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Endoscopy and Endoscopic Ultrasound in Assessing and Managing Neuroendocrine Neoplasms

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Abstract

Despite advances in radiological and metabolic imaging, standard axial endoscopy and endoscopic ultrasonography (EUS) still play a pivotal role in a number of neuroendocrine neoplasms (NENs) of the gastrointestinal and duodenopancreatic region. Upper gastrointestinal endoscopy is essential for the detection and characterization of NEN up to the angle of Treitz (esophageal, gastric and duodenal). Ileocolonoscopy allows the assessing and diagnosing of rectal, colonic and very occasionally distal ileal lesions. Endoscopic assessment is the mainstay for diagnosing gastric NENs associated with hypergastrinemia, but is also useful in detecting and diagnosing duodenal NENs (both functional and nonfunctional) and ampullary NENs. As rectal NENs are on the increase, standard colonoscopy (often combined with endorectal EUS) is also useful in detecting and treating small rectal NENs. EUS is the modality of choice for diagnosing pancreatic NENs and for locoregional staging of esophageal, gastric, duodenal, pancreatic and rectal NENs. This chapter will expand on the diagnostic and therapeutic role of endoscopy and EUS in the field of gastrointestinal and pancreatic NENs.

Gastrointestinal Neuroendocrine Neoplasms

Gastric Neuroendocrine Neoplasms

Gastric neuroendocrine neoplasms (NENs) have a varied spectrum with regard to histology, clinicopathologic background, stage and prognosis [1]. They are usually discovered incidentally and are for the most part benign. Two broad categories exist: (1) hypergastrinemia-related tumors – secondary to chronic atrophic gastritis (type 1

Table 1. Gastric and/or duodenal NENs: key factors for the endoscopist

	Comments
Atrophy?	Pernicious anemia or nonimmune-related chronic atrophic gastritis[1]
Hypertrophic gastric folds?	In cases of hypergastrinemia due to gastrinoma in ZES and MEN1
Association of gastric and duodenal nodules?	ZES and MEN1
Stigmata of hyperacidity?	ZES and MEN1
Gastric aspirate for random fasting pH!	If pH is high in a fasting patient, then suspect atrophic gastritis and achlorhydria[2]
Lesion assessment	Number, location, size, morphological aspect
Tumors approaching 1 cm	Perform EUS
Biopsy protocol (for gastric NENs) Predominant lesion(s) Random biopsies	 ++ Gastric antrum Gastric body and fundus (check for atrophy and also for ECL-cell hyperplasia)
Check for metaplasia, adenomas, early neoplasia in chronic atrophic gastritis	Careful inspection using HRE and/or electronic chromoendoscopy and a proper sampling protocol

ZES = Zollinger-Ellison syndrome; HRE = high-resolution endoscopy.
[1] Antibodies to parietal cells or intrinsic factor antibodies are useful.
[2] pH is usually low in the setting of fasting for endoscopy.

gastric NENs) or more infrequently associated with Zollinger–Ellison syndrome as part of multiple endocrine neoplasia type 1 (MEN1; type 2 gastric NENs), and (2) sporadic or type 3 gastric NENs.

Type 1 Gastric NENs

Type 1 gastric NENs result from hypergastrinemia in chronic atrophic gastritis [either immune-related (pernicious anemia) or nonimmune] resulting in enterochromaffin-like (ECL) cell hyperplasia and eventually small gastric NENs. The natural history of type 1 gastric carcinoids is generally (>95%) favorable and simple surveillance is usually recommended for small (<1 cm) T1 tumors, with local (endoscopic or surgical) resection for larger lesions [1–3]. Larger tumors may require oncological resection or other forms of therapy (somatostatin analogs, gastrin receptor antagonists or chemotherapy, if stage IV). Rarely, gastric NENs have a malignant course and this is usually confined to type 2 and especially type 3 tumors; the latter mimic a biological course close to that of gastric adenocarcinoma and require radical oncological therapies.

Careful assessment with upper gastrointestinal endoscopy is required for gastric NENs (table 1). Biopsies should be obtained from the dominant tumor(s), but

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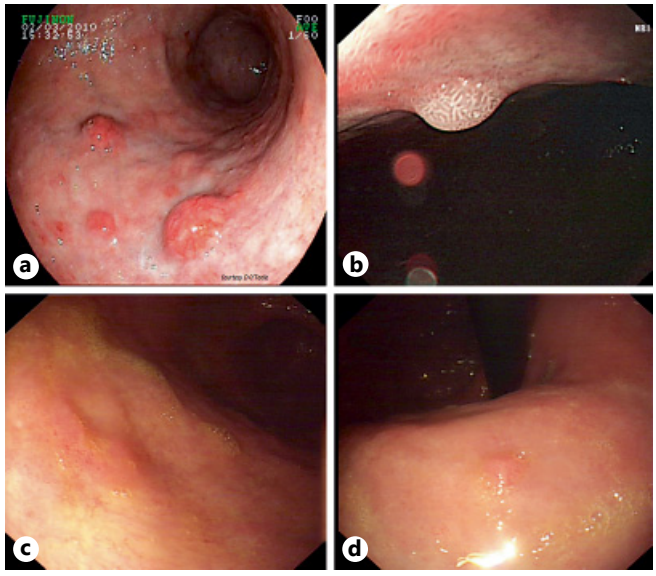

Fig. 1. Various endoscopic appearances of gastric NENs. **a** Gastroscopy revealing multiple sessile gastric NENs of various sizes located in the gastric body on a background to clearly define gastric atrophy. Note the rich vascular network on the surface of the two predominant lesions (gastric NENs with Ki-67 of 5%). Other smaller nodules <1 cm are also seen and correspond to either microcarcinoids or aggregates of ECL hyperplasia. **b** Polypoid gastric NENs on the anterior wall of the proximal gastric body (using narrow band imaging). **c** A flat and predominantly submucosal NEN. **d** A micropolyp.

in addition it is mandatory to sample the gastric antrum (2 biopsies) and body/fundus (4 biopsies) to establish a potential diagnosis of atrophic gastritis and ECL cell hyperplasia. In type 1 gastric NENs, careful inspection of the gastric cavity following full air insufflation usually reveals a lack of gastric folds and is often accompanied by a low volume of gastric mucus/acid pool. On-site pocket pH meters can be useful in confirming a high pH (thus confirming achlorhydria and 24-hour pH is rarely necessary to establish the diagnosis). Gastric NENs may take several forms (fig. 1), but are usually sessile and multiple and located in the gastric body and fundus. These tumors involve both mucosa and submucosa and occasionally display a rich vascular network on their surface (fig. 1a). Generous tumor sampling is necessary to look for standard histological features of NEN (and immunohistochemistry for chromogranin A, synaptophysin and Ki-67 proliferative marker). Random sampling from the gastric body/fundus mucosa should also be performed to search for associated ECL-like cell hyperplasia (the precursors of microcarcinoids and full tumors). Endoscopic ultrasonography (EUS; fig. 2) enables assessment of the degree of depth extension (invasion of the muscularis propria) and locoregional lymph node invasion (essential in patients with gastric tumors ≥1 cm) and is recommended before resection of polyps 1–2 cm in diameter [1–3] (fig. 2, 3).

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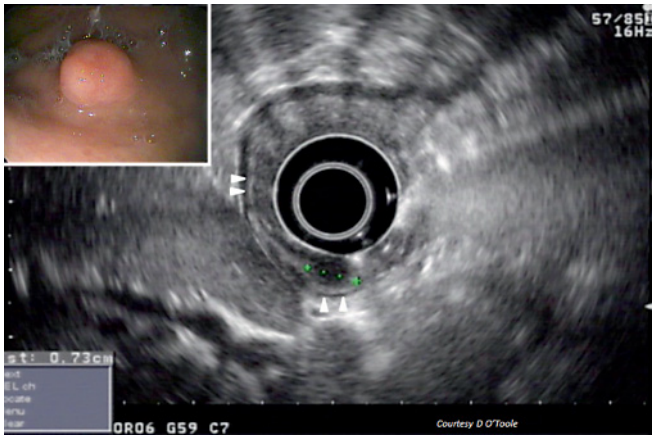

Fig. 2. EUS of a small 7-mm hypoechoic and homogeneous gastric neuroendocrine tumor. **insert** The corresponding axial endoscopic image of a small sessile nodule in the proximal gastric body. At EUS, the tumor is confined to the submucosa at a distance from the dark rim of the muscularis propria (arrow head) (uT1N0).

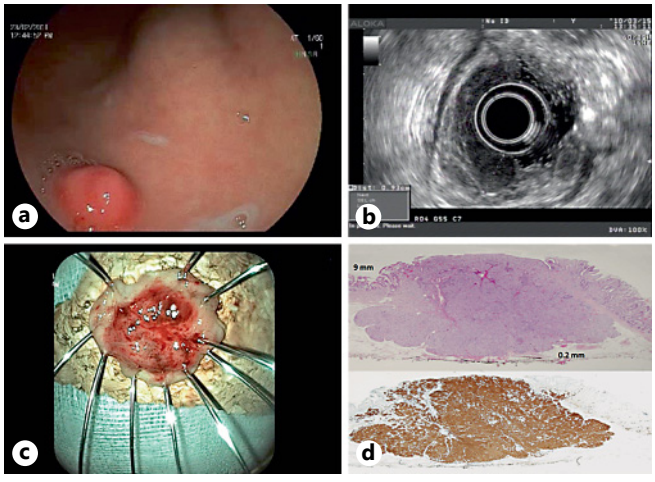

Fig. 3. Endoscopic evaluation of a gastric NEN (**a**) that is almost 1 cm in maximal diameter located in the gastric body and classified as uT1N0 on EUS (**b**). The tumor was fully excised using an EMR technique (**c**), pinned to spread the lesion before fixing in formalin and histology (**d**) revealing clear deep and peripheral margins: HE (upper image) and chromogranin A (lower image).

Finally, patients with chronic atrophic gastritis may harbor intestinal metaplasia or dysplasia and endoscopic assessment for mucosal field changes should be performed carefully using chromoendoscopy or electronic chromoendoscopy techniques and sampling.

Type 2 Gastric NENs

Patients with gastric NENs associated with hypergastrinemia from Zollinger-Ellison syndrome in the setting of MEN1 [4] can have tumors of similar distribution to type 1 tumors, but careful inspection of the duodenum is also required to search for duodenal NENs (gastrinomas) (fig. 4) [5, 6]. Type 2 gastric NENs can be multiple and can attain quite large sizes (fig. 4) and they are reported to have a malignant potential of up to 15%. At upper gastrointestinal endoscopy, the discerning endoscopist will also note the hypertrophied gastric folds (fig. 4c) and a large volume of gastric mu-

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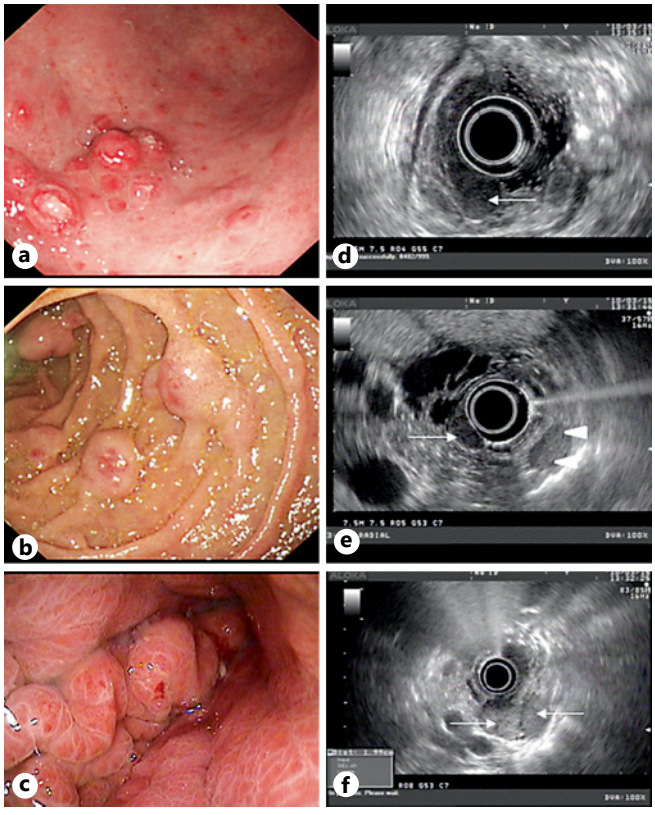

Fig. 4. Patient with type 2 gastric neuroendocrine tumors in the setting of Zollinger-Ellison syndrome and multiple endocrine neoplasia type 1. The patient has numerous gastric tumors of various sizes in the gastric body (**a**), some of which are ulcerated. There are also numerous duodenal NENs (**b**), some of which are responsible for the hypersecretion of gastrin that results in hypertrophic gastric folds (**c**). At EUS the gastric (**d**) and duodenal NENs (**e**, arrow) can be easily seen as well as periduodenal lymph nodes (**e**, arrow heads) and multiple sizable pancreatic NENs in the tail of the pancreas (**f**, arrows).

cus/acid: the secretory capacity is often quite heightened in these patients, such that following aspiration of a large volume of mucus/acid, this frequently replenishes by the end of the examinations. EUS in type 2 tumors needs to be meticulous and may take some time, as in addition to staging of the gastric tumors, evaluation is also required to assess for the presence of intraparietal duodenal gastrinoma (fig. 4d; often small, requiring a hyperinflated balloon, and occasionally the instillation of water to obtain better acoustic coupling) of pancreatic NENs and of adjacent lymphadenopathy (fig. 4).

Type 3 Gastric NENs

In cases of sporadic tumors (type 3 tumors), the tumors are usually sessile and located in the gastric antrum [7, 8]. They can be large (fig. 5), are usually single and may have a nonspecific aspect, but are distinguishable for their adenoma counterparts by the absence of a villiform mucosal pattern, which is easily recognizable using modern high-resolution endoscopy with electronic chromoendoscopy. Biopsies are required from the tumor site and also noninvolved mucosa (biopsies form mucosa more proximally reveals preservation of nonatrophic mucosa) and tumor grades here are often high. EUS is mandatory to aid staging (fig. 5) and, in addition,

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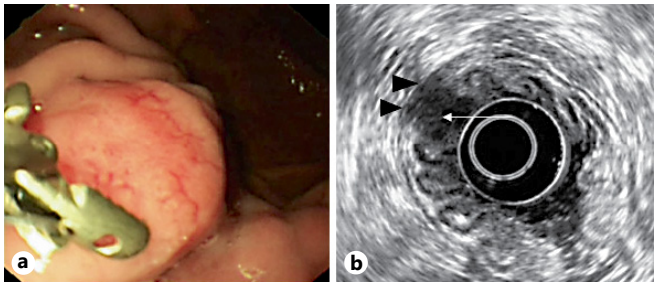

Fig. 5. A patient with a sporadic type 3 gastric neuroendocrine tumor. **a** The tumor is situated in the distal gastric body (junction with the antrum) and measures 2 cm in maximal dimension. **b** At EUS the tumor (arrow) is demonstrated to clearly involve the outer limits of the gastric wall (black arrow heads); surgery was performed with a partial gastrectomy and the tumor was confirmed to be pT3 with 1 of 13 lymph nodes positive.

a more extensive imaging protocol should be performed, such as a CT scan and somatostatin receptor scintigraphy (SRS) to assess for locoregional nodes and liver metastases.

Treatment of Gastric NENs

Management of gastric NENs is determined by subtype, and whether the disease is localized or metastatic. Since the most common subtype of gastric NENs is type 1, these usually display a benign and indolent clinical behavior; simple surveillance or localized endoscopic treatment modalities can be employed for small tumors [2]. For tumors <1 cm, surveillance can be recommended; for tumors between 1 and 2 cm confined to mucosa/submucosa (guided by careful EUS appraisal – uT1), endoscopic resection is recommended with an experienced endoscopist in this field and full endoscopic mucosal resection (EMR) or endoscopic submucosal dissection (ESD) techniques (fig. 3) should be employed to ensure complete resection. Endoscopic resection can be easily repeated provided tumors do not grow beyond uT1 [7, 8], and this strategy appears to be universally accepted now. Nonetheless, recurrences do occur. A recurrence rate in a recent series of patients treated endoscopically was 64% (21/33) at a median of 8 months and, of these, 67% (14/21) had a second recurrence [9]. A recent study in 82 patients demonstrated excellent recurrence-free and disease-free survival following endoscopic (n = 41) or surgical (n = 16) resections in patients with type I gastric NENs [10]. In our personal, nonpublished experience of more than 150 patients, EMR for lesions of 1 cm and above is infrequently required and the vast majority of patients have multiple small lesions that do not appear to grow over many years. The TNM staging system uses 1 cm in size as a cut-off to define T1/2 tumors, although there is inconsistency in the guidelines as to whether tumors between 1 and 2 cm should be treated with local resection. Surgery should be performed in the case of involvement beyond the submucosa (fig. 6), or positive margin after endoscopic resection and either a local resection (e.g. wedge resection)

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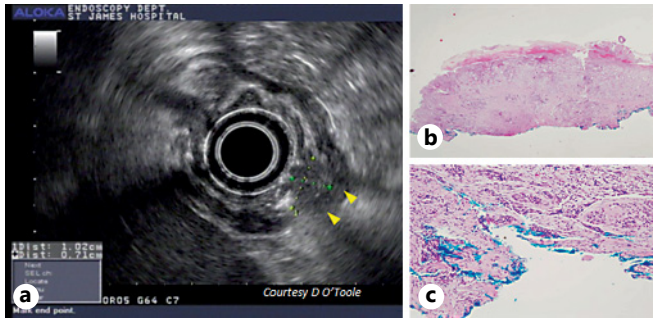

Fig. 6. A large (>1 cm) type 1 gastric NEN in a patient with pernicious anemia that clearly invades the muscularis propria on EUS (**a**) and in whom surgery was deemed a high-risk procedure. The lesion was resected using EMR and as predicted by EUS the deep margins were involved (**b**, **c**) and the patient went on to have a local gastrectomy with resection of the EMR scar site with one node involved (uT2N1).

and antrectomy or total gastrectomy (depending on tumor histological features, invasion and localization) have been recommended. While antrectomy has the theoretical advantage of removing the stimulus for gastrin secretion, this technique have become outdated by many expert groups [11] as the adequacy of antrectomy has been questioned in the past and a simple wedge or localized excision followed by endoscopic surveillance may be more appropriate [1, 11, 12].

Treatment of type 2 gastric NENs is dictated by the presence of other pancreatic and often duodenal NENs in the setting of MEN1 and Zollinger-Ellision syndrome. Endoscopic or surgical resection can be employed for large gastric NENs; however, given the complexity of the individual cases, this should be performed in a specialized center following careful multidisciplinary assessment [13].

While endoscopic resection of small (uT1) sporadic type 3 NENs is theoretically possible, these tumors often have a high proliferative capacity (whether well or poorly differentiated) and frequent nodal metastases. Oncological resection is therefore recommended after careful staging.

Duodenal NENs

Aside from the duodenal gastrinomas, other duodenal NENs are rare and can be summarized as nonfunctioning duodenal NENs (often incidentally discovered), somatostatinomas, poorly differentiated neuroendocrine carcinoma (including those of the ampulla of Vater) and duodenal paragangliomas [14]. Assessment is as for gastric NENs, axial endoscopy with biopsy is recommended and EUS to confirm the diagnosis and local stage of the disease [15, 16] (fig. 7, 8); the latter is especially important as their size is usually small and may be localized to the submucosa and not detected on axial endoscopy. In fact, duodenal gastrinomas are hard to detect even with the aid of EUS, and a combination with SRS or ^{68}Gallium PET-CT can increase detection rates.

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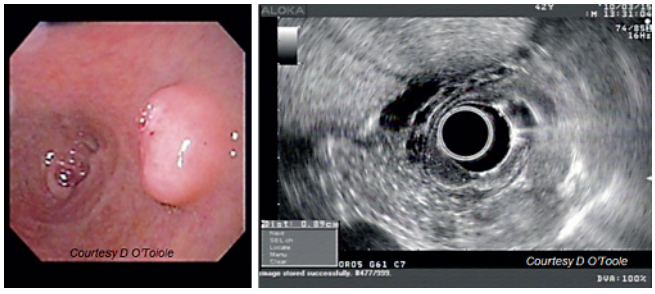

Fig. 7. Endoscopic view and EUS of a sporadic gastrinoma located in the duodenal bulb. At EUS the tumor is well defined and situated within the mucosal and submucosal space (uT1).

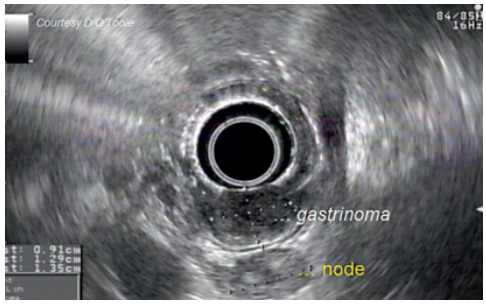

Fig. 8. EUS image using a radial probe of a duodenal gastrinoma (hypoechoic and homogeneous with clearly defined outlines) and a clearly demarcated local (periduodenal) lymph node (uT1N1).

Rectal NENs

Rectal NENs are increasing in incidence (0.2–0.9/100,000 from 1973 to 2004 in the SEER dataset) [17]. This rise – found not only in the USA, but also in Europe and Japan – may be due to a real increase in incidence, but might also be due to the larger number of incidentally discovered tumors at colonoscopy performed for unrelated reasons (especially colorectal screening programs). Some estimate that at least 50% are discovered incidentally [18] and, therefore, the majority are detected in a 'non-NEN expert' community. There are no accurate data pertaining to the site within the rectum, but they appear to localize to the mid or lower rectum. Their endoscopic aspect may vary (fig. 9–11) – the vast majority are small and are usually bland-appearing mucosa/submucosal firm bumps, often with a yellowish appearance. When evaluated using white light endoscopy and a high resolution endoscope and quality monitor they should not be mistaken for adenomatous or hyperplastic polyps as the mucosa covering these lesions is usually smooth and almost never villiform. They may have a predominant submucosal tumor aspect. In fact, general endoscopists are poor in reporting either the location or in marking rectal lesions that undergo resection, and this makes for follow-up analysis of incompletely resected rectal NENs very challenging [19]. The metastatic risk for rectal NENs is proportional to size: tumors <1 cm (3%), 1–2 cm (10–15%) and >2 cm (60% and more) [20]. In addition, special care must be taken with lesions demonstrating a centrally depressed zone, as they are often more advanced (fig. 10). Rectal NENs should be excised using

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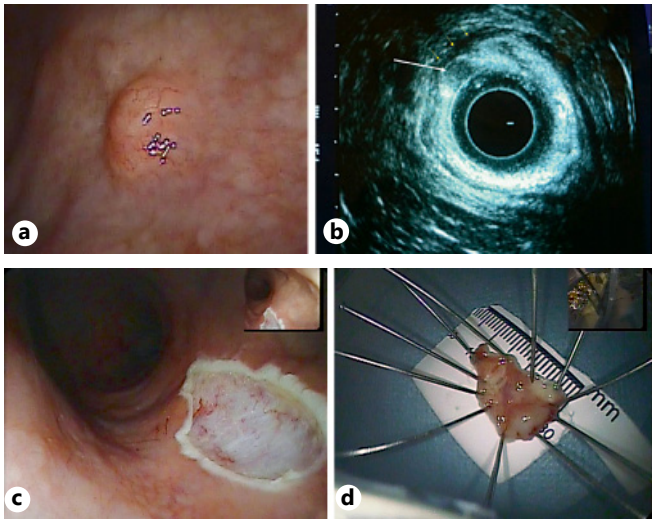

Fig. 9. Example of a rectal NEN incidentally discovered at screening colonoscopy for colorectal cancer. **a** At rectoscopy (endoscopic image) the lesion is a smooth sessile bump with a rich vascular network located in the mid rectum. **b** The tumor is also clearly seen on the rectal EUS (large arrow) as hypoechoic and well-defined within the mucosal and submucosal space, against the outer dark rim of muscularis propria (short arrows). In the same patient following EMR using a band EMR technique, the clear EMR scar site (**c**) and the pinned-down EMR resected margins prior to fixing for histology (**d**) are shown of the final well-differentiated NEN with a Ki-67 of 5% (grade 2) that was fully excised (0.3-mm-deep margins).

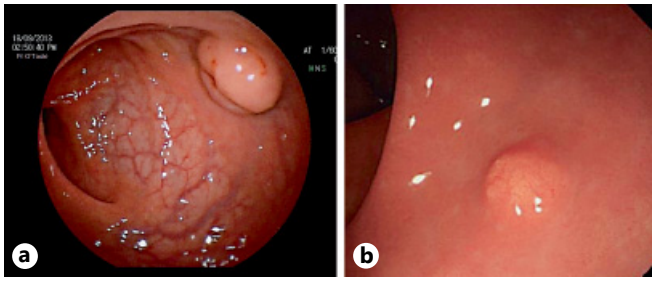

Fig. 10. Rectal neuroendocrine tumor measuring approximately 15 mm with a central depressed zone. **a** EUS revealed the lesion to be uT2 with involvement of the muscularis propria. Rectal resection (total mesorectal excision) confirmed a pT2 with 2 positive nodes. **b** Small 6-mm sessile rectal NEN with a predominantly submucosal aspect (faint yellow hue). Experienced endoscopists do not mistake this for a hyperplastic or adenomatous polyp and should perform a generous EMR and not a snare polypectomy.

a complete endoscopic resection technique. Selecting patients for treatment should always rely on accurate staging using EUS even for smaller tumors, as this has both an excellent correlation with tumor size, local staging and capacity to fully excise the tumors [21, 22]. EUS-guided biopsy can be performed on doubtful perirectal nodes (fig. 11).

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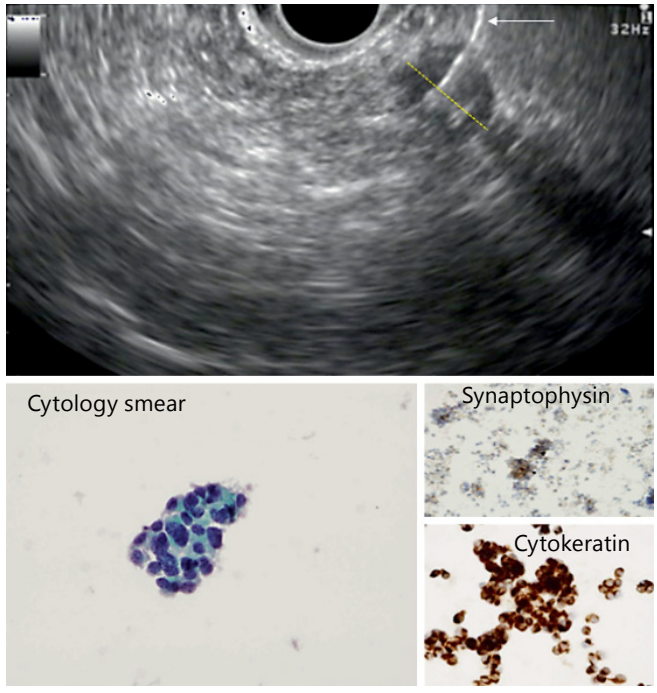

Fig. 11. Perirectal lymph node in a patient who had an incomplete snare polypectomy excision of a 13-mm rectal NEN. The previous polypectomy scar site was not recognizable at rectoscopy but at EUS an 11-mm perirectal lymph node can be seen (dotted line) that was sampled using EUS-guided biopsy (the arrow indicates the 25-gauge needle) and smear cytology confirmed the neuroendocrine nature after staining positive for synaptophysin and CD56 (chromogranin A was negative). Ki-67 was 3% (not shown).

In treating small rectal NENs, snare polypectomy (unfortunately frequently employed by the general endoscopist) often results in incomplete excision (83% in some series) [23]. Even when performing EMR it has been shown that band-ligation EMR techniques are to be preferred to standard inject-lift-snare EMRs and several series have shown that ESD is better in terms of complete histological resection results (90 vs. 71% in one recent series) [24, 25]. In a pooled analysis or endoscopic techniques for resecting rectal NENs, Zhou et al. [25] demonstrated that ESD was superior to EMR (risk ratio 0.89, 0.79–0.99); they also found that modified EMRs (using band ligation techniques) was superior to standard EMR and equivalent to ESD. Complete local endoscopic excision yields excellent results but some patients may require additional local endoscopic resection (e.g. TEMS) or radical surgery.

Pancreatic Neuroendocrine Neoplasms

EUS has been the reference examination for accurate preoperative detection of duodenal and pancreatic NENs for over 30 years now. This is especially true for insulinomas and gastrinomas, two of the most frequent functional NENs of this region. EUS performs well due to the excellent resolution with accurate detection of small lesions (even <5 mm). Insulinomas are often small and hard to see on both CT scan

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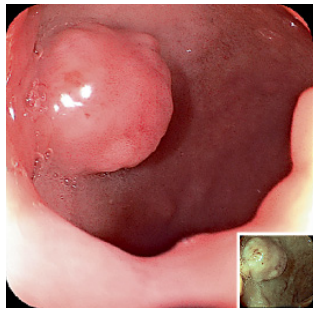

Fig. 12. Axial endoscopy showing a 10-mm postpyloric sporadic gastrinoma in the duodenal bulb. **insert** The same image using FICE.

and SRS (due to the absence of somatostatin receptor type 2), and gastrinomas are often very small and are predominantly found in the wall of the duodenum and, more rarely, the pancreas. In the past, nonfunctioning pancreatic NENs were often detected when the tumors were either large of metastatic, but now increasingly incidentally found small pancreatic NENs are a frequent occurrence (imaging for unrelated reasons) and EUS plays an integral role here [26]. When EUS is performed by an experienced operator (especially one versed in recognizing NENs), the diagnostic precision for detecting and localizing insulinomas is close to 95%; the diagnostic precision is lower for small duodenal gastrinomas, but remains high for gastrinomas of the pancreas and, when combined with SRS, overall gastrinoma detection exceeds 90% [27]. Standard axial endoscopy is also important in searching for sporadic or MEN1-related gastrinomas and should precede the EUS. Careful inspection of the entire duodenum should be performed, paying particular attention to the duodenal bulb (fig. 12) and postpyloric space where small tumors can be easily missed hiding behind the pyloric canal, and passing the scope several times via the pylorus is necessary to identify some lesions. EUS has also been shown to be a very sensitive method in the detection of pancreatic NENs as part of the MEN1 syndrome and indeed it is recommended in the follow-up of patients in detecting increases in size [28–30]. It is important to use methods capable of accurately determining size increases as guidelines have suggested surgical resection when tumors exceed 2 cm due to an enhanced metastatic risk [31].

The typical features of pancreatic NENs include hypoechoic and homogeneous, round, or oval-shaped, well-defined lesions (fig. 13). The tumors often display posterior enhancement with a hyperechoic rim corresponding to the rich vascularity (fig. 13–16). The tumors can be hard to detect once isoechoic with surrounding parenchyma, more infrequently hyperechoic to the pancreas and rarely cystic. Cystic spaces can also occur in larger lesions outgrowing their vascular supply. A smaller cystic pancreatic tumor is invariably imaged with a peripheral crest of solid tissue, often isoechoic and quite vascular in nature on Doppler; this feature is unique to cystic NENs. Overall, pancreatic NENs are often richly vascular on Doppler flow and the use of contrast-enhanced techniques can aid in determining the neuroendocrine tumor

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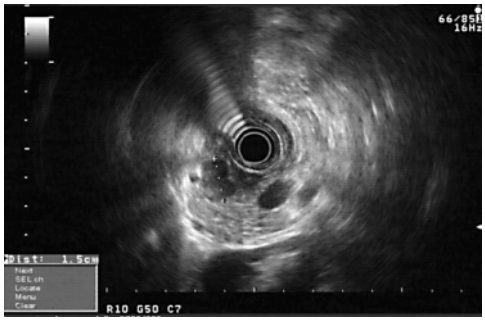

Fig. 13. Insulinoma on EUS measuring 15 mm in a 48-year-old patient, presenting classical symptoms of organic hyperinsulinism (hypoglycemic episodes with Whipple's triad over 12 years and in whom multiple CT scans and MRIs were normal). Calcium stimulation tests with venous sampling were positive, but failed to regionalize the lesion. EUS clearly identified the single hypoechoic tumor lying in the superior portion of the right body of the pancreas and at a distance from the main pancreatic duct that allowed a limited pancreatectomy with simple enucleation.

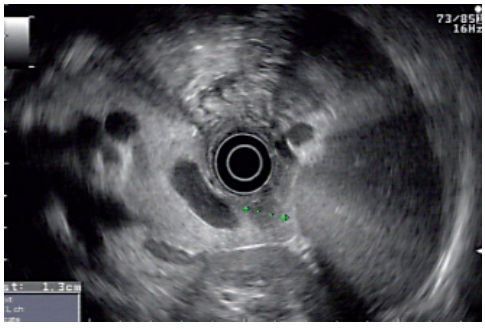

Fig. 14. Metastatic insulinoma in a pregnant 35-year-old lady complaining of episodes of significant hypoglycemia associated with documented low blood sugars (<1.8 mmol with high serum insulin and C-peptide). Transabdominal ultrasound and MRI demonstrated metastases in the liver, but the pancreas was normal. A single 1.2-cm, minimally hypoechoic, almost isoechoic, well-circumscribed tumor is seen to lie in the anterior portion of the pancreatic tail – just to the right of the junction body/tail and lies in front of the splenic vein and not far from the main pancreatic duct. The rest of the pancreatic parenchyma is well visualized and is normal.

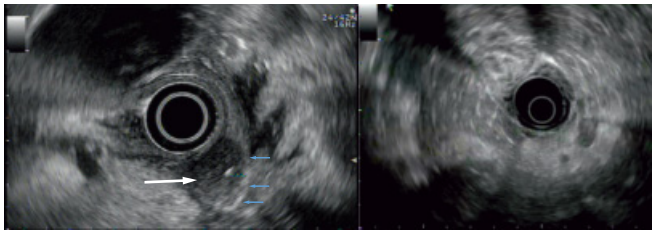

Fig. 15. Duodenal gastrinomas in a 35-year-old lady with MEN1 (with a history of parathyroidectomy at age 17 and peptic ulcer disease), presenting with 6 months of diarrhea and elevated serum gastrin (6 times the upper normal limit). No lesions were identified on CT scan or SRS, but EUS identified a well-defined 13-mm intraparietal duodenal tumor (large arrow) surrounded by a rim of hyperechoic submucosa (small arrows). Note also the intratumoral calcified spot. The adjacent image in the same patient shows two small (<10 mm) pancreatic NENs in the body and tail of the gland.

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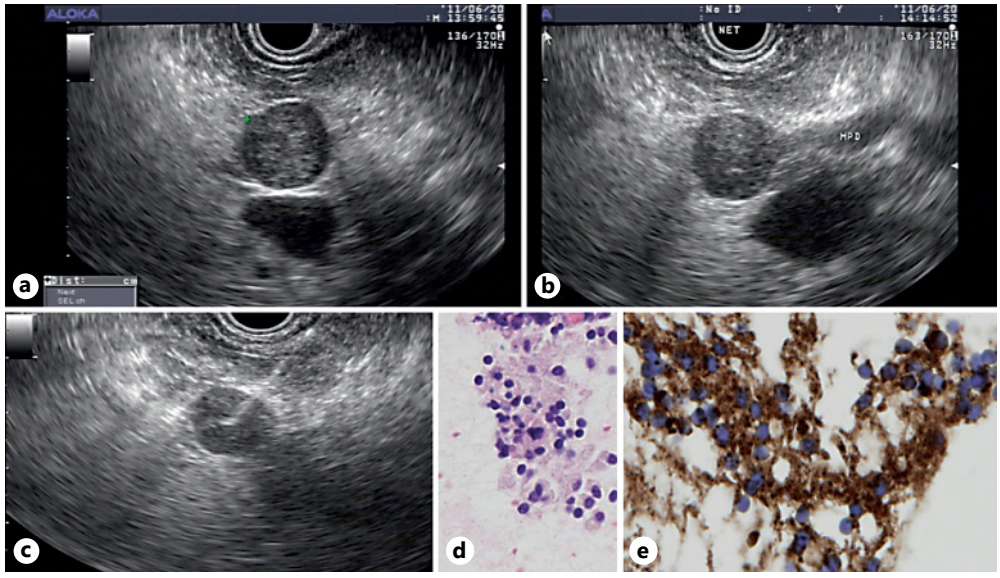

Fig. 16. EUS demonstrating a 10-mm incidentally discovered pancreatic neuroendocrine tumor in the right side of the body. **a** The tumor is hypoechoic and homogenous with a hyperechoic (slightly white periphery) attesting to its vascular nature. **b** The tumor is abutting the main pancreatic duct resulting in proximal dilatation of the duct (arrow), making it unresectable via enucleation. **c** EUS-FNAB with the needle (25 G) well centered in the tumor provided a fine core of tissue for cytology and immunohistochemistry. **d** ThinPrep cytosmear with characteristic cellular aspect of NEN. **e** Immunostaining for chromogranin A.

nature in cases of doubt. The presence of calcified spots (fig. 15), while not specific to NENs, can also give a clue to the diagnosis.

EUS is also essential in aiding to plan surgery. Attention to detail as to the precise localization within the pancreas, the possibility of regional nodal involvement, the proximity of main pancreatic and bile ducts and proximity to vascular structures are all vital in preoperative decision making. Surgery, especially for small lesions (non-functioning NENs or sporadic insulinomas) is encouraged to be as 'sparing' as possible and planning limited resections, enucleations or median pancreatectomies requires a solid symbiosis between the pancreatic EUS specialist and surgeon.

EUS-Guided Fine-Needle Aspiration and Biopsy, and Newer Techniques

EUS-guided fine-needle aspiration and biopsy (FNAB) of pancreatic NENs and locoregional nodes is also very sensitive in obtaining a cyto/histological proof of diagnosis. This technique not only provides cytology, but fine cores of tissue can be obtained in 90% of biopsies (EUS-FNAB) and this provides tissue for immunostaining that is invaluable in NENs [32]. The global sensitivity of FNAB is approximately 80%;

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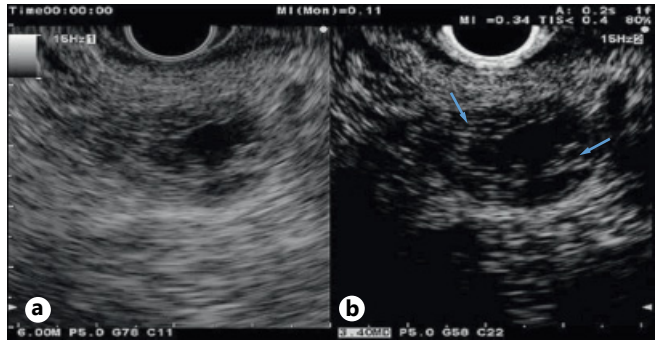

Fig. 17. a Contrast-enhanced EUS demonstrating a pancreatic neuroendocrine tumor with a cystic central zone. **b** The hypervascular nature is clearly visible with rapid incorporation of microbubbles after the injection of Sonovue© (arrows).

Table 2. Sensitivity of EUS-FNAB in the detection of pancreatic neuroendocrine tumors

First author and year	Sensitivity, %
Voss [35], 2000	75
Ardengh [36], 2004	83
Figueiredo [37], 2009	90
Atiq [38], 2012	91

this is higher in personal experience, especially with on-site pathology and careful processing with the aid of modern cytological techniques. EUS-FNAB is frequently requested in patients with incidental nonfunctioning small NENs; the biopsy permits the establishment of a certain diagnosis and avoids misdiagnosing a small adenocarcinoma or metastasis. Surveillance strategies are being employed more and more for small (<2 cm) pancreatic NENs [26] and, thus, getting the diagnosis correct at the outset is important. In addition, SRS using OctreoScan can be limited by tumor size, whilst EUS is highly performant regardless of size. Provision of fine cores of tissue can also aid in predicting the biological behavior as it is possible to obtain samples providing a clear cellular morphological aspect with immunostaining for Ki-67 to grade tumors. A recent series demonstrated good correlation between tissue obtained at EUS-FNAB and overall final pathological stage and outcome [33]. In another recent report, using a larger needle provided Ki-67 grading in up to 90% of patients [34]. In these authors' experience, EUS-FNAB for small nonfunctioning tumors is routine in helping to plan management algorithms; when tumors are small and well differentiated with a Ki-67% <5%, surveillance can be offered with more confidence.

Newer techniques – especially the use of contrast enhancement – have also been shown to help in detecting pancreatic NENs (table 2). Theses tumors rapidly incorporate the microbubbles following intravenous injection of contrast (e.g. Sonovue©; fig. 17), and impressive detection rates comparable with EUS-FANB have

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been reported [39]. In addition, a Japanese group demonstrated that EUS combined with contrast enhancement was useful in the differential diagnosis of malignant versus benign and preoperative localization of pancreatic NENs; this is similar to previous studies on the importance of vascular enhancement using contrast-enhanced CT [40].

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