REVIEW

Endoscopic Ultrasound in Gastroenteropancreatic Neuroendocrine Tumors

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Endoscopic ultrasound (EUS) is an advanced endoscopic technique currently used in the staging and diagnosis of many gastrointestinal neoplasms. The proximity of the echo-endoscope to the gastrointestinal tract lends itself to a detailed view of the luminal pathology and the pancreas. This unique ability enables endoscopists to use EUS in patients with gastroenteropancreatic neuroendocrine tumors (GEP-NETs). Diagnostic EUS allows previously unidentified NETs to be localized. EUS also determines tumor management by staging the GEP-NETS, enabling the clinicians to choose the appropriate endoscopic or surgical management. The ability to obtain a tissue diagnosis with EUS guidance enables disease confirmation. Finally, recent developments suggest that EUS may be used to deliver therapeutic agents for the treatment of NETs. This review will highlight the advances in our knowledge of EUS in the clinical management of these tumors. **(Gut Liver 2012;6:405-410)**

Key Words: Endoscopic ultrasound; Neuroendocrine tumor; Carcinoid; Pancreas; Stomach

INTRODUCTION

Neuroendocrine tumors (NETs) are rare, but increasingly recognized entities. Endoscopic ultrasound (EUS) is an invaluable technique in the diagnosis and management of these tumors. In this review, we will describe the current status of EUS in the staging, localization, and diagnosis of these tumors. We will also address potential future applications of EUS in the treatment of NETs.

BACKGROUND

Gastroenteropancreatic (GEP)-NETs represent a group of neoplasms with neuroendocrine phenotype which are frequently dispersed throughout the gastrointestinal tract and have diverse biologic behavior. With an incidence of approximately 0.5% of all neoplasms, NETs are generally considered to be rare.[1] In recent years, however, the incidence has risen, generally thought to be due to improved detection, with the widespread availability and accessibility of endoscopy and cross sectional imaging modalities, rather than an actual increase in frequency.[2-4]

Recently, various organizations have made efforts to classify and to standardize the nomenclature of these tumors. In 2010, the World Health Organization created a standard classification for these tumors, clarifying terminology and creating a uniform grading system that could be used worldwide (Table 1).[5] This has clarified both clinical care and research investigation.

NETs are a heterogeneous group of tumors that may present with quite variable symptoms and also may or may not be associated with an overproduction of a group of hormones (Table 2). Tumors may be functional, with the often dramatic symptoms of a gastrinoma or insulinoma, or nonfunctional, which is frequently detected incidentally or with symptoms related to mass effect of the tumor or its metastases.

Endoscopy has typically successfully localized and enabled confirmation of the disease in gastroenteropancreatic (GE-NETs). Standard cross-sectional imaging modalities such as ultrasound, computed tomography (CT), and magnetic resonance imaging (MRI) are also frequently used to diagnose and localize NETs, particularly pancreatic (P)-NETs (Table 3). Because NETS frequently express somatostatin receptors on their surface, somatostatin receptor scintigraphy (SRS) has particular avidity for NETS and may frequently elucidate the location of these lesions.

There are limitations to these imaging modalities, however (Table 4). For examples, as insulinomas infrequently express somatostatin receptors, SRS is frequently negative with these particular tumors.[6] The current sensitivities and specificities for NETs with CT and MRI range from 64% to 82% and 74% to 100%, respectively.[7] EUS, with its unique combination of endos-

Table 1. World Health Organization (WHO) Classification of Gastroenteropancreatic Neuroendocrine Tumors

WHO classification	Tumor grade
Neuroendocrine tumor, grade 1	Low grade <2 mitotic figures per 10 HPF and <3% Ki-67 proliferative index
Neuroendocrine tumor, grade 2	Intermediate grade 2-20 mitotic figures per 10 HPF or 3-20% Ki-67 proliferative index
Neuroendocrine carcinoma, grade 3, small cell neuroendocrine carcinoma	High grade >20 mitotic figures per 10 HPF or >20% Ki-67 proliferative index
Neuroendocrine carcinoma, grade 3, large cell neuroendocrine carcinoma	High grade >20 mitotic figures per 10 HPF or >20% Ki-67 proliferative index

HPF, high-power field.

Table 2. Gastroenteropancreatic Neuroendocrine Tumors (GEP-NETs) and Their Syndromes

GEP-NET	Secretion product	Syndrome	Diagnostic laboratory tests	% malignancy rate at presentation
Carcinoid	Serotonin	Flushing, diarrhea, palpitations, wheezing	24 hr urinary 5-HIAA	20% metastatic at presentation
Gastrinoma	Gastrin	Reflux, gastrointestinal bleeding, diarrhea	Gastrin >1,000, secretin stimulation test	1/3 present with metastases
Insulinoma	Insulin	Hypoglycemia, confusion, visual changes, tremulousness	Insulin C-peptide	Rarely metastatic
Glucagonoma	Glucagon	Necrolytic migratory erythema (rash on face, perineum, extremities), diabetes	Glucagon Hyperglycemia	Often metastatic; rates quoted at over 50%
VIPoma	VIP	Profuse, watery diarrhea, electrolyte abnormalities	VIP	40% malignant
Somatostatinoma	Somatostatin	Diabetes, cholelithiasis, steatorrhea	Somatostatin	75% metastatic

HIAA, hydroxyindoleacetic acid; VIP, vasoactive intestinal peptide.

Table 3. Imaging Methods

Ultrasonography
Computed tomography
Magnetic resonance imaging
Somatostatin receptor scintigraphy
Endoscopy
Colonoscopy
Endoscopic ultrasound

copy and ultrasound, is able to address these limitations. EUS can provide additional information to the endoscopist regarding GE-NETs. In addition, it allows access to P-NETS. In this way, EUS is now able to localize, stage, and confirm and treat disease.

STAGING EUS FOR GE-NETS

With increased access to endoscopy, GE-NETs in the stomach, duodenum, and rectum are increasingly frequently incidentally detected on upper endoscopy and colonoscopy.[8-10] Patients are frequently asymptomatic without any symptoms referable to the GE-NET. Management of these tumors frequently involves endoscopic resection for appropriate patients. Before proceeding with endoscopic resection, however, endoscopists frequently perform a staging EUS to confirm the appropriateness of an endoscopic resection, usually endoscopic mucosal resection (EMR).

Multiple studies have assessed the utility of EUS prior to endoscopic resection of GE-NETs. The most extensive literature has been conducted with rectal NETs. The largest study by Kobayashi et al.[11] studied 66 rectal tumors. Fifty-seven rectal NETs were smaller than 10 mm and were limited lesions without muscularis propria infiltration. These were all able to be removed endoscopically. In those 9 rectal NETs measuring greater than 11 mm, 5 demonstrated muscularis propria involvement and 4 demonstrated metastatic disease.

Similarly, gastric NETs that are smaller than 1 cm in size without evidence of deep invasion on EUS may be managed endoscopically by polypectomy or EMR.[12] Larger lesions, measuring between 1 and 2 cm, may be removed endoscopically or surgically.[8,12-16] The exception here is that type 3 gastric NETs, which are sporadic and not associated with hypergastrinemia, are typically treated surgically because of their more aggressive nature.[8,17,18]

A similar approach applies to duodenal NETs. EUS is particu-

Table 4. Accuracy of CT, MRI, and EUS in the Diagnosis of Gastroenteropancreatic Neuroendocrine Tumors (GEP-NETs)

Imaging modality	Sensitivity	Strengths and limitations
CT	Sensitivity 57-94%	P-NET detection increases with tumor size; duodenal NET detection often limited
MRI	Sensitivity can approach 94%	P-NET detection increases with tumor size; duodenal NET detection often limited
Somatostatin receptor scintigraphy	Sensitivity 58-86% in noninsulinomas	Most frequently used to stage GEP-NETs; frequently negative in patients with insulinoma
EUS	Sensitivity 87%	Particularly useful in identification of small P-NETs (<2 cm), especially gastrinoma and insulinoma

CT, computed tomography; MRI, magnetic resonance imaging; EUS, endoscopic ultrasound; P-NET, pancreatic neuroendocrine tumor.
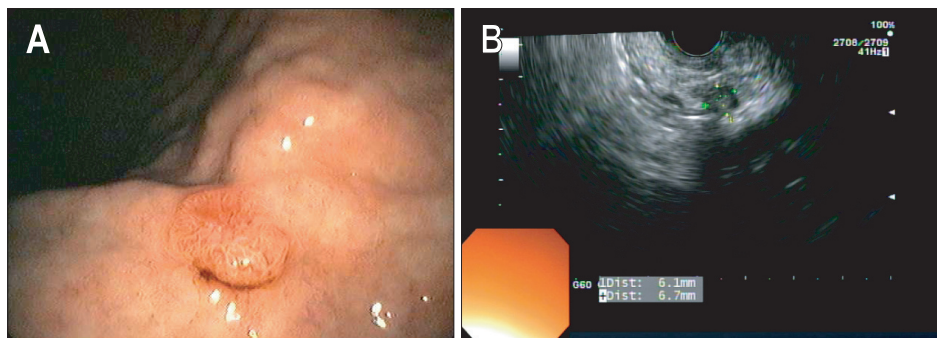

Fig. 1. (A) Endoscopic image of a gastric neuroendocrine tumor (NET). (B) Endosonographic image of a small pancreatic NET, measuring 6×7 mm.

larly useful for assessment of depth of lesion involvement, again prior to consideration of an endoscopic procedure such as EMR.

Overall, in a recent study reviewing 18 patients with 23 GE-NETs, EUS was performed before endoscopic resection to confirm the limited nature of the lesion and the appropriate candidacy of the lesion for endoscopic resection.[19] EUS sensitivity was 94% in detection of appropriate candidates for endoscopic resection. Complete resection was achieved in 90.5% of lesions.

Endoscopic submucosal dissection (ESD), initially evaluated in the endoscopic treatment of early gastric cancer, has also been evaluated as a mode of endoscopic resection for GE-NETs.[20] In a study looking at 22 rectal NETs, all 22 tumors were located in the submucosal layer.[20] EUS was 100% accurate in assessing the depth of the lesion. ESD was able to be performed in all cases, with postprocedure bleeding in 9% of cases and without any perforations. No postprocedure recurrence was noted during the mean follow up period of 30 months. Although ESD is more technically difficult to perform than EMR and may offer a more complete resection of rectal NETs, the added utility of this procedure still needs to be evaluated in further studies.

DIAGNOSTIC EUS FOR LOCALIZATION OF P-NETS

The important ability of EUS to localize P-NETs was first described in the paper authored by Rosch et al.[21] In this study, 50 patients with clinical suspicion of NET whose tumors were undetected by radiologic imaging underwent EUS with successful localization of NETs in 82% of patients. EUS was particularly successful in identification of P-NETs with 82% sensitivity and 92% specificity.

With the unique proximity of the echoendoscope to the pancreas, EUS is particularly well suited to identification of small pancreatic lesions, able to detect lesions as small as 2 to 5 mm (Fig. 1).[21] EUS is particularly able to localize gastrinomas and insulinomas. Nearly all insulinomas are located in the pancreas. The average size of insulinomas at initial diagnosis is under 1 cm, with 90% under 2 cm.[22] Reported detection rates have ranged from 79% to 94%, with higher sensitivity in the head and lower sensitivity in the tail.[23]

EUS is also well suited to identification of gastrinomas. Fifty percentage are located in the pancreas, while the other 50% are located in the duodenum. Pancreatic gastrinomas are generally localized in 75% to 94% of cases, while extrapancreatic (duodenal) gastrinomas are less frequently visualized, thought to be a result of their generally smaller sizes. EUS is also helpful for detection of adjacent metastatic lymph nodes within the so-called gastrinoma triangle.[24]

EUS has also been used to survey patients at increased risk of developing pancreatic NETs. For example, patients with multiple endocrine neoplasia (MEN) typically have P-NETs in 36% to 81% of patients. In one study describing a surveillance program of 51 MEN1 patients, EUS identified a median of 3 tumors per patient, with median size 6 mm.[25] Over 5 years, 37.5% developed additional or enlarging tumors. Less than 10% of these lesions were detected by other imaging modalities including CT, MR, or SRS.

Recently, there has been the development of adjunctive techniques with EUS to further increase potential detection of small lesions. In one study from Japan, contrast enhanced harmonic EUS detected hypervascular enhancement in P-NETs.[26] Contrast

enhanced EUS was also found to be superior to multidetector CT in diagnosing small pancreatic cancers less than 2 cm.

EUS FOR P-NETS

P-NETs typically appear as a hypoechoic, well-demaracated, round, homogeneous lesion.[27] While the majority of P-NETs are solid lesions, P-NETs may less commonly also appear cystic; this is particularly important in light of the increased detection of pancreatic cystic lesions.[28] A peripancreatic lymph node may also mimic a P-NET. Potential pitfalls include an isoechoic appearance, small size, multiplicity, and pedunculated lesions at the pancreatic tail.[29] In addition, because patients may present with multiple NETs, it is important to examine the entire pancreas to exclude a synchronous lesion. In one study evaluating risk factors for a negative EUS, female gender, low body mass index, and young age were found to be associated with a negative study. The authors hypothesized that this may be due to weak contrast of the tumor to healthy pancreatic tissue; the pancreas of a slim young woman may be more hypoechoic than in others due to low fat content.[30]

EUS-GUIDED TISSUE ACQUISITION OF P-NETS

There are multiple techniques used to obtain tissue confirmation of NETs. The most commonly used is EUS-guided fine needle aspiration (EUS-FNA). With this technique, the endosonographer gently inserts a 22 gauge or 25 gauge needle into the target lesion. The FNA may be performed with or without suction. The aspirate is then examined by a cytopathologist, ideally on site. The diagnosis, however, is generally confirmed with immunohistochemical studies from the cell block. Commonly performed stains include chromogranin and synatophysin; other stains may include neuron specific enolase, CDX, and CD56 (Table 5).[31,32] As with other pancreatic tumors, the ideal number of passes to perform is 5 to 7 for a pancreatic tumor, 2 to 3 for a liver metastasis, and 2 to 5 for lymph nodes.[33,34]

Another method that has been used to obtain tissue is the Trucut core biopsy. This method offers the benefit of a more substantive specimen, providing cellular architecture for pathologic analysis. These core biopsies may provide microscopic information such as degree of atypia, presence or absence of necrosis, mitotic index, and Ki-67 (proliferative index). This information is particularly important as it may provide prognostic information and aid in the grading of P-NETs.[35] However, the use of the Trucut needle has been limited by the technical difficulties of using this device. Studies are currently in process of evaluating biopsy needles that might be easier to use; in particular new needles will need to address current challenges such as maneuvering in the duodenum.

INTERVENTIONAL EUS

Recently, there has been an increased trend toward not only diagnostic EUS and FNA to acquire tissue, but also EUS delivery of therapeutic agents. This technique, termed EUS-guided fine needle injection (EUS-FNI) has been used in multiple contexts. It was first described in NETs in 2002, when a P-NET was tattooed with India ink to allow for more readily identifiable tumor in the operating room.[36] A similar study described a patient who underwent tattoo of a P-NET after a previous laparotomy without identification of the tumor. The tattoo enabled a successful resection of the pancreatic tumor in the operating room.[37]

Using the same reasoning that EUS is a sensitive tool in evaluating the pancreas in real time, able to simultaneously visualize normal structures, pathologic lesions, and especially to avoid vascular structures, endoscopists have also used EUS to deliver therapeutic agents (Table 6).[38] There have been multiple reports of ablation of insulinomas, leading to dramatic improvement of

Table 5. Immunohistochemistry (IHC) Performed in Gastroenteropancreatic Neuroendocrine Tumors

IHC	Comment
Chromogranin A	Confirms diagnosis
Synaptophysin	Confirms diagnosis
CDX	Indicates bowel origin
CD56	Less specific marker for neuroendocrine tumor
Neuron specific enolase	Less specific marker for neuroendocrine tumor

Table 6. Potential Therapeutic Approaches for Gastroenteropancreatic Neuroendocrine Tumors

Therapeutic approach	Comment
Ethanol ablation	Has been used successfully to treat hypoglycemia in insulinoma patients who are nonsurgical candidates
EUS-guided delivery of anti-tumor agents	Allogenic mixed lymphocyte culture, ONYX-015, TNFerade have been used in pancreatic adenocarcinoma
Radiofrequency ablation/Photodynamic therapy	Mostly performed in animal studies
Brachytherapy	Performed in preliminary studies in patients with pancreatic adenocarcinoma

EUS, endoscopic ultrasound; TNFerade, tumor necrosis factor gene.

refractory hypoglycemic symptoms.[39] Although EUS-FNI is still considered investigational, this technique may ultimately allow for a way to treat symptoms in a minimally invasive way in patients who are poor surgical candidates.

EUS-FNI has also been tried most often in pancreatic adenocarcinoma. Multiple antitumor agents have been used to selectively target pancreatic tumors. These include allogenic mixed lymphocyte culture (cytoimplant),[40] an adenovirus which preferentially kills malignant tumor cells (ONYX-015),[41] and an adenovector containing the human tumor necrosis factor gene (TNFerade).[42,43]

Immunotherapy has also been used in an attempt to stimulate the body's immune system against tumor cells. In one study by Hirooka et al.,[44] five patients received intravenous gemcitabine was combined with EUS-administered OK432-pulsed dendritic cells. One patient demonstrated partial remission, while 2 others had stable disease for more than 6 months.

Other ablative techniques have also been delivered via EUS. These include modalities such as radiofrequency ablation,[45] photodynamic therapy,[46] and brachytherapy.[47,48] While the first two techniques have mostly been evaluated in animal models, brachytherapy has been reported in pilot studies in human patients.[45,46] In these studies, radioactive seeds of iodine-125 were injected under EUS guidance into advanced pancreatic tumors. Their results demonstrated partial response or stable disease in 30% of patients.

CONCLUSIONS

EUS is an invaluable tool in the evaluation and management of NETs. EUS can effectively stage patients with localized GE-NETs, often enabling identification of those patients who could safely undergo endoscopic resection of GE-NETs. EUS also adds significant ability to identify previously unlocalized tumors, particularly in the case of insulinomas, gastrinomas, and MEN patients. The addition of FNA to EUS has enabled tissue confirmation. Finally, recent developments in EUS-FNI offer hope that EUS may contribute not only to diagnostic purposes, but also therapeutic ones. Future studies will identify the utility of EUS-FNI in the management of patients with NETs.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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