound-guided fine needle aspiration; Ablation; Injection; Drainage; immunohistochemistry; Gastroenterology

**Core tip:** Since its advent in 1980, endoscopic-ultrasound has growing to include a wide range of indications and it is now being incorporated as an integral part of everyday practice in the field of gastroenterology. Its use is extending from just an adjuvant imaging aid to be utilized as a therapeutic tool in various gastrointestinal disorders. In this review, we tried to highlight this expanding spectrum of endoscopic-ultrasound indications and utilities in the field of gastroenterology.

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**Introduction**

Endoscopy, ultrasound, and computed tomography (CT) have revolutionized the field of clinical gastroenterology in the past decades. Despite their rapid development, these modalities do not allow a systematic assessment of the gastrointestinal tract (GIT) wall and its immediate surroundings. Awareness of this obstacle prompted the development of a complementary procedure that would allow clinicians to close this gap. By combining a high-frequency ultrasound probe with endoscopes, what so-called "echoendoscope" or “endoscopic-ultrasound (EUS)”, a clearly detailed imaging of the nearby structure to the GIT wall was achieved. In 1980, the first applicable mechanical radial EUS was presented to clinical use[1,2]**.** Since that date, a rapid development in the field of EUS was achieved to cover a wide range of indications that exceeding the diagnostic spectrum to cover also therapeutic implications. Herein, we will try to highlight this revolution and to delineate the applications of EUS and its related maneuvers.

**EUS: Diagnostic indications**

The indications for EUS are determined by the anatomic conditions and the technical capabilities of the equipment. The high-resolution capacity and low penetration depth of EUS make it possible to obtain high-detailed images of the GIT-wall and its immediate surroundings at depth of 4-5 cm and lesions[3]. The primary role of EUS is to delineate GIT lesions that located beyond the gastric wall. The major indications are GIT cancer staging, and mass delineation. Table 1summarizes these indications.

**GIT cancer staging**

Cancer staging is probably one of the earliest indications for EUS. Because it can delineate the component layers of the GIT-wall, EUS is very well suited to classifying gastrointestinal cancers arising from the mucosa using the widely accepted TNM classiﬁcation. It is also useful for some extra-luminal malignancies, such as pancreatic cancer[4,5]. Also, one of the imminent indication of its use, is to unearth a submucosal tumor (SMT) that bulges in conventional endoscopic image and to detect its layer of origin which in-turn help to characterize its nature[2-5].

**GIT mass imaging and delineation**

The advent of EUS enables to delineate the extra-luminal lesions with a high rate of accuracy especially the pancreatico-biliary lesions. The characterization of various pancreatic, biliary, gall-bladder (GB) lesions is now widely accepted and the utility of EUS was considered as an integral part of the diagnostic algorithm of these lesions[4,5]. New indications become now more familiar to the physician in the field of gastroenterology, such as follow up of intraductal papillary mucinous neoplasm (IPMN) of the pancreas, chronic pancreatitis, suspected pancreatic mass or cyst, GB-mass lesions[3-5]. The EUS-image also jumped to areas outside the GIT, *e.g.* assessment of mediastinal lymph nodes of unknown etiology[5].

**Contrast-Enhanced EUS**

Contrast agents are new adjuvant tools in the field of ultrasound. It is made of gas-filled microbubbles encapsulated by a phospholipid or albumin shell that injected intravenously and then its uptake-washout characteristics through a given lesion is captured by a special technical color or power doppler mode of the ultrasound machine[6,7]. Therefore, by using CED-EUS, differentiation of vascular-rich area and hypovascular area is possible with clarity. After development of harmonic imaging methods (CE-harmonic-EUS), it is possible also to get images of the microcirculation and parenchymal perfusion, which allows a better visualization, and differentiation of tissue enhancement and to classify them accordingly[8,9].

**EUS-elastography**

Tissue elastic image represents a technical mode that allows calculation and visualization of tissue stiffness for non-invasive evaluation of fibrosis. The operating characteristics of the technique for detecting malignancy in pancreatic focal lesions were examined and it yielded a sensitivity rate of 93%, and a specificity rate of 66%[10,11].A further evaluation in the nearby future may enhance its diagnostic accuracy rates and help to bypass the tissue acquisition needed for diagnosis**.**

**Safety, Complications and Cost**

The issue of safety and complications of diagnostic EUS was extensively reviewed and most of related literature conclude that the diagnostic EUS procedures were dedicated to be a safe procedure and its related complications were extremely low[12,13].

As regard, the cost-effectiveness, Studies showed that EUS when incorporated into a diagnostic algorithm is cost–effective, especially if incorporated with fine needle guided procedures and when compared with other imaging modalities (*e.g.* CT and MRI) and/or surgery[11-14]. Unfortunately, the survey of Schembre and Lin, which conducted to evaluate the cost burden of EUS-procedures stated that the EUS equipment maintenance and repair is highly expensive and should be taken into consideration when conducting EUS unit[15].

**Forward-viewing EUS**

Recently, forward-viewing EUS (FV-EUS) was developed to overcome the limitations of conventional oblique-viewing one, for example; the lack of on-procedure evaluation of the mucosa of the GIT-wall, the difficult oblique approach to some target lesions, the diminished penetration force, and the angling of the tip that reduces the possibility of deploying large bore devices in some positions[16] (Figure 1).

Many recent studies and systematic reviews conducted to evaluate the capabilities of FV-EUS, comparing it to the conventional one, revealed a similarity in image quality and penetration force, in spite of its narrow imaging field. Moreover, they stated that the interventional procedures with FV models are easier to perform compared to oblique-viewing EUS models and operators can reach difficult locations, such as the cecum. The main shortcomings reported were the difficult intubation of the esophagus or the second part of the duodenum in some patients and the difficulty in aspirating pancreatic pseudocysts because of lack of fixation of the guide wire due to absence of the elevator, however, they recommended further comparative trials to investigate its usefulness in new indications[17,18].

**EUS-guided Needle Sampling**

The most fascinating advent in the field of EUS and its related interventions is the utility of needle guided tissue sampling. Cytological or histological confirmation of the diagnosis is often required in order to distinguish between different possibilities. The idea of biopsy-needle was first emerged in 1992 as a modification of those used for variceal injection[19] and first reported case of EUS-guided biopsy was from a pancreatic lesion. Subsequently, EUS-guided needle sampling was studied for its safety, accuracy and indications with the development of different needles and techniques. Nowadays, the most widely used term for EUS-guided sampling is EUS-guided fine needle aspirate (EUS-FNA)[20].

**EUS-guided needle sampling: Indications**

A fundamental principle of EUS-FNA is to obtain information that would have the potential to affect patient management such as: (1) differentiating between benign and malignant lesions; (2) staging of cancer; and (3) obtaining histological evidence of malignancy before chemotherapy and/or radiotherapy, or even surgery[21]. Currently, most of the recent guidelines assign EUS-FNA as an integral part for sampling the pancreas, mediastinal lymph nodes (esophageal/lung cancer), celiac lymph node, intra-abdominal lymph node, peri-rectal lymph node/mass, posterior mediastinal mass of unknown etiology, and intra-pleural/intra-abdominal fluid. In addition to the lesions indicative for EUS–FNA mentioned above, the indications have been expanded to submucosal tumor (SMT), small liver lesions, left adrenal mass, and suspected recurrent cancers in and adjacent to an anastomosis[9-22].

In spite of the growing list of EUS-FNA indications, a counter minor list of contraindications should be considered. In general, EUS-FNA should not be used in situations in which FNA results would not affect the management strategy, the presence of bleeding diathesis, and if a high risk of tumor seeding is suspected. On-procedure, the inability to clearly visualize a lesion or the presence of vessel that interposed in the path between the needle and target might be considered as contraindications also[16-22].

**EUS-guided needle sampling: Safety and complications**

As an interventional modality, the possibility for complications of EUS-FNA must be taken in considerations. Many recent multicenter studies were designed to thoroughly evaluate this issue and their pooled conclusions considered the complication rates from EUS-FNA in qualified institutes are quite rare[16-23]. In an interesting systematic review, the pooled rates of EUS-FNA complications of 51 articles (*n* = 10941 patients) revealed an overall rate of morbidity of 0.98% and in this small proportion of patients with complications, pancreatitis and the post-procedure pain were the most reported complications[24]. However, some major complications were reported in the published guidelines, such as perforation, infection, and/or hemorrhage, and fortunately, they addressed these complications as an extremely rare[16,18]. The use of careful add-on color/doppler-EUS examination reduce some potential complications especially the possible intervening blood vessel injury[18-25]. An exception of this low rate of complications may be in cyst aspiration, where infection has been reported to occur in up to 15% of cases[26,27].

**EUS-guided needle sampling: Cyto-pathologic issues**

Generally speaking, the main role of EUS -FNA, and all other interventional biopsy devices, is to obtain a sufficient tissue sample amenable to pathological examination and subsequently the formulation of the proper diagnosis. A smear slide is the standard method of preparing cells obtained from FNA, however, a “cell-block” which is a preparation of cells placed into a liquid medium or fixative, is the standard for hematoxylin and eosin (H and E) staining[28].

One way to ensure the adequacy of materials obtained from FNA-procedure is the use of immediate cytologic evaluation (ICE) or that also known as rapid on-site cytologic evaluation (ROSE). The goal of this adjuvant option is to provide a real-time feedback about the content and quality of the smears, in order to reduce the number of non-diagnostic or atypical biopsies and maximize the efficiency of the procedure.ICE or ROSE was more likely to result in a definitive diagnosis and less likely to involve an inadequate specimen[29-32].

Another adjuvant add-on staining procedure is the application of immunohistochemical (IHC) stains for the identification of cytoplasmic or nuclear differentiation. Panels of immunoperoxidase stains can be used to identify a tumor type, characterize a lesion, or provide information used for prognosis or treatment which likely changing the face of the use of EUS-FNA dependent results[33].

**EUS-guided Therapeutic implications**

Once a needle gets into a target, the spectrum of EUS-guided-needle-related maneuvers is expanded to endorse many therapeutic rather than diagnostic indications. EUS-therapeutics are broadly classified to either EUS-guided fine needle injections (EUS-FNI) or EUS-guided drainage (EUS-FND) indications. Table 2 summarized these therapeutic indications.

***EUS-FND***

**EUS-guided biliary drainage:** The first reported EUS-guided-cholangiopancreatography was done in 1996 by Wiersema *et al*[34], and a subsequently, EUS-guided biliary drainage (BD) has been emerged for biliary decompression in patients with inoperable bile duct obstruction. EUS-guided biliary drainage (EUS-BD) have been reported as salvage techniques for failed conventional BD and, in general, it is indicated in circumstances in which conventional endoscopic retrograde cholangiopancreatography (ERCP) is difficult due to altered anatomy or tumor site that prevents the access into the biliary tree[35-38].

To date, data for EUS-BD is still limited and most published trials are retrospective studies including small numbers of patients; however, the results are promisingas its overall success rate was around 90% (range from 75% to 100%) and its reported major complications; such as perforation, peritonitis and bleeding requiring surgery are uncommon[36-38]. There are three known techniques for EUS-guided BD: (1) EUS-guided transpapillary rendezvous; (2) EUS-guided choledochoduodenostomy (EUS-CDS); and (3) EUS-guided hepaticogastrostomy[37,38]. A brief summary for these procedures will be highlighted here. However, the detailed techniques of these maneuvers are beyond the scope of this review.

Through the EUS-guided transpapillary rendezvous technique, double-step endoscopies are performed to bypass biliary obstruction. EUS rendezvous is used solely to puncture the obstructed bile duct and pass a guide wire in an antegrade manner through the native papilla to allow subsequent ERCP. The first step is to perform EUS-guided puncture of the bile duct through the stomach or duodenum. Then a contrast agent is injected to visualize the intra-hepatic and extra-hepatic bile ducts. After confirmation of bile duct puncture, a guide wire is pushed through the obstructed segment across the papilla with a fluoroscopic guidance to the duodenum. The next step is to remove the EUS scope leaving the guide wire in place and then a duodenoscope is passed up to the papilla. Finally, the guide wire is pulled back out the working channel of the duodenoscope for subsequent over-the-wire cannulation, and stent placement. The estimated overall success rate was about 80%, however, the guide wire cannot be advanced across the obstruction in some difficult cases[33,38,39].

EUS-choledochoduodenostomy (CDS) was first reported by Giovannini *et al*[40] in 2001. Through a multistep technique, EUS-guided biliary fistula is induced to connect the bile duct with the duodenum. In spite of the unique idea, comparatively a high complication rate (about 15%) has been reported, including biliary peritonitis and pneumoperitoneum[39-41].

The EUS-guided hepaticogastrostomy technique is broadly similar to EUS-CDS; in which a fine needle followed by a needle knife or cystotome, were used to puncture the intrahepatic bile ducts. The procedure was successful in almost all patients (> 96%)[33,42].

**EUS-guided cyst/abscess drainage:** Based on the same concept of targeting a needle into a known lesion, EUS-guided drainage of an abscess or cyst can be done easily. Lesions such as pancreatic pseudocyst and intra-abdominal collections and abscesses are targets for this technique[43,44]. Many recent reports commented on the success rate of EUS-FND to drain remote abscess and pseudopancreatic cyst and they reported better outcome[45,46].

***EUS-FNI***

EUS-guided FNI is a modified technique that utilized the same idea of needle-guidance to deliver a therapeutic target into a remote lesion/organ. In addition, this approach is effective in delivering a concentrated drugs or chemotherapy[47]**.**

The most exciting and promising subject in this context involves the delivery of antitumor agents in patients with locally advanced cancer, such as cancer of the pancreas, or esophagus. EUS-FNI has been used for precise delivery of antitumor agents into the targeted lesions to achieve a localized rather than systemic delivery of the chemotherapeutic agents, which, in turn, might reduce the systemic toxicities, maximize the delivered dose to the targeted lesions and might also lowering the cost[42,48,49]. This area of medical trials is still primitive and a much intense researching efforts are needed.

Cystic lesions of the pancreas have been also treated with EUS-guided ablation through injection sclerosing materials or absolute alcohol. However, this intervention remains investigational, although data have been encouraging[50].

Another utility for EUS-FNI is the injection of ganglion blocking agents by performing celiac plexus neurolysis or block for pain relief in patients with pancreatic cancer. Celiac plexus block and neurolysis (CPN) can improve pain and decrease the need for analgesic and opioid[51,52]. EUS provides a more direct and targeted approach secondary to better delineation of anatomic landmarks, close proximity of the transducer to the celiac plexus, and visualization of neural ganglionic structures that are not visible with other imaging modalities (Figure 2).

**EUS-guided vascular interventions:** EUS has also invading the field for control of GIT bleeding. To date, most reports are of animal studies and small case reports/series[53]. EUS-guided new maneuvers for the management of upper GIT variceal and non-variceal bleeding, pseudo-aneurysms control, and coiling application and also the embolization procedures, as well as the creation of intrahepatic portosystemic shunts and endoprostheses placementhad been reported. However, these studies still primitive and a lot of work in the nearby future may be expected[54,55].

**EUS-guided photodynamic therapy:** EUS-guided needle injection can be used also to deliver a photosensitizing drug, which induces a targeted tissue necrosis on exposure to light of a proper wavelength. The feasibility of this therapy was tested in a healthy swine model and it is on its way to test the cost-effectiveness and biological side effects[30,56].

**EUS-guided fiducial placement and brachytherapy:** A fiduciary marker or fiducial is an object used as a point of reference in external beam radiation therapy. Gold fiducials are available to facilitate stereotactic body radiotherapy for the treatment of locally advanced pancreatic cancer[57,58]. Likewise, implanting radioactive seeds in the interstitial brachytherapy has showed some beneficial effects for the local control of malignant pancreatic tumors. These implants emit steady gamma rays that lead to local ablation[30,59-61]. Placement of such implants with the guide of EUS-FNI enables a precise targeting and avoids undue laparotomy. Investigations in this area reported a successful placement in around 90% of patients.

**Conclusion**

EUS utility has now considered as a gold standard tool for many gastrointestinal diseases especially the pancreatico-biliary one and its adjuvant needle insertion gives an access to remote lesions that was difficult to reach in the past. With the growing spectrum of indications, its clinical applicability expanded to cover therapeutic applications rather than diagnostic only, and some of these show great promise. A major breakthrough in the technical advances of EUS technology was achieved in the last decades especially in the scope design, accessory devices, and the add-on facilities, which will put the EUS and its related maneuvers as a front-foot modality of choice in many gastrointestinal indications.

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**Table 1 Endoscopic-ultrasound: Diagnostic indications**

|  |
| --- |
| **GIT cancer staging** |
| Staging of gastresophageal cancer  Staging of rectal cancer  Staging of ampullary cancer |
| **Mass imaging and delineation** |
| Pancreas  Gallbladder  Biliary tree  GIT-submucosal lesions  Mediastinal and retroperitoneal mass |

GIT: gastrointestinal tract.

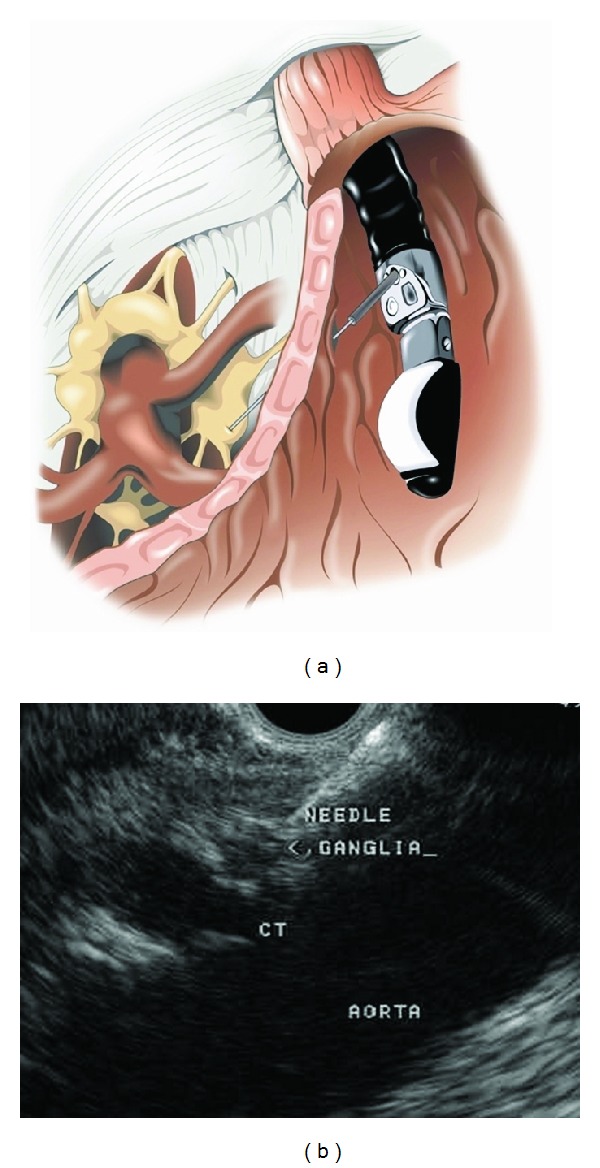
**Table 2** **Endoscopic-ultrasound-guided-therapeutic implications**

|  |
| --- |
| **EUS-guided needle drainage** **(EUS-FND)**  Biliary drainage  EUS guided transpapillary rendezvous technique  Choledochoduodenostomy  Hepaticogastrostomy  EUS-guided cyst drainage |
| **EUS-guided needle injection (EUS-FNI)**  Celiac plexus neurolysis (EUS-CPN)  EUS-guided tattooing  EUS-guided ablation |

EUS: Endoscopic-ultrasound; EUS-FND: EUS-guided fine needle drainage; EUS-FNI: EUS-guided fine needle injection; CPN: Celiac plexus block and neurolysis.

|  |  |
| --- | --- |
| A | B |

**Figure 1 The difference between conventional oblique view and forward-view endoscopic-ultrasound.** A:The oblique view endoscopic-ultrasound (EUS). Note the maximum angulation and the needle direction; B: The forward-viewing EUS. Note the more angle of retroflexion compared with the conventional EUS.



**Figure 2 endoscopic-ultrasound-guided celiac plexus neurolysis.** Red arrow: celiac ganglion; blue arrow: endoscopic-ultrasound-needle transfixing the gastric wall.