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Review Article

Diagnostic and therapeutic role of endoscopy in gastroenteropancreatic neuroendocrine neoplasms

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ABSTRACT

Gastroenteropancreatic neuroendocrine neoplasms have substantially increased over the last decades. Because of the indolent clinical course of the disease even in advance stages and the rise in the incidental diagnosis of small asymptomatic lesions, the prevalence of gastroenteropancreatic neuroendocrine neoplasms is higher than that of pancreatic, gastric and oesophageal adenocarcinomas, making them the second most prevalent cancer type of the gastrointestinal tract. This increase in the overall prevalence of gastroenteropancreatic neuroendocrine neoplasms has been paralleled by a growth in the importance of the endoscopist in the care of these patients, who usually require a multidisciplinary approach. In this manuscript the diagnostic and therapeutic role of endoscopic for gastroenteropancreatic neuroendocrine neoplasms will be reviewed.

1. Introduction

The incidence of gastroenteropancreatic neuroendocrine neoplasms (GEP-NENs) has substantially increased over the last decades [1,2]. However they are still considered rare neoplasms. The most common primary sites for GEP-NENs are the stomach and the small intestine, but pancreatic and rectal NENs are often the most aggressive and challenging forms [3,4].

The clinical course of the disease is almost indolent, since although up to two-thirds of patients with GEP-NENs present with distant metastases at the time of diagnosis, the 5-years survival exceeds 60% [4]. For this reason, the prevalence of GEP-NENs is higher than that of pancreatic, gastric and oesophageal adenocarcinomas, making them the second most prevalent cancer type of the gastrointestinal (GI) tract [5]. Furthermore, the wide-spread use of both endoscopic diagnostic procedures and radiological imaging modalities has exponentially increased the incidental discover of asymptomatic, usually small lesions [6,7]. These lesions pose different dilemma to the clinicians taking care of GEP-NENs.

GEP-NENs are heterogeneous neoplasms and their prognosis is strictly dependent on several factors: the primary site, with pancreatic tumours presenting a worse prognosis as compared to those originating from the stomach or small intestine; the histological classification, as assessed by the specific WHO classification, which mainly depends on their proliferative activity and, finally, the stage, as evaluated by imaging, and classified in a specific TNM system (TNM ENETs) [8].

In this scenario, the correct localization of the primary tumour site in metastatic disease as well as the correct staging of incidentally discovered lesions are of paramount importance. A correct histological diagnosis including the grading has also important prognostic implications. The knowledge of all of these parameters allows estimation of the risk of progression and death, and the risk of recurrence after attempted curative resections [9–11].

In the last decade, the development of new and more sophisticated diagnostic and therapeutic endoscopic instruments and tools have enriched the armamentarium available to the endoscopist, the importance of whom in the care of patients with GEP-NENs has consequently grown. GEP-NENs, however, still represent a clinical challenge to the endoscopist because of their small size, which may render their search very difficult, if not sometime impossible.

The diagnostic and therapeutic role of endoscopy in the care of patients with GEP-NENs can be divided into several paragraphs. Each of these paragraphs will be separately reviewed in this paper, highlighting the current role of the endoscopic techniques and areas where further research is recommended.

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2. Localization of the primary tumour site in metastatic disease

Most GEP-NENs, especially those arising from the pancreas and the small intestine, are metastatic at the time of the diagnosis [12]. In about 10% of patients after the discovery of liver or lymph node metastases, the primary site following a standard diagnostic work up with cross-sectional imaging studies such as whole body computed tomography (CT) scan can remain undisclosed, thus configuring the clinical picture of a neoplasm of unknown primary. In this setting, a biopsy of the metastatic site would not only diagnose NENs, but also provide additional information that may indicate the most probable location of the primary lesion. A positive immunohistochemistry for CDX2 would indeed suggest an origin from the GI tract, staining for thyroid transcription factor-1 (TTF1) a lung primary, while a positive pancreatic duodenal homeobox 1 (PDX-1) or pancreatic polypeptide (PP) staining would point out towards a primary pancreatic neoplasm [8,12,13].

In the work up of patients with metastatic NENs of unknown primary (MNENs-UP), both oesophagogastroduodenoscopy (EGD) and colonoscopy should be performed, regardless of the results of immunohistochemical studies. Duodenoscopy should also be performed in case of negative EGD to take a better look of the papilla's area, while ileoscopy should always be part of the colonoscopic examination to explore the terminal ileum. In a retrospective analysis of 123 patients with MNENs-UP, Wang et al. [14] found that EGD was able to diagnose a primary gastric lesion in 100% of cases, while colonoscopy was effective in diagnosing a primary colorectal lesion in about 86% of cases. Colonoscopy also identified a small quote of lesions located in the terminal ileum. Importantly, in this study most of the lesions that were eventually found intraoperatively were located in the small intestine [14]. The small intestine is indeed the most frequent primary site in patients with a MNENs-UP and should be actively investigated. Non-invasive techniques in this setting include both nuclear medicine techniques such as Octreoscan or more recently (68)Ga-DOTA-NOC receptor positron emission tomography/CT (PET/CT), and CT enteroclysis [15,16]. Endoscopic techniques such as videocapsule endoscopy (VCE) and enteroscopy that are capable of exploring the small intestine are very attractive options in these patients. A case of small intestine NENs detected with VCE is shown in Fig. 1. The accuracy of VCE, however, has been reported in only few case series with a limited number of patients [17–19]. van Tuyl et al. [17] investigated the ability of VCE to localize an occult intestinal primary lesion in 20 consecutive patients with MNENs-UP. VCE revealed a small-intestinal tumour in 9 patients, with some other abnormalities such as external compression or erosions found in 3 additional patients [17]. However, not all patients underwent surgery, preventing the actual accuracy of the technique to be determined. Johanssen and colleagues compared the accuracy of VCE and computed tomography enteroclysis (CTE) in 8 patients with MNENs-UP, with surgery as the gold standard [18]. CTE detected the primary neoplasm in 50% of the patients as compared to 37.5% for VCE, and also provided additional information on extra-luminal disease, which is an important issue in small intestine NENs [18]. The better performance of CTE as compared with VCE has been recently confirmed in a larger series of 41 patients, where the sensitivity of CTE and VCE were 92% and 29%, respectively ($p = 0.004$) [19]. Furthermore, as NENs of the small intestine often cause significant strictures due to mesenteric involvement with fibrosis development, the use of VCE should also be preceded by another imaging study to rule out stenosis because of the risk for capsule retention. Indeed, a few cases of capsule retention due to small intestine NENs have been reported [20,21]. Differently, the data on the usefulness of enteroscopy performed with double or single balloon are scanty, thus suggesting a relatively low diagnostic yield of this procedure in the search for primary neoplasm in patients with MNENs-UP [22].

3. GEP-NENs of the GI wall

Gastric, duodenal, and rectal NENs of the wall of the GI tract are diagnosed with increased frequency, mostly incidentally, because of the widespread use of diagnostic upper and lower endoscopic examinations [23]. Recent epidemiological studies indicate that gastric NENs are the most common form of GEP-NENs [2]. Similarly, rectal NENs are very frequent [1,2], while duodenal NENs are more rare accounting for only 1–2% of all GEP-NENs and are usually associated with specific genetic syndromes, such as gastrinomas in multiple endocrine neoplasia type 1 (MEN-1) or Von Recklinghausen's disease, and can be functioning (somatostatinoma, gastrinoma) or non-functioning.

Tumour size, degree of infiltration of or layer of origin within the GI wall, and presence or absence of metastatic loco-regional lymph nodes are very important parameters that influence treatment strategy and are best assessed by endoscopic ultrasound (EUS).

3.1. Gastric NENs

Type 1 and 2 gastric NENs, accounting for about 70–85% of cases of gastric NENs, develop in the gastric fundus and body as a consequence of chronic hypergastrinemia and are usually small (<10 mm) and multiple. In about 90% of cases they are limited to the mucosa/submucosa, while infiltration of the muscolaris propria is usually observed only when their size is greater than 10–20 mm [24,25]. Lymph node metastases are found in 2–9% of type 1 and in 10–30% of type 2 lesions and usually occur with tumours that are greater than 20 mm, infiltrating the muscolaris propria and/or becoming angioinvasive [26–28]. Type 3 gastric NENs are sporadic

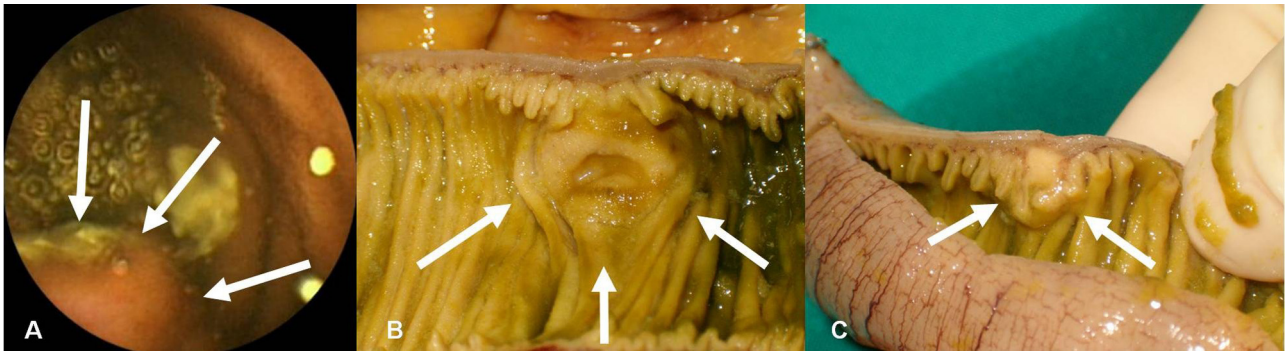

Fig. 1. An example of small intestine neuroendocrine neoplasm detected with videocapsule endoscopy.

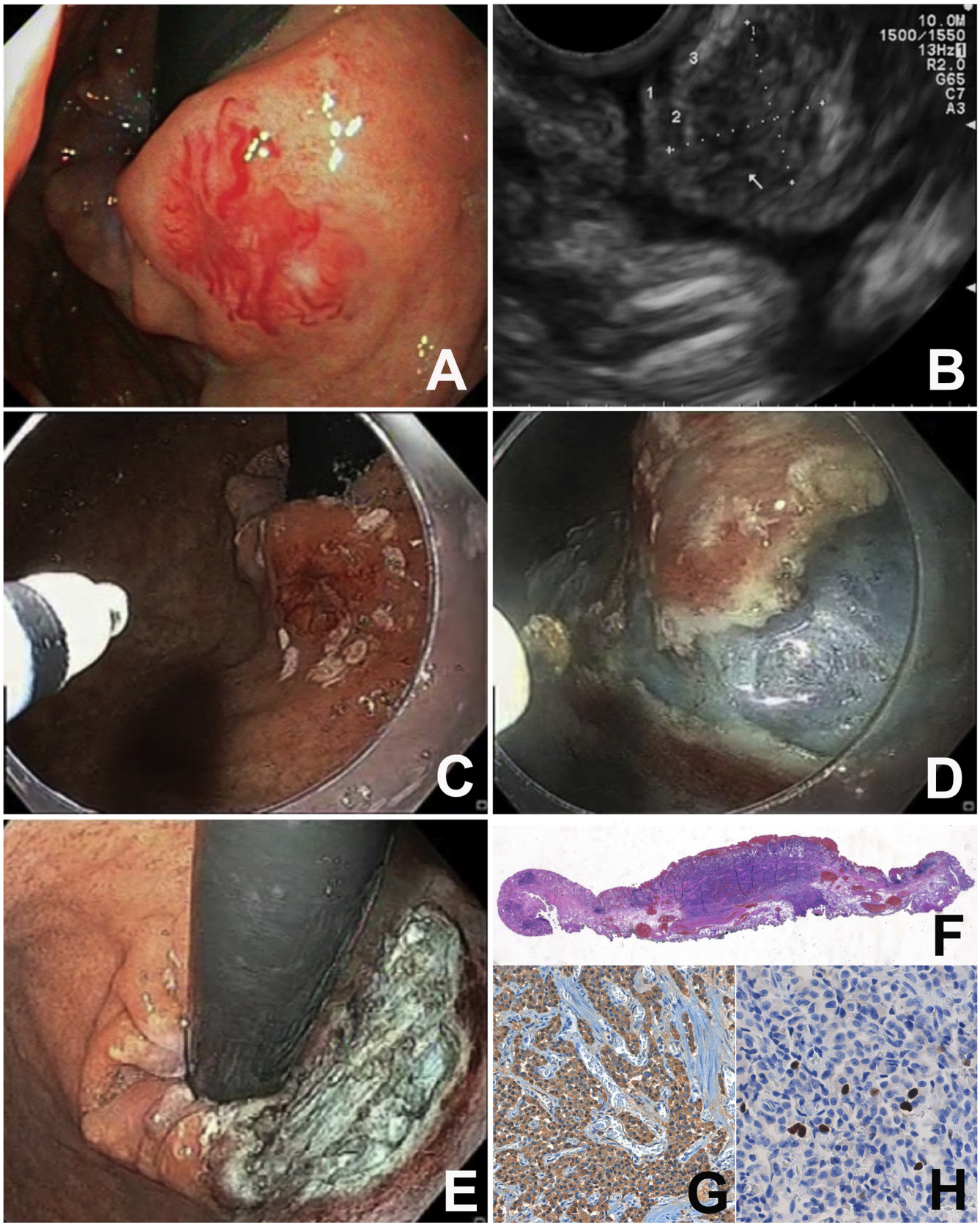

Fig. 2. Endoscopic submucosal dissection of a gastric cardia neuroendocrine neoplasm. Endoscopic view of the gastric cardia neuroendocrine neoplasm (A). After the gastric lumen was filled with water, EUS examination showed a 7 mm × 6.3 mm hypoechoic lesion confined to the submucosal layer (B). The lesion was then marked all around using the tip of a water jet assisted knife (C). Complete dissection of the previously marked area was achieved showing the underlying submucosa that appears blue because of the previous injection of indigo carmine (D). Large ESD defect after complete en bloc resection of the lesion (E). Macroscopic image of the one section of the resected specimen with margins inked (F). Neuroendocrine neoplasia with typical trabecular structure infiltrating the submucosa and extensive immunohistochemical expression of chromogranin A (G). Ki-67 determination deemed to be 2%, which is indicative of low grade neuroendocrine tumour NET G1 (H). H&E (F); immunoperoxidase (G and H).

neoplasms, not associated with hypergastrinemia [29], that appear as a solitary polypoid lesion that can be found in any part of the stomach. At the time of diagnosis, more than 70% of type 3 gastric NENs are larger than 10 mm, infiltrate the muscolaris propria, and/or are angioinvasive, thus accounting for the high rate of metastases found at presentation (75%) [30]. For small type 1 and 2 tumours confined to the mucosal layer after EUS examination, endoscopic mucosal resection (EMR) is the treatment of choice allowing removal of the tumour en bloc and complete histological assessment [26]. Conversely, for bigger lesions confined to the mucosa or for those infiltrating the submucosa without lymph nodes involvement at EUS, endoscopic submucosal dissection (ESD) has been proposed as the treatment of choice (Fig. 2) [31,32]. However, only a study has evaluated the effectiveness of ESD for gastric NENs and proved this method to be effective [33]. Twenty-four gastric lesions with submucosa infiltration as determined by EUS were successfully removed en bloc. R0 resection was obtained in all lesions that being found G1 or G2 tumours with no lymphovascular invasion, therefore any further treatment was required. After a follow up of two years, no lymph node or distal organ metastases were found and all patients were alive. Of note, 8 lesions were type 3 gastric NENs that are usually more aggressive than types 1 and 2 and are treated similarly to gastric adenocarcinomas (partial or total gastrectomy with lymph node dissection and chemotherapy). However, for those lesions that are small (<10 mm) and well differentiated (G1), conservative endoscopic treatment may be an option [31]. For type 3 gastric NENs, EUS may play an additional role by assessing the presence of regional lymph-node involvement, even in the presence of a small lesion, and eventually allows for cytological confirmation by fine-needle aspiration [30]. In these patients, endoscopic treatment is not an option and they should be sent for surgical intervention. Finally, type 1 gastric NENs have a tendency to recur; thus endoscopic surveillance every 1 or 2 years for early detection is recommended. Biopsy of any visible lesion/polyp and a complete gastric map with multiple random biopsies in the fundus (at least 4 samples) and the antrum (at least two samples) in addition to any visible lesion/polyps should be performed.

3.2. Duodenal and rectal NENs

Duodenal and rectal NENs are usually localized in the submucosal layer (third layer) and characteristically appear as rounded, hypoechoic, well demarcated small lesion with a salt and pepper appearance at EUS examination.

Most of the duodenal NENs are small (<10 mm) and can be treated with EMR [34], after EUS examination has excluded loco-regional lymph node metastases [33]. Surgical resection is indicated for larger tumours, which are associated with a high rate of lymph node metastases, as well as for ampullary NENs. Endoscopic ampullectomy may represent an option in case of small ampullary NENs without local angio-invasion and lymph node metastases and with a EUS-guided fine needle aspiration (EUS-FNA) showing high differentiation, especially in high risk surgical candidate [35].

Similar to duodenal NENs, most rectal NENs are ≤10 mm, thus allowing safe endoscopic removal [36]. In clinical practice, most lesions present as incidental polyps that only after completely removed by snare polypectomy are disclosed to be NENs. In such cases the status of the resection margins and the grading of the tumours will indicate the need for additional investigations and for follow-up, but a complete colonoscopy is usually advocated to exclude synchronous lesions [37]. The presence of mucosal depression or ulceration suggests an invasive behaviour and endoscopic removal should thus be avoided in such cases. When planning the removal of large lesions (within 20 mm), there is the need to exclude an aggressive behaviour by histology with Ki-67

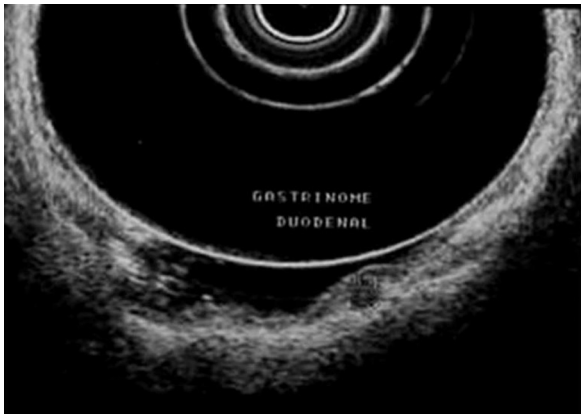

Fig. 3. Radial EUS image of a 2.5 mm gastrinoma of the second duodenal portion. The lesion appears hypoechoic and confined to the third wall layer corresponding to the submucosa.

evaluation, and to rule out invasion of the muscularis propria. Tumours exceeding 20 mm, with muscolaris propria invasion or aggressive histological features should undergo surgery. In this setting, EUS plays a critical role, as it is capable of accurately assessing depth of invasion and the presence or absence of pararectal lymph node metastases. For this reason, the ENET guidelines algorithm for rectal NENs is based on EUS findings [37]. In a recent study investigating more than 160 patients with rectal carcinoid, the rate of pathologically complete resection obtained by standard polipectomy has been shown to be only 31%, as compared to the 72% obtained with EMR or ESD [38]. In this setting, the combined use of EUS and ESD has been shown to be safe and effective to treat rectal carcinoids, and should be taken into consideration, especially for lesions larger than 10 mm in diameter [39].

4. Gastrinoma detection

Gastrinomas are rare GEP-NENs that secrete gastrin and cause a clinical syndrome known as Zollinger–Ellison syndrome (ZES), which is characterized by gastric acid hypersecretion resulting in severe acid-related peptic disease and diarrhoea [40]. In more than 70% of the cases these tumours are located in the duodenum (most frequently in the first and second duodenal portion), while a smaller part is localized in the pancreas [41]. About 60–90% of gastrinomas are malignant [42,43]; thus localization of the primary tumour is essential to assess whether surgical resection is indicated, to determine the extent of the disease and whether metastatic disease to the liver or distant sites are present and, finally, to assess changes in tumour extent with treatments.

This task, however, can be extremely difficult especially for duodenal lesions that in most cases have a diameter less than 1 cm (Fig. 3), while the vast majority of pancreatic gastrinomas have a larger diameter (mean diameter 3.8 cm) and only 6% of cases have a diameter less than 1 cm [40]. The performance of EUS reflects this different behaviour of the pancreatic and duodenal lesions, being extremely good for detection of pancreatic gastrinomas with an overall sensitivity of about 90%, and not sufficient for duodenal lesions with a sensitivity that drops to less than 50% [44]. Based on these performance results, the utility of EUS for gastrinoma detection outside the pancreas has been questioned and its use remains controversial [40]. However, as the accuracy of other imaging modalities including CT, magnetic resonance imaging (MRI), and nuclear medicine investigations such as Octreoscan and (68)Ga-DOTA-NOC receptor PET/CT is also limited [45,46], EUS remains part of a diagnostic armamentarium available to try to localize gastrinomas [33]. In case of failure, intraoperative transillumination of

the duodenum is frequently used to help identifying the site for the duodenotomy, with a sensitivity of about 83% [47].

5. Pancreatic neuroendocrine neoplasms

The intragastric and intraduodenal position of the EUS probe in close proximity to the pancreas allows the obtainment of high-resolution images and the visualization of local anatomic details not detected by other imaging techniques. This peculiarity, coupled with the ability to perform EUS-FNA to acquire tissue samples [48], has rapidly made EUS one of the most important and accurate tool for the evaluation of pancreatic neurondocrine neoplasms (p-NENs) [49]. At EUS examination, p-NENs typically appear as well rounded, hypoechoic lesions with a homogeneous pattern and with clear and regular margins (Fig. 4). In more advanced cases, however, all these features are lost and p-NENs may present as irregular pancreatic hypoechoic masses that are completely indistinguishable from the most common pancreatic adenocarcinomas.

Pancreatic NENs are rare, but their incidence has significantly increased in the last decades. Although they represent about 1% of all pancreatic neoplasms, their prevalence is around 10%, mostly accounting for low to intermediate grade NENs with a relatively "indolent" clinical course [1,50]. Pancreatic NENs are classified as functional or non-functional depending on the presence or absence of a clinical hormonal hypersecretion syndrome [51]. The functional status of these neoplasms changes substantially the reason why and the questions that need to be answered by EUS examination. Localization of functional p-NENs, mainly insulinomas, before surgery (see the previous chapter for gastrinoma), is the most important indication to perform EUS in these patients. However, because of their small diameter that in about 50% of the cases is less than 1 cm [52], these neoplasms can be very difficult to detect. For this task, EUS appears the most sensitive imaging modality with a sensitivity ranging from 57% to 94% [53–60]. Because of this high sensitivity, EUS has been considered in the recently published ENETS consensus guidelines as the imaging study of choice to be performed after other non-invasive imaging studies are negative [61]. The superiority of EUS over CT is clear and remarkable in the studies published up to 2000 and probably reflects the use of old generation CT scan. A study in 2003 by Gouya et al. has pointed out for the first time that this difference in performance could be overcome by the use of more sophisticated CT [60]. In their study involving 30 patients with 32 insulinomas, detection of tumours with the use of a dual-phase thin-section multidetector CT (MDCT) reached a sensitivity of 94%, which was absolutely comparable to the one obtained by EUS [60]. More recently, in an attempt to better clarify the role of EUS for detection of p-NENs in institutions that use MDCT for pancreatic imaging, the John Hopkins's group have reviewed its experience over a 25 years period [62]. In the 56 patients with 60 p-NENs who had both CT and EUS and who underwent surgical resection of their tumour(s), the overall sensitivity of EUS for p-NENs detection was significantly greater than that of CT (91.7% versus 63.3%, $p < 0.001$). Relevantly, this better performance was related to the significant higher detection rate of insulinomas (84.2% versus 31.6%, $p = 0.001$), which represented 76% of all functional p-NENs of the evaluated cohort. Moreover, when taking into account only those patients who underwent 64-slice MDCT, a trend very close to a significant difference in favour of EUS versus CT was also found [93% (95% CI, 83–100%) versus 74% (95% CI, 58–91%), $p = 0.06$] [62]. An equal trend of EUS detection of p-NENs over MDTC has been found in another study involving a smaller number of patients [63]. These results highlight that the real advantage of EUS over MDCT is related to its potential to detect small functioning insulinomas, which often are still missed by the latest generation of MDCT. Moreover, the capability of localizing small functional p-NENs can be further enhanced by the use of contrast-enhanced harmonic EUS [64,65], which can also have a prognostic value helping the distinction between benign and malignant p-NENs [65].

Another important information that can be determined in patients with functional p-NENs by EUS is the distance between the lesion and the main pancreatic duct, a factor that can drive the decision of which surgical approach to utilize (i.e. enucleation versus resection) [61]. Finally, even though usually not required, in same cases such as the presence of multiple lesions in different sites and with different EUS patterns or the presence of lesions that can mimic p-NENs like accessory spleen in patients with symptoms suggestive of functional p-NENs, a definitive diagnosis with EUS-FNA may be required [66].

Differently from functional p-NENs, non-functional p-NENs are classically discovered because of the development of symptoms due to tumour compression or invasion of adjacent organs, or when they metastasize. Moreover, possibly due to the wide spread use of cross-sectional radiological imaging studies, non-functioning p-NENs are now most frequently detected incidentally when completely asymptomatic [67]. The suspicious of non-functioning p-NENs is raised because of findings of hypervascular lesions at CT and/or MRI and even more when the lesion is found to express somatostatin receptors at the somatostatin-receptor scintigraphy (SRS) or at [68] Ga-DOTATOC PET [60,68,69].

In the evaluation of patients with non-functioning p-NENs, EUS has a manifold role. First of all, EUS-FNA should be performed to confirm that the lesion is, indeed, a non-functioning p-NEN. Recent studies on a meaningful number of patients have reported a very high sensitivity of EUS-FNA for the diagnosis of these neoplasms, ranging from 87% to 90% [70–72]. This high sensitivity coupled with the very low rate of complication reported for sampling solid lesions including p-NENs [73], make EUS-FNA the procedure of choice to reach the definitive diagnosis. Importantly, not only can EUS-FNA confirm the neuroendocrine nature of the pancreatic lesion, but can also give prognostic information by predicting the 5 year survival of these patients [74] and by assessing the grading of the neoplasia by determining the Ki-67 proliferation index [70,75–77]. Pre-operative knowledge of tumour differentiation may be crucial for management decision for non-functioning p-NENs. For small tumours less than 2 cm in diameter, where no study has demonstrated a survival benefit of surgery [78], and the risk of malignancy is low [79], the choice between surgery with the associated morbidity and mortality, and clinical follow up with the possibility of leaving an aggressive tumour in place, strongly depends on the tumour site and the value of Ki-67 proliferation index. In this scenario, in the era of personalized medicine [80], pre-operative Ki-67 determination may prove fundamental for the discussion

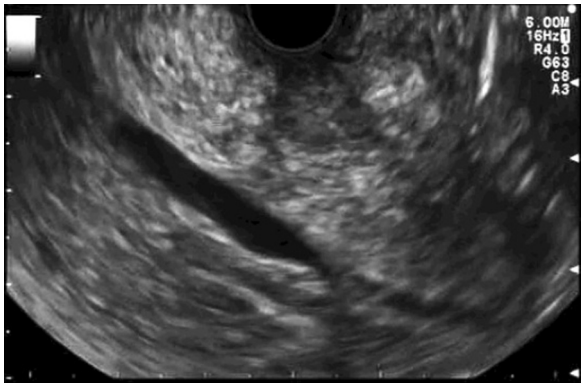

Fig. 4. EUS image of a small 13 mm × 14 mm of a well rounded, hypoechoic lesion with regular margin in the head of the pancreas highly suggestive for NENs. The diagnosis was confirmed after examination of the core biopsy tissue specimen gathered using the EUS-guide fine needle tissue acquisition technique.

with a patient regarding the available therapeutic options. Similarly, in patients with unresectable tumours, the choice of the most appropriate first-line therapeutic regimen is critically based on the degree of cell proliferation index and may include different somatostatin analogues, targeted therapies (i.e. everolimus and sunitinib), peptide receptors targeted therapy, and different chemotherapeutic schedules [81–83]. Up to recently, only few studies have reported the use of EUS-FNA cytological specimens for Ki-67 measurement showing promising results [70,75–77]. In the largest and best designed prospective study published to date (including both functioning and non-functioning p-NETs), Ki-67 measurement was successful in 18 (75%) of the 24 patients evaluated [75]. All patients underwent surgery and there was 89% agreement in Ki-67 determination between cytological and histological samples by the ENETS grading system criteria [84]. Despite these results, Ki-67 expression on cytological specimens has still not gained

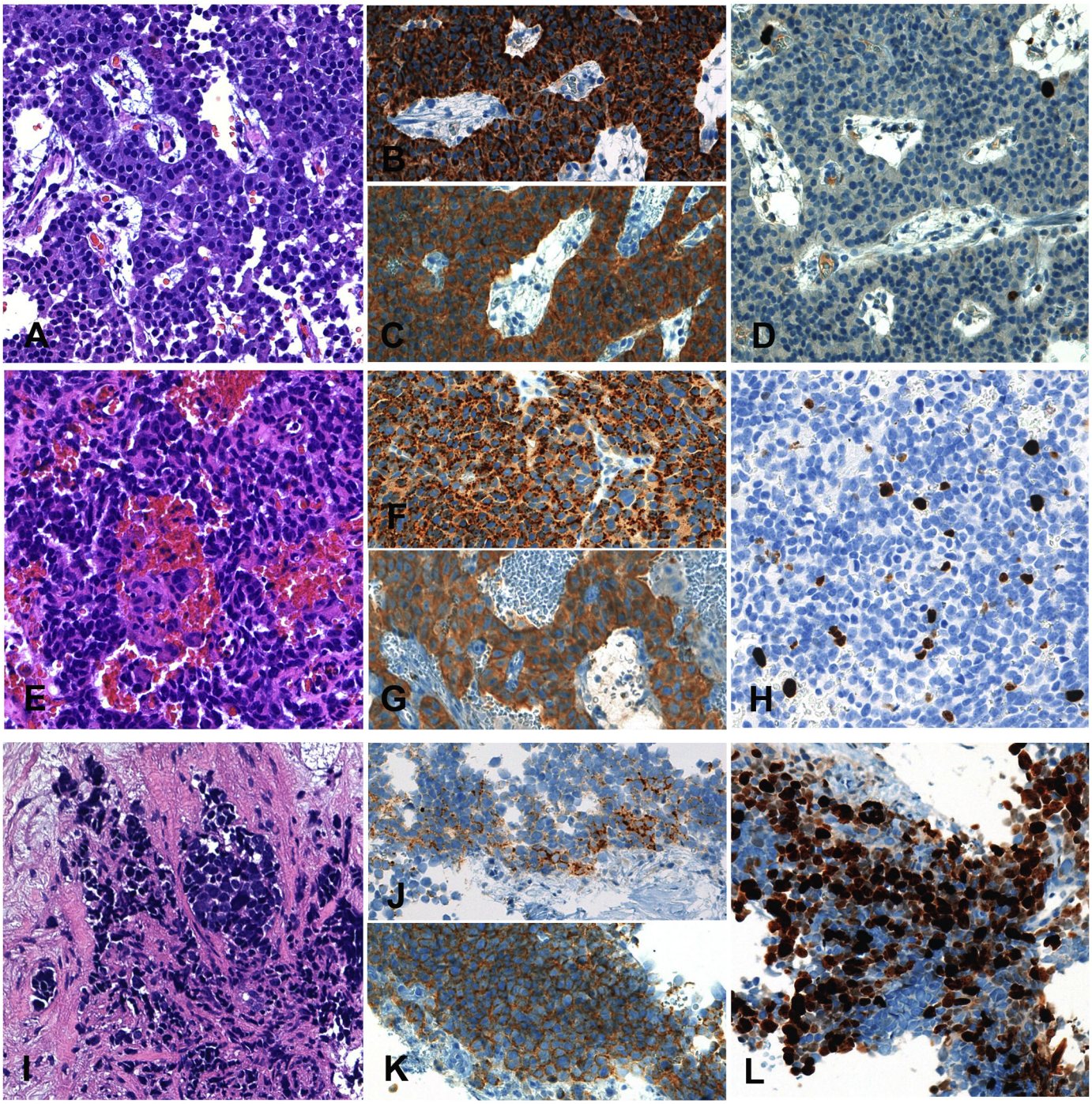

Fig. 5. Examples of grading for neuroendocrine neoplasms in EUS-fine needle tissue acquisition samples. Grade 1 p-NET showing trabecular histology, mild atypia (A), intense immunoreactivity for chromogranin A (B) and synaptophysin (C) and rare cells with nuclear labelling for Ki-67 (D). Grade 2 p-NET showing large trabecular structure, moderate cell atypia (E), intense immunoreactivity for chromogranin A (F) and synaptophysin (G) and discrete cells with nuclear labelling for Ki-67 (H). High grade, G3, p-NEC fragmented sample showing abundant desmoplasia and solid islets of cells with severe atypia and scarce cytoplasm (I), focal and often faint immunoreactivity for chromogranin A (J), intense and diffuse immunoreactivity for synaptophysin (K) and diffuse nuclear labelling for Ki-67 (L). (A, E, and I) Haematoxylin and eosin; (B–D, F–H and J–L) immunoperoxidase.

widespread use due to the difficulty to obtain reproducible results and the availability of tissue biopsy specimens has been advocated [78].

To overcome these limitations of cytological Ki-67 determination, our groups have used a recently developed technique that we refer as to EUS-guided fine needle tissue acquisition (EUS-FNTA) to distinguish it from EUS-FNA [85], to gathered sample for histological examination in patients with suspicious non-functioning p-NENs [86]. Thirty patients with a mean diameter of the lesions of 16.9 ± 6.1 mm were enrolled. The procedure, which is performed using a 19-gauge EUS needle, was technically successful in all patients without complications. In 28 of them, tissue samples for histological examination were obtained and the diagnosis of non-functioning p-NENs confirmed (Fig. 5). Of note, tissue samples were also successfully obtained from lesions in the head of the pancreas and uncinate process, two sites that require the trans-duodenal approach, a known limitation of the large gauge biopsy EUS needles [87,88]. In 26 of the 28 patients with available tissue specimens (92.9% and 86.6% of the initial entire cohort), we were able to also perform Ki-67 determination (Fig. 5). In 12 patients who underwent surgery we could compare Ki-67 expression on EUS-FNTA samples and the surgical specimens that represent the reference gold standard. Using a cut-off of 2% to distinguish G1 from G2 tumours, concordance between pre- and post-surgical Ki-67 determination was found in 83.3% of the patients. Interestingly, when a cut-off of 5% that several strands of evidence suggest that may be more useful than the 2% value to define G2 tumours was applied [89,9], the concordance was found in all cases [86]. These very promising results need to be reproduced by other groups before this procedure can become the standard of care to evaluate these patients.

Another emerging application of EUS for both functioning and non-functioning p-NENs is the performance of EUS-guided fine needle tattooing (EUS-FNT) of the lesion to facilitate its precise localization during surgery. Pre-operative tattoo can be very important when laparoscopic surgery is performed, because of the limited ability of the surgeon to clearly identify and palpate small pancreatic lesions, which can lead to conversion to an open procedure in as high as 30% of cases [90]. After the publication of few case reports that demonstrated the lack of complications [91–94], the John Hopkins' group reported the first case series involving 13 patients (6 of whom had p-NENs) who underwent EUS-FNT to facilitate recognition of the lesion during laparoscopic distal pancreatectomy [95]. The tattoo was done by injecting 1–5 ml of sterile purified carbon particles (GI Spot; GI Supply, Camp Hill, PA), 3–5 mm into the pancreatic parenchyma to the patient's right of the lesion (towards the pancreatic head). The procedure was feasible in all cases, without complications and all lesions were easily recognized at surgery. The same group clearly showed that the increased recognition of the pancreatic lesion during resection was associated with a significant decrease in the operative time as compared with patients who undergo the same surgical procedure without a tattoo [96]. This has led in their institution to the routine use of EUS-FNT when small pancreatic lesions are resected laparoscopically.

Finally, p-NENs can become a target for EUS-guided tumour ablation therapies that are under development and represent the natural evolution of EUS from a diagnostic into a more therapeutic/interventional [97,98]. Three cases of EUS-guided alcohol ablation of symptomatic functioning p-NENs in high-risk surgical patients have been reported in the literature [99–101]. In all cases, ablation led to long-term symptoms resolution. However, in one patient with MEN I and two Vipomas, the second tumour ablation was complicated by formation of a small pancreatic necrotic lesion secondary to minimal effusion of ethanol during needle retraction, which was treated with laparoscopic necrosectomy [101]. This underlying the difficulty of treating small p-NENs that are surrounded by normal pancreatic tissue that if involved by the ablation treatment can lead to dangerous complications. Moreover, alcohol may not represent the best treatment because of the possibility of distant complication such as portal vein thrombosis that has been described after alcohol ablation of pancreatic cysts [102]. However, the possibility of minimally invasive treatment of small p-NENs by EUS remains attractive and future research will better clarify the potential role for this procedure.

6. Conclusions

In conclusion, endoscopic procedures have a pivotal role in the diagnostic work-up and in the therapy of GEP-NENs.

Upper and lower standard GI endoscopy should represent the first step in patients with MNENs of unknown primary, followed by an intense investigation of the small intestine, since this latter is the most frequent primary site. VCE has showed suboptimal diagnostic accuracy and should be proposed only after the exclusion of strictures, since cases of retention have been described. Studies on the role of enteroscopy in patients with MNENs of unknown primary origin are still scanty to draw any firm conclusion.

EUS has a crucial role in the setting of GEP-NENs of the GI wall, since it provides information on size, deep of invasion and locoregional metastasis. EUS-guided FNA can also provide a definite diagnosis and useful information (i.e. Ki-67 evaluation) for the correct management of this type of lesions. Furthermore, EUS can correctly select ideal candidates for endoscopic resection (EMR and ESD).

EUS has a decisive role in the setting of pancreatic neuroendocrine neoplasms. It can help to correctly localize the tumour when other non-invasive procedures have failed and can provide useful additional information (i.e. distance from the pancreatic duct, Ki-67 proliferation index) for the best therapeutic management (surgery, conservative approach, type of anti-tumour therapy in case of unresectable tumours). Furthermore, the possibility of EUS-guided FNA tattooing of pancreatic lesions may help surgeons to find the neoplasm and avoid demolitive surgery. Finally, EUS-guided therapies (i.e. alcohol ablation), especially in patients unsuitable for surgery, are under investigation and will definitively represent the future field of interest.

Conflict of interest statement

None declared.

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