Current updates and future directions in diagnosis and management of gastroenteropancreatic neuroendocrine neoplasms

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Abstract

Gastroenteropancreatic neuroendocrine neoplasms are a heterogenous group of rare neoplasms that are increasingly being discovered, often incidentally, throughout the gastrointestinal tract with varying degrees of activity and malignant potential. Confusing nomenclature has added to the complexity of managing these lesions. The term carcinoid tumor and embryonic classification have been replaced with gastroenteropancreatic neuroendocrine neoplasm, which includes gastrointestinal neuroendocrine and pancreatic neuroendocrine neoplasms. A comprehensive multidisciplinary approach is important for clinicians to diagnose, stage and manage these lesions. While histological diagnosis is the gold standard, recent advancements in endoscopy, conventional imaging, functional imaging, and serum biomarkers complement histology for tailoring specific treatment options. In light of developing technology, our review sets out to characterize diagnostic and therapeutic advancements for managing gastroenteropancreatic neuroendocrine tumors, including innovations in radiolabeled peptide imaging, circulating biomarkers, and endoscopic treatment approaches adapted to different locations throughout the gastrointestinal system.

Key Words: Gastroenteropancreatic neuroendocrine neoplasms; Neuroendocrine tumors; Neuroendocrine carcinoma; Gastrointestinal; Pancreas; Small intestine

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Canakis A et al. Diagnosis and management of GEP-NENs

Core Tip: Diagnostic technology for neuroendocrine tumors continues to advance. Radiomics promises to enhance morphologic imaging. Gallium-68 DOTA-peptide positron emission tomography/computed tomography has replaced Octreoscan as the preferred functional imaging modality. Newer radiolabeled peptides may further improve detection. A novel liquid biopsy biomarker (NETest) has proven more accurate than chromogranin A in monitoring treatment response and predicting disease activity. Therapy has also progressed with treatment adapted based on the predicted behavior of the tumor. Advanced endoscopic resection techniques have revolutionized treatment. Preliminary evidence suggests endoscopic ultrasound guided radiofrequency ablation may prove useful in treating pancreatic lesions. Multimodality therapy continues to evolve for metastatic pancreatic tumors.

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INTRODUCTION

Gastroenteropancreatic neuroendocrine neoplasms (GEP-NENs) are a heterogenous group of rare neoplasms with a wide clinicopathologic spectrum of disease activity[1]. These neoplasms arise from the secretory cells of the neuroendocrine system and can occur anywhere along the gastrointestinal tract[2]. Nearly 95% occur sporadically, though genetic testing should be considered for patients less than 40 years old, family history of NENs, features concerning for multiple endocrine neoplasia type 1, von Hippel-Lindau disease, tuberous sclerosis or neurofibromatosis type 1[3]. Traditional terminology including carcinoid tumor and APUDoma were replaced by neuroendocrine neoplasm in 2010 by the World Health Organization (WHO), which also discouraged using the terms benign and malignant. NENs are grouped as well-differentiated neuroendocrine tumors (NET) or poorly differentiated neuroendocrine carcinomas (NEC)[4]. NECs are highly aggressive with significantly worse prognosis. Nearly 80%-90% of GEP-NENs are NETs, which are slow growing and graded from G1 (low), G2 (intermediate), to G3 (high)[2].

With the advent of high-resolution cross-sectional imaging, GEP-NENs are increasingly being discovered-notably without any significant change in rates of metastasis[5]. In a large population-based study of 64971 patients, the age-adjusted incidence rate of NETs increased from 1.09 per 100000 in 1973 to 6.98 per 100000 in 2012, with the greatest increase occurring in localized NETs and G1 NETs[6]. These observations suggest that many of these lesions are incidental and/or asymptomatic at the time of discovery. Incidence of gastric and rectal NETs has increased the greatest unlike small bowel NETs, which likely correlates with greater use of endoscopic procedures. Similar trends have been noted in Europe and Asia[7].

GEP-NENs are divided into gastrointestinal and pancreatic NENs with the most common being rectal (29%) and small intestinal (28%) (Figures 1 and 2)[8,9]. These tumors exhibit a wide range of behavior with varying degrees of disease activity including growth rate, grade, differentiation and metastatic potential[10]. Generally speaking, small intestinal NENs have high malignant potential while gastric, duodenal, appendiceal, and rectal NETs are less likely to metastasize[11]. A recent cohort of 43751 patients in the United States noted that the majority of GEP-NENs were localized (51.7%) and grade 1 (71.7%)[12]. This study also found that the most lesions (73%) occurred in whites, followed by black (16.2%) and Asian (7.3%) populations with no difference in three or five year survival based on race.

The majority of GEP-NENs are non-functional while functional NENs secrete hormones and substances that lead to clinical symptoms. Functioning gastrointestinal NENs are not classified separately from nonfunctioning gastrointestinal NENs and manifest with carcinoid syndrome while functioning pancreatic NENs are classified distinctly according to the hormone secreted by the tumor. Nonhormonal products are also produced by both non-functional and functional NENs, which include chromogranin A, pancreastatin and pancreatic polypeptide, and may offer aid in diagnosis and follow-up.

DIAGNOSIS

Diagnosis relies on morphological imaging, functional imaging, endoscopic procedures, biomarkers, and pathology. All patients should undergo computed tomography (CT) and/or magnetic resonance imaging (MRI). Functional imaging serves as an adjunct to conventional imaging in advanced NETs and is helpful for identifying primary tumors and staging. Endoscopic procedure with biopsy diagnoses gastric, duodenal and colorectal NENs while endoscopic ultrasound (EUS) aids in identification of
Pancreatic NENs. The mainstay of biomarkers is chromogranin A although newer markers have been identified, which may expand the role of biomarkers in post-treatment surveillance and detection of recurrence.

Pathology (staging and grading)
Tumor staging and grading are essential to assess prognosis and disease activity as reflected in the 2019 WHO classification based on tumor differentiation and grading (mitotic rate or Ki-67 index) (Table 1)[2, 4]. The degree of differentiation is based on the extent the tumor cells resemble their endocrine cell counterparts[11]. Grading is based on the proliferative rate from either mitotic counts or Ki-67 labeling index with higher values associated with more aggressive behavior, independent of stage[2]. Mitotic counts rely on the number of mitotic figures in 10 consecutive high-power fields while Ki-67 Labeling index is the percent of positive tumor cells. Small biopsy samples and heterogeneity within the tumor all pose challenges to accurate assessment of tumor grade of the entire lesion. Whether there is incremental benefit from larger core samples obtained during EUS-fine needle biopsy and whether artificial intelligence technology will help partially automate calculating Ki-67 index require further study[12]. Radiomics may supplant or supplement histologic diagnosis by assessing the whole lesion and will be discussed further below.

Morphologic imaging
NETs typically are highly vascular, hyperenhancing in the early arterial phase with washout during the delay portal venous phase of CT (Figure 3). Differentiating liver metastases from hepatocellular carcinomas may be aided by exploiting the fact that hepatocellular carcinomas have higher attenuation levels with contrast and higher iodine uptake with a threshold value of 0.22 for normalized iodine uptake having 100% sensitivity and 90% specificity[13]. Attenuation assessment of lymph nodes on CT
Table 1 World Health Organization 2019 Classification

| Terminology, grade | Differentiation     | Mitotic count (HPF) | Ki-67 index (%) |
|--------------------|---------------------|---------------------|-----------------|
| NET, G1            | Well-differentiated | < 2/10              | < 3             |
| NET, G2            | Well-differentiated | 2-20/10             | 3-20            |
| NET, G3            | Well-differentiated | > 20/10             | > 20            |
| NEC, G3 (small or large cell type) | Poorly differentiated | > 20/10 | > 20 |

NET: Neuroendocrine tumor; NEC: Neuroendocrine carcinoma; HPF: High powered field.

Figure 3 Computerized tomography scan of hyperenhancing pancreatic neuroendocrine tumor (white arrow).

may also help identify malignant nodes with a cutoff value of 7.5 Hounsfield units distinguishing 96% of positron emission tomography (PET) positive and 89% of PET negative lymph nodes[14]. Limitations of CT include lower sensitivity with a recent study suggesting only 76% of CT scans identified the primary tumor in patients with metastatic GEP-NETs, and difficulties with identifying small (< 1 cm) lesions especially in the small bowel where only 21% of small intestine NETs were identified in one study[15-17]. CT enteroclysis has been used for localization of small bowel tumors[18] with luminal distension using neutral contrast aiding in defining small mucosal features with a positive predictive value of 95%[18].

MRI with contrast enhancement is superior in detecting lesions in the liver and pancreas[15]. With higher tissue resolution, MRI is also better for evaluating bone and liver metastases[19,20]. NENs typically have low T1 and high T2 signal on imaging (Figure 4). Adding diffusion weighted MRI to standard MRI imaging increased metastatic findings in 71% of patients, which changed patient management in 19% of patients[21]. A comparative study showed that while contrast enhanced MRI is superior, adding diffusion weighted MRI images on non-contrast MRI imaging may suffice for everyday practice[22].

Radiomics appears to augment the ability of MRI to differentiate pancreatic NET from adenocarcinoma and solid pseudopapillary neoplasms.[23,24].

Grading pancreatic NETs by CT or MRI is challenging and relies on assessing tumor margins, pattern of venous phase contrast washout, and enhancement pattern[10,18]. Irregular margins on CT have 71% sensitivity and 82% specificity for predicting grade 2/3 tumors while a model incorporating margins and fusion signature had 0.90 AUC for differentiating grade 1 from grade 2/3 tumors. Tumor texture analysis of CT and MRI images suggests entropy may be most useful in differentiating the different grades with 91% sensitivity and 85% specificity for distinguishing grade 1/2 NET from grade 3 NEC on CT and 83% sensitivity and 61% specificity for separating G2/3 from G1 tumors on MRI[25,26]. Whole tumor apparent diffusion coefficient histogram analysis may help predict the aggressiveness of pancreatic NET with kurtosis being the most useful marker[26]. While exciting, further studies are needed to understand the capabilities and role of radiomics in diagnosing, grading, and potentially prognosticating and guiding treatment.

Functional imaging

Somatostatin receptor imaging provides whole body imaging for NETs based on the wide expression of somatostatin receptors in most well-differentiated NETs. Nearly 70%-90% of gastrointestinal NETs and
50%-70% of pancreatic NETs express somatostatin receptors[27]. Quantification of somatostatin receptor expression can diagnose, stage, and assess response to therapy with somatostatin analogues (SSAs) or peptide receptor radionuclide therapy (PRRT)[15]. Gallium (Ga)-68 DOTA-peptides with PET/CT have replaced traditional OctreoScan [octreotide single-photon emission computed tomography (SPECT)/CT or 111-Inpentetreotide with SPECT] as the preferred modality due to its higher accuracy and shortened procedure time, which reduces radiation exposure (Figure 5)[28]. The sensitivity and specificity to detect NET is 92% and 95%, respectively[29]. Of note, there are different labeled peptides that can be used (DOTA-TOC, DOTA-NOC, and DOTA-TATE), but they are regarded as equally efficient[30]. One meta-analysis of 1561 patients found that using 68-DOTATATE changed management in one third of patients who previously had an OctreoScan[31]. Another study of 101 patients with well/moderately differentiated NETs showed that 68-DOTATATE imaging altered management in 36 patients, which included avoiding the need for biopsy (n = 4), initiating systemic therapy (n = 14), and altering operative plans in half of patients referred to surgery (n = 14)[32]. When available, this modality is preferred due to its high sensitivity and ability to influence management strategies in more than 70% of cases[33,34].

However, it should be noted that the accuracy of Ga-DOTAs-peptides PET-CT imaging declines as NET tumor grading increases due to decrease in somatostatin receptor expression[15]. As NETs lose somatostatin receptors, their cells increase glucose utilization[35]. In this context, 18F-fluorodeoxyglucose (18F-FDG) PET/CT may be the preferred method for identifying high grade lesions. In a large study with 104 biopsy proven NETs where both Ga-DOTATATE and 18F-FDG PET/CT were performed, 18F-FDG PET/CT was most useful in changing management of G3 tumors while not helpful for G1 tumors[36]. Therefore, these authors suggested only limited use of 18F-FDG PET/CT for tumors with Ki-67 ≤ 12%. Ga-DOTATATE and 18F-FDG PET/CT may be complementary imaging modalities. Other studies have suggested this as well with FDG PET-CT being 100% sensitive for identifying poorly differentiated G3 tumors while Ga-DOTATATE had 83% sensitivity for well-differentiated G2/G3 tumors[37]. A retrospective study of pathology-proven NENs demonstrated increased sensitivity (94%) for diagnosing NENs when both tracers were used compared to either alone (Ga-DOTATATE 63.8% and 18F-FDG 74.7%)[37]. Ki-67 index also negatively correlated with Ga-DOTATATE while positively correlated with 18F-FDG. Another group developed a NETPET grade from 0 to 5: P0 is negative for both 18F-FDG and 68Ga-DOTA-peptide scans, P1 is 68Ga-DOTA scan positive and 18F-FDG negative, P2-4 are positive for both with varying intensity of uptake, P5 is 18F-FDG positive and 68Ga-DOTA scan negative. This grading system correlated with tumor grade and survival with P5 having lowest median overall survival (11 mo)[38]. NETPET may allow selection of patients for PRRT which relies on the presence of somatostatin receptors to uptake therapeutic radionuclide into the NET cells. Patients with significant 18F-FDG positivity and 68Ga-DOTA negative disease may not respond well to PRRT alone and likely would benefit greater from systemic chemotherapy.

64Cu-DOTA is a new tracer with longer half-life and potentially superior spatial resolution compared to 68Ga[39]. The longer half-life (12.7 h vs 1.1 h) would potentially allow 64Cu-DOTA to be used more routinely and readily compared with 68Ga-DOTA. In 59 patients who underwent both 64Cu-DOTATATE and 68Ga-DOTATOC PET/CT, more patients had more lesions detected using 64Cu-DOTA than with 68Ga-DOTA (13 vs 3, respectively, P = 0.013)[40]. A phase III US study confirmed the safety and high accuracy of 64Cu-DOTA PET/CT[41].

18F (fluoro-dihydroxyphenylalanine)-DOPA is another radiopharmaceutical that has high sensitivity of 97% and specificity of 90% for small intestinal NETs, and alters management in 50% of small intestinal NETs[42]. In a comparative prospective study, 18F-DOPA outperformed combined CT and somatostatin-receptor scintigraphy imaging in localizing low grade small intestinal NETs[43]. However, other studies have suggested 68Ga-DOTA is superior to 18F-DOPA for detecting well-differentiated
NETs, including small intestinal NETs. F-DOPA is not readily available in Western countries, but may be complementary in the evaluation of small intestinal NETs.[39,44]

Insulinomas are notoriously difficult to detect using morphological and somatostatin receptor imaging. Because they over-express glucagon-like peptide-1-receptors (GLP-1R), these offer targets for PET-based imaging.[39]. 68Ga-DOTA-exendin-4 is a PET agent targeting GLP-1R. In a prospective randomized crossover study of 52 patients with suspected insulinoma, patients underwent 68Ga-DOTA-exendin-4 PET/CT, SPECT/CT and MRI with 68Ga-DOTA-exendin-4 imaging being more accurate than MRI for detecting insulinomas (93.9% and 67.6%, respectively).[45]

There is little literature on the value of PET-MRI, however, one small study demonstrated comparable image quality between 68Ga-DOTA-TOC PET/CT with PET/MRI while another suggested more lesions were identified with PET/MRI[46,47]. Advantages of PET/MRI include use in patients with renal insufficiency and better detection of liver lesions.

Biomarkers
Functional NETs secrete hormones that lead to various clinical symptoms and syndromes. These hormone levels should only be checked in patients with clinical symptoms and syndromes suggestive of a functional NET. Hormone levels may be followed in patients with functional pancreatic NETs to monitor response to treatment and recurrence[48].

Carcinoid syndrome may occur with metastatic NETs, typically from the small intestine. Twenty four hours measurement of urinary 5-hydroxyindoleacetic acid (5-HIAA), an end product of serotonin metabolism, has a specificity and sensitivity of over 90%.[49]. Patients should avoid tryptophan-rich foods and certain medications for several days before urine collection. Urinary 5-HIAA may also help predict patients at risk for carcinoid heart disease and carcinoid crisis during surgery as well as those who may respond to SSAs and PRRT[50]. If urine collection is difficult, plasma testing may be more convenient. Compared to urinary measurements, plasma 5-HIAA has a sensitivity and specificity of 89% and 97%, respectively, in diagnosing carcinoid patients[51]. Its widespread use is limited by institutional preferences and lack of validation in clinical studies.

Nonhormonal secretory products are also produced by both functional and nonfunctional NETs and can serve as biomarkers. Chromogranin A, a nonhormonal serum glycoprotein, is the main biochemical marker. However, its use has been deemphasized with the National Comprehensive Cancer Network and North American Neuroendocrine Tumor Society (NANET) not recommending its routine use due to limitations in accuracy, lack of standardization across laboratories (differing assays and isoforms), and unclear added value beyond imaging findings[48,52,53]. It should be measured fasting and at least 2 wk after discontinuation of proton pump inhibitors[54]. Sensitivity is lower in localized disease[35], and chromogranin A levels may drop with use of SSAs due to decreased production of hormones from cells rather than reduction in tumor burden[56].

Consequently, other biomarkers have been investigated. Genetic mutations in DAXX and ATRX expression (which interact with centromeric and telomeric regions) have recently been associated with well-differentiated NENs and poor survival in pancreatic NETs[57]. DNA hypermethylation has been associated with worse prognosis in pancreatic NETs. There is also interest in a new biomarker that measures cell-free DNA which circulates in the plasma following apoptosis, necrosis or active secretion, whereby it may have the potential to differentiate metastatic vs localized pancreatic NETs[57,58].

A novel liquid biopsy biomarker (NETest) measures 51 different RNA transcripts relevant to NET using quantitative real-time polymerase chain reaction[59]. Scores range from 0%-100% with 0-20 normal, 4-80 intermediate and ≥ 80 high activity. NETest has recently been reported with favorable
results compared to chromogranin A for monitoring treatment response following both surgery and PRRT\[60,61\]. In a cohort of 253 GEP-NENs, NETest out performed chromogranin A in terms of accuracy (99% vs 53%) and also proved reliable in correlating the grade, stage and progression of GEP-NENs\[62\]. Another prospective study confirmed high diagnostic accuracy (91%) of NETest, ability to differentiate metastatic from local disease, 91% concordance with CT/MRI/ Ga 68-DOTA peptide PET, correlation with curative vs palliative surgeries, and higher diagnostic accuracy compared with chromogranin A \[63\]. NETest predicted postoperative recurrence at postop day 30 with 94% accuracy while chromogranin A was not helpful\[64\]. No patients with R0 resection and normal NETest developed recurrence while all R1/R2 patients had elevated NETest. This would allow early identification of patients with residual disease postoperatively who need to be followed more intensely while those with R0 resection and normal NETest likely can have fewer follow-up imaging studies. These exciting results need further confirmation in larger studies, and the utility of using this blood test rather than imaging to adjust treatment in advanced disease requires study as well.

**Endoscopy**

For gastrointestinal NETs, endoscopy with biopsy should be performed to obtain pathological diagnosis \[20\]. Endoscopic imaging is insufficient for definitive diagnosis as differential diagnosis includes other subepithelial lesions, such as gastrointestinal stromal tumor especially in the stomach and duodenum and cysts and Brunner’s gland hyperplasia also in the duodenum. When imaging modalities fail to localize a small bowel tumor, video-capule endoscopy (VCE) and device-assisted enteroscopy (DBE) are often needed\[10\]. VCE has a diagnostic yield of 45% for detecting tumors in the small intestine\[65\]. A retrospective study conducted over a seven year period found that small bowel tumors were detected in 1.5% of patients undergoing VCE (with a mean number of 4.7 tests used prior to VCE)\[66\]. In a study of 390 patients with metastatic NETs, radiology failed to localize a primary tumor in 2.8% whereas VCE identified NETs in 8/10 patients, which were confirmed histologically. As such, VCE should be used in select patients to identify small intestine NETs. While more invasive, antegrade and retrograde DBE may serve as an adjunctive tool prior to surgery by providing a histologic diagnosis and allowing tattooing areas of interest for surgeons\[65\]. Its diagnostic yield for detecting small intestine NETs ranges from 33%-80%\[67,68\]. Multifocal small intestinal NETs occur in 20%-30% of patients. CT and MRI have low accuracy for detecting these, and while CT or MR enterography, VCE, and DBE improve detection, the gold standard remains digital palpation of the small bowel intraoperatively\[69\].

EUS is valuable for diagnosing pancreatic NETs and differentiating from pancreatic adenocarcinoma or metastatic disease with 87.2% sensitivity of 87.2% and 98% specificity (Figure 6)\[70\]. Mean detection rate of pancreatic NET for EUS is 90% while about 73% for both CT and MRI\[71\]. EUS identified pancreatic NET in 26% of cases where CT and other radiology studies including MRI and PET were negative\[72\]. EUS is particularly helpful for detecting small NETs < 10 mm, 68% of which were missed by CT\[73\]. EUS also provides more accurate size estimate than CT (11.2% vs 46.5% inaccurate, respectively). Therefore, in patients with suspected pancreatic NET and negative imaging, EUS should be performed.

A limitation of EUS sampling is inaccurate assessment of grade and Ki-67 index compared with surgical specimens. This discordance is accentuated in tumors > 2 cm because Ki-67 immunoreactivity can be focal and therefore, potentially missed by EUS sampling\[74\]. EUS-FNB may improve assessment of Ki-67 as well as diagnostic yield compared with EUS-FNA\[75,76\]. Diagnostic yield of EUS-FNA in cystic pancreatic NETs is lower at 73% compared with solid NETs although higher than mucinous cysts. Cystic pancreatic NETs may have thick wall with low carcinoembryonic antigen levels (< 5 ng/mL)\[77\].

Adjunctive EUS technologies include elastography and contrast harmonic EUS (CH-EUS). Elastography assesses the relative stiffness of tissue qualitatively and semi-quantitatively with strain elastography and more recently shear wave elastography. It may help differentiate pancreatic ductal adenocarcinoma from pancreatic NET, but was unable to distinguish NET from benign lesions in one study\[78\]. Another study suggested modest ability to diagnose malignant vs benign pancreatic NETs (67% sensitivity and 71% specificity)\[79\]. Further studies are needed with shear wave elastography, which may lead to improved results. CH-EUS uses intravenous microbubble-based contrast agents to assess microvasculature in lesions. With pancreatic NETs being hypervascular, they appear hyperenhancing on CH-EUS with sensitivity 79% and specificity 99%\[80\]. CH-EUS may be particularly helpful in assessing tumor grade as microvasculature density inversely correlates with grade. Therefore, higher grade tumors have more heterogeneous enhancement with 90% accuracy for predicting malignancy and > 95% negative predictive value for tumor aggressiveness\[81\]. Quantitative CH-EUS may allow accurate differentiation of G1/G2 pancreatic NET from G3 pancreatic NEC\[82\].

**MANAGEMENT**

The next sections will highlight updates and controversial areas needing further research for the various GEP-NETs.
Figure 6 Endoscopic ultrasound of pancreatic neuroendocrine tumor appearing well-defined and hypoechoic.

**Stomach**

Gastric NETs are typically diagnosed incidentally during endoscopy, and it is important to understand the subtypes of gastric NETs and their corresponding treatment recommendations (Table 2). Metastases occur in less than 10% of type I gastric NETs ≤ 2 cm (Figure 7), but in nearly 20% greater than 2 cm\[^{83, 84}\]. A long-term study of small (<1 cm) type I gastric NETs followed endoscopically over an average of 7 years found that none developed advanced disease or significant growth of the tumor\[^{85}\]. For larger lesions, EUS should be performed to assess depth of invasion and presence of lymph node metastases before performing endoscopic or surgical resection. Regarding endoscopic resection, endoscopic mucosal resection (EMR) or endoscopic submucosal dissection (ESD) can be considered although ESD should be reserved for larger lesions with superficial submucosal invasion\[^{86}\]. A retrospective study of 87 Lesions less than 1 cm resected by ESD or EMR found that while complete resection rates trended higher with ESD (94.9% vs 83.3%, \(P = 0.174\)), it was associated with increased procedural time (26.1 min vs 9.5 min) and a tendency towards higher complications (15% vs 6%, \(P = 0.28\))\[^{87}\]. For rare type 1 gastric NETs with invasive disease, regional metastases, or grade 3 Lesions, surgery may be considered\[^{88}\]. A Japanese multi-center study of 144 Lesions (90 G1 and 54 G2) with median size 8 mm compared surgical (81 patients) and endoscopic (63 patients) resection outcomes during long-term follow-up\[^{93}\]. Patients undergoing endoscopic resection had smaller lesions confined to the mucosa or submucosa, and 24% of these patients needed subsequent surgical resection. Overall, 5-year survival was similar for both groups, and in the endoscopic resection alone cohort, only one patient developed recurrence with no mortality over median 32-mo follow-up. Another recent study comparing 45 patients undergoing surgical or endoscopic resection found that tumor size greater than 1 cm was associated with lymph node metastases\[^{94}\]. In a cohort of 50 patients undergoing endoscopic resection (41 EMR and 9 ESD) with a median follow up of 46 mo, mean size was 10 mm with nonsignificant trend towards larger lesions resected with ESD (14.2 mm vs 9.3 mm) and greater lymphovascular invasion in ESD patients (22.2% vs 2.4%). However, there was no evidence of tumor recurrence in either group. Of note, all lesions were no deeper than the submucosa layer and well-differentiated\[^{95}\]. Given the more aggressive biology of type III gastric NETs, ESD may be favored over EMR although further study is needed. The resection approach should be carefully tailored to a patient’s tumor size, depth of invasion, grade and presence of regional metastases\[^{71}\].

**Duodenum**

Table 3 summarizes evaluation and management of small intestinal (duodenal, ampullary, and jejuno-ileal) NETs\[^{96, 97}\]. Nearly 90% of duodenal NETs are non-functional, well-differentiated and incidentally discovered as small, polypoid lesions in the first and second portion of the duodenum (Figure 8)\[^{88}\]. For small duodenal NETs undergoing EMR, the optimal EMR technique remains unclear (standard, underwater, ligation, ligation without resection) with the main complications being bleeding in up to 20% of patients and perforation. For lesions greater than 2 cm without evidence of metastatic
Table 2 Gastric neuroendocrine tumors[88,90,91]

| Type | Proportion of gastric neuroendocrine tumors | Associated conditions | Location | Endoscopic findings | Gastrin level | Prognosis | Metastasis | Evaluation | Treatment | Surveillance |
|------|---------------------------------------------|-----------------------|----------|---------------------|--------------|-----------|-----------|------------|-----------|--------------|
| 1    | 70%-80%                                     | Atrophic gastritis    | Gastric fundus and body | Multiple, small polyps | Increased   | Excellent | 10%-20%   | Gastric pH, gastrin, EUS 1-2 cm lesions | Endoscopic resection for larger lesions and surveillance for lesions < 2 cm | EGD every year |
| 2    | 5%                                         | Zollinger-Ellison and MEN-1 | Gastric fundus and body | Multiple, small polyps | Increased   | Good      | 10%-30%   | Gastric pH, gastrin, EUS 1-2 cm lesions | Similar to type 1 | EGD every 6-12 mo, abdominal imaging every year |
| 3    | 15%-25%                                     | Sporadic              | Antrum   | Solitary, larger     | Decreased   | Poor      | 30%-80%   | Gastric pH, gastrin, EUS, abdominal imaging | Surgery, endoscopic resection for superficial, well-differentiated lesions < 1 cm | EGD every 6-12 mo, abdominal imaging every 3 mo |
| 4    | Very rare                                   | Sporadic              | Anywhere | Solitary, larger     | Normal      | Very poor | 80%-100%  | Gastric pH, gastrin, EUS, abdominal imaging | Surgery for local disease, systemic chemotherapy for metastatic | |

Table 3 Small intestinal neuroendocrine tumors[96,97,101,102,104,108,109]

| Duodenal | Ampullary | Jejuno-ileal |
|----------|-----------|-------------|
| Epidemiology | 2%-3% GEP-NETs | 0.3%-1% GEP-NETs | 1.2 cases/100000 incidence quadrupled over past 30 yr |
| Evaluation | > 2 cm: CT and EUS | CT, EUS | Chromogranin A, urine 5-HIAA, CT/MRI, gallium-DOTATATE PET CT, colonoscopy into terminal ileum |
| 5-yr survival | No metastases: 80%-95%; Regional metastases: 65%-75%; Zollinger-Ellison or MEN-1: > 90% | 59% | Local disease: 80%-100%; Regional disease: 70%-80%; Distant metastases: 35%-80% |
| Treatment | < 1 cm: Endoscopic resection; 1-2 cm: Endoscopic or surgical resection; > 2 cm: EMD or ESD, surgical resection for regional disease | < 2 cm superficial without metastases: Pancreatoduodenectomy or consider endoscopic ampullectomy; > 2 cm: Pancreatoduodenectomy | Surgery; Carcinoid syndrome: Long-acting SSA (octreotide LAR 20-30 mg IM) |
| Surveillance | EGD at least every 2 yr | EGD at 1-2 yr interval | NANETS: Curative surgery-CT every 3-6 mo then 6-12 mo for 7 yr; Advanced disease- CT every 6 mo; ENETS: Curative surgery: Chromogranin A, urine 5-HIAA, CT every 6-12 mo; Slow-growing treated without curative intent: every 3-6 mo |

EUS: Endoscopic ultrasound; EGD: Esophagogastroduodenoscopy; MEN1: Multiple endocrine neoplasia type 1.

disease, ESD should be reserved for larger lesions because perforation and bleeding appear higher than with EMR or ESD[20,86,98]. The optimal strategy for duodenal NETS between 1 and 2 cm remains unclear. A multicenter study of 60 patients found that lesions larger than 11 mm had significantly higher rates of lymphovascular invasion and incomplete endoscopic resection with none having complete pathologic resection compared with smaller lesions[99]. Therefore, the authors suggested surgical resection for lesions larger than 11 mm. However, a recent study suggested EMR is efficacious and safe for 1-2 cm lesions without regional or distant metastases with similar overall survival to surgical resection during median 56-mo follow-up[100]. As expected, patients undergoing EMR were older (72.6 years vs 59.2 years,
respectively) with more node negative disease (89.5% vs 50%, respectively). The decision to pursue endoscopic or surgical resection should be considered based on local expertise and the individual case.

Ampullary NETs (Table 3) appear different in nature than non-ampullary duodenal NETs, and are often more advanced at presentation (G3 in 17% vs 2% for duodenal NETs) with higher incidence of lymph node metastasis (34% vs 10% for duodenal NETs)[101,102]. In a large pathology series of 203 duodenal NETs, most of the 27 NECs occurred in the ampullary region[103]. While pancreaticoduodenectomy is recommended regardless of size, its morbidity and mortality make endoscopic resection an attractive option. Small ampullary NETs less than 2 cm without muscularis propria invasion or lymph node metastases were completely resected endoscopically in one small study, and 71% had no recurrence during median 56 mo follow-up[104]. Further studies are needed to understand which patients may be managed with endoscopic ampullectomy.

Jejuno-ileal tumors
The true incidence of jejuno-ileal NETs (Table 3) likely remains underappreciated as in autopsy studies, the incidence is much higher (1.2 cases per 100000) than in population studies (0.67 cases per 100000)[96, 105]. This implies that many early jejuno-ileal NETs remain undiagnosed[106]. Early diagnosis remains challenging as most patients are asymptomatic or have nonspecific symptoms, and carcinoid syndrome occurs in only 20%-30% of patients with metastatic disease[106]. Unlike gastric, duodenal and colorectal NETs, incidental diagnosis of jejuno-ileal NETs is unlikely with 89% found in the ileum[105,107].

Segmental resection and wide lymphadenectomy is the definitive approach for jejuno-ileal NETs with localized and regional metastatic disease[108]. Intraoperative exploration with small bowel palpation is recommended as up to 70% of pre-operative imaging may understage tumors[109]. This is likely due to limitations of diagnostic imaging including VCE and DBE, which may miss small, multifocal lesions[52, 110]. For patients with distant metastatic disease, surgical resection of the primary tumor may still be considered to alleviate symptoms resulting from the lesion (for example, obstructive symptoms or bleeding), to achieve potential cure if the distant metastases may be completely resected as well, and to improve outcome although data on this is mixed and further study is needed[106].

Appendiceal tumors
Traditionally appendiceal NETs were the most common appendiceal tumors although recent data
suggests mucinous neoplasms may have surpassed them[111,112]. Most present incidentally and are asymptomatic as the majority are located in the distal one-third of the appendix rather than the base. Because risk of metastases correlates with tumor size, recommendations for evaluation and management vary depending on the size (Tables 4 and 5). However, a study of 418 patients noted that risk of nodal metastases was affected by age, depth of invasion, extent of surgery as well as tumor size with 0.89 area under the curve[113]. Another study analyzing 435 patients found that tumor size > 1.5 cm, G2 grade, lymphovascular infiltration, and mesoappendiceal invasion were associated with nodal metastasis[114]. Therefore, some guidelines suggest right hemicolec tomy for 1-2 cm tumors with any of these high-risk features. However, in a study of 916 patients with 1-2 cm NETs, right hemicolec tomy was not associated with increased survival despite being associated with larger and higher stage tumors (hazard ratio = 1.14, \( P = 0.72 \))[115]. The most appropriate surgical approach for appendiceal NETs especially between 1-2 cm remains unclear as well as the definitive triggers to send a patient for completion right hemicolec tomy.

Colonic neuroendocrine tumors

With increased colon cancer screening, the incidence of colonic NETs has increased dramatically from 0.02 to 0.2 per 100000 people in the United States between 1973 to 2004[116]. The majority are high-grade, poorly differentiated lesions that typically occur in the right colon (70%), especially in the cecum [117,118]. Well-differentiated colonic NETs have significantly worse prognosis than well-differentiated NETs anywhere else in the GI tract. A recent study using the SEER database developed a novel nomogram to predict survival incorporating patient’s age ≥ 68 years, sex, tumor size, grade, chemotherapy, N stage and M stage. This outperformed the traditional TNM staging system in predicting overall survival[119].

With aggressive behavior and poor survival outcomes, colonic NETs require multidisciplinary care (Table 5). Tumors < 2 cm may be considered for endoscopic resection, however surgery is required for incomplete resection or high-grade pathology[116]. Very little data exists about the efficacy and safety of ESD with one study including only 6 non-rectal, colonic NETs. This study demonstrated that non-rectal NETs were significantly associated with risk of non-R0 resection and while complications were higher, this was not significant compared with ESD of rectal NETs[120]. On the other end of the spectrum in patients with metastatic disease, chemotherapy can also be utilized[117]. Survival improved with chemotherapy alone, surgery alone and even more with the combination of surgery and chemotherapy (5-year survival 37% for combination vs 32% surgery alone, \( P < 0.001 \))[121]. However, other studies noted that surgery did not provide significant survival benefit in localized and metastatic disease[122, 123]. Further study is necessary to understand the optimal treatment combination as well as role of immunotherapy.

Rectal neuroendocrine tumors

Similar to colonic NETs, rectal NETs have been increasingly diagnosed with improved screening colonoscopy rates, experiencing a 10-fold rise in incidence over the past 30 years[124,125]. They are more common in women in the United States although in Korea men are more likely to have rectal NETs. In the United States, Asian and African American patients have higher incidence than Caucasians [126]. The majority (70%-88%) of rectal NETs are small (< 1 cm) and localized at the time of diagnosis [124,127]. Lymph node metastasis occurs in about 2% and distant metastases in about 8% of rectal NETs at diagnosis. Tumor size, depth of invasion, grade and lymphovascular invasion all affect prognosis. Regarding tumor size, it appears to correlate with metastasis at the time of diagnosis (3%, 66%, and 73% metastases with tumor size ≤ 1 cm, 1-1.9 cm, and ≥ 2 cm, respectively)[128]. A study using the SEER database of 788 patients with T1 rectal NETs noted tumor size and submucosal invasion were predictive of metastasis, and no tumors ≤ 19 mm without submucosal invasion had metastases[129]. At diagnosis, 1.5% of patients had metastases with 1.1% in tumors ≤ 10 mm and 6.6% in NETs 11-19 mm.

Usually, rectal NETs are not recognized before polypectomy by the endoscopist and only later discovered when pathology returns. If the endoscopist is suspicious of a rectal NET during the procedure, biopsies can be obtained with photograph documentation and tattoo adjacent to the lesion. In terms of treatment, endoscopic resection should be performed for lesions smaller than 1 cm without invasion beyond the submucosa. Options include EMR, EMR band ligation, and ESD; however, given the greater procedure time and complications with ESD, EMR or EMR band ligation are preferred. A prospective study comparing EMR band ligation (n = 53) to ESD (n = 24) in lesions ≤ 10 mm demonstrated the superiority of EMR band ligation with higher complete resection rates (100% vs 54.2%, \( P = 0.00 \))[130]. In addition to 100% negative margins, EMR band ligation was associated with shorter procedure times (5.3 vs 17.9 min, \( P = 0.00 \)). Similarly, a retrospective study of 82 tumors < 10 mm reported higher complete resection rates with EMR band ligation compared to ESD (95% and 75%, \( P = 0.025 \)) with shorter procedure times[131]. A recent retrospective comparative study of underwater EMR (n = 36) to ESD (n = 79) found no difference in achieving R0 resection for lesions ≤ 10 mm[132]. Yet underwater EMR was associated with a significantly shorter procedure time (5.8 min vs 26.6 min, \( P = 0.0001 \)) and no adverse events while there were two cases of delayed bleeding and minor perforation in the ESD group. Therefore, for small rectal NETs < 1 cm, EMR band ligation is the endoscopic method of choice while underwater EMR may be considered as well.
If incomplete resection occurs, then salvage therapy with ESD or transanal endoscopic microsurgery should be pursued to minimize recurrence[133,134]. Optimal management for rectal NETs 1-2 cm remains uncertain. NANETS recommends transanal excision although noted this could be considered after endoscopic resection if that resulted in positive margins. ESD may have a role and may be preferred to cap-assisted EMR as higher complete resection (100% vs 70%) and lower recurrence (0% vs 17%) was achieved with ESD[135]. However, ESD may not be the ideal approach in patients with lymphovascular invasion, grade 2, and/or positive margins as distant metastasis occurred in 2.5% following ESD of small (< 2 cm) rectal NETs[120]. With advanced metastatic disease, palliative surgery and systemic therapies should be considered through a multidisciplinary approach considering availability of local resources.

**Pancreas**

Pancreatic NETs make up 16% of GEP-NETs with annual incidence of 0.5 per 100000 people[6,9]. The majority are sporadic and malignant with metastatic disease present in 60% of patients at the time of diagnosis (Table 6)[96,136]. If there are no distant metastases or if the metastatic disease is resectable (for example, isolated hepatic metastases), surgery is the primary method of treatment for all functioning pancreatic NETS, irrespective of size (Figure 9). It is also recommended for localized (confined to the pancreas and regional lymph nodes) nonfunctioning pancreatic NETS greater than 2 cm. Lesions less than 1 cm can safely undergo surveillance in the absence of symptoms and pancreatic duct dilation [137]. In a cohort comparing nonoperative and operative management of nonfunctioning NETS less than 1 cm, there was no difference in mortality or disease progression over median 45-mo follow up with surgical patients experiencing relatively high 46% rate of complications postoperatively[138].

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| Tumor size | Nodal metastases | Distant metastases |
|------------|-----------------|--------------------|
| ≤ 1 cm     | 0%              | 0%                 |
| 1-2 cm     | 7.5%            | 4%                 |
| ≥ 2 cm     | 33%             | 12%                |

Table 4 Risk of metastases by tumor size in appendiceal neuroendocrine tumors[169]

| Tumor size | Nodal metastases | Distant metastases |
|------------|-----------------|--------------------|
| ≤ 2 cm     | 0%              | 0%                 |
| 2-3 cm     | 12%             | 29%                |
| ≥ 3 cm     | 39%             | 14%                |

Table 5 Colorectal neuroendocrine tumors[103,112,114,121,124,126,170-173]

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1Incomplete resection: Positive margin and/or lymph nodes.

2High-risk features: Large tumor size, G2, lymphovascular invasion, mesoappendiceal invasion.

NET: Neuroendocrine tumor; EUS: Endoscopic ultrasound; EGD: Esophagogastroduodenoscopy; GEP-NETs: Gastroenteropancreatic neuroendocrine neoplasms; PET: Positron emission tomography; CT: Computed tomography; MRI: Magnetic resonance imaging; HIAA: Hydroxyindoleacetic acid.
Table 6 Diagnosing pancreatic neuroendocrine tumors[136,174]

| Diagnostic evaluation |
|-----------------------|
| All pancreatic NET    | Multiphasic CT/MRI |
|                       | If results impact management, gallium DOTATATE PET CTEUS with biopsy |
| Insulinoma            | 72 h fast test: Hypoglycemia with elevated insulin |
|                       | Oral glucose tolerance test: May be necessary in minority with only postprandial hypoglycemia |
| Gastrinoma            | Fasting gastrin 10 times upper limit of normal + gastric pH < 2 |
|                       | If gastrin less elevated + gastric pH < 2, measure BAO with secretin test |
|                       | BAO > 15 mEq/h or serum gastrin increase > 120 pg/mL |
| Glucagonoma           | Fasting serum glucagon > 500 pg/mL |
| Somatostatinoma       | Fasting plasma somatostatin > 30 pg/mL |
| VIPoma                | Large volume diarrhea + serum VIP > 75 pg/mL |

NET: Neuroendocrine tumor; CT: Computed tomography; MRI: Magnetic resonance imaging; PET: Positron emission tomography; EUS: Endoscopic ultrasound; BAO: Basal acid output.

Figure 9 Treatment algorithm for pancreatic neuroendocrine tumors. NET: Neuroendocrine tumor; SSA: Somatostatin analogue; PRRT: Peptide receptor radionuclide therapy.

However, observation vs surgery for nonfunctioning pancreatic NETs measuring between 1-2 cm remains controversial. Several studies have supported observation, as smaller tumor size correlates with lower malignancy potential[138-141]. On the other hand, other studies have suggested surgery is superior[42-145]. One study that followed 39 resected lesions less than 2 cm for a median 34.2 mo found that 7.7% developed late metastasis or recurrence[143]. Two other comparative studies supported surgical resection for pancreatic NETs less than 2 cm, as five-year overall survival rates were greater than the observation group (82.2%-92.8% vs 34.3%-67.4%, respectively)[142,145]. Regardless of tumor
size, if surgery is pursued, follow up with cross-sectional imaging is recommended annually for the first three years then every two years for a total of 10 years[146].

EUS-guided radiofrequency ablation (RFA) has recently been studied as a potentially safe and minimally invasive treatment option. Through the use of targeted electromagnetic energy and alternating high-frequency currents, EUS-RFA induces coagulative necrosis, fibrotic changes, and a delayed immune response to the pancreatic tissue of interest[147]. Only a few human studies have investigated treatment outcomes, but have demonstrated feasible and promising results[148,149]. In one study, 18 patients (including seven insulinomas and 11 non-functioning lesions) with a mean diameter of 1.4 cm demonstrated no signs of recurrence during mean follow-up of 8.7 mo[149]. Furthermore, all seven patients with insulinomas had normalization of glucose within 24 h of EUS-RFA. A prospective multicenter study of 14 pancreatic NETs (G1 lesions with median size 1.3 cm) found that 12 (85.7%) lesions completely resolved at 12 mo follow up[148]. The other two lesions were considered treatment failures with one increasing by 3 mm and the other remaining unchanged in size. A recent video case report used EUS-guided microwave ablation to safely and effectively treat a symptomatic inoperable pancreatic neck NET (35 × 32 mm) invading the splenic artery without any complications[150]. Further prospective and longer-term studies are needed to determine how this technology may improve patient outcomes and how it fits into the treatment algorithm.

For patients with isolated liver metastases, optimal management remains uncertain in the absence of randomized controlled studies and ranges from surgical resection of all visible metastatic disease to local therapy with ablation. Candidates for resection of liver metastases include those with isolated unilobar disease, preserved liver function and well-differentiated pathology[151]. However, even patients with bilobar disease could undergo multiple wedge resections and/or hepatectomy provided at least 20 percent of the total liver volume remains preserved. Five-year survival rates ranging from 85% to 90% have been reported with selected patients undergoing curative resection[152,153]. However, recurrence rates are as high as 54% despite negative margins, which implies that preoperative imaging misses small metastatic disease[154].

Whether the primary tumor should be resected as well in these patients remains debated although retrospective studies suggest improved survival with this approach[155].

Ablation is mainly effective for small (< 3 cm) lesions and includes RFA, cryoablation and microwave ablation with a more favorable morbidity profile than surgery or hepatic arterial embolization. The optimal use of this technique remains unclear although it is often used as an adjunct to surgical resection especially when complete resection of multifocal or bilateral disease is not feasible or in patients who have already undergone hepatic resection. Comparative studies remain limited with one nonrandomized study suggesting high overall 5-year survival (84%) following RFA compared to surgery (90%)[152]. If RFA is contraindicated (especially for lesions near the liver surface or adjacent to vital structure) or technically not possible, cryoablation can be used[156]. While cryoablation is relatively underutilized, a small case series demonstrated 77.8% complete response and 22.2% partial response in 9 patients undergoing ablation with a median follow of 7 mo[157]. Cryoablation may be considered in technically challenging tumor locations. Further studies are needed to delineate its role relative to other ablative techniques.

For unresectable liver disease in symptomatic patients, hepatic arterial embolization is suggested for palliation as an alternative to medical treatment alone. Techniques include injection of different substances [bland embolization (gel foam powder), chemoembolization (chemotherapy), radioembolization (radioactive isotopes)]. In liver predominate disease, chemoembolization is associated with a tumor response rate over 50%, which appears comparable to the other techniques[158]. A randomized trial is underway to compare liver progression-free survival and complications of these three techniques.

For unresectable widespread disease, treatment options include systematic therapy with SSAs to treat symptoms and control disease, chemotherapy, molecular targeted therapy, PRRT, and immunotherapy. SSAs suppress hormone release in pancreatic NETs by binding somatostatin receptors, which prevents the release of hormonal peptides, and is thus most helpful for VIPomas, glucagonomas, and somatostatinomas and less helpful for insulinomas and gastrinomas. When used to control disease by exploiting the ability of SSAs to decrease proliferation in nonfunctioning NETs, SSAs are administered to patients with high tumor burden[159]. The CLARINET study, a randomized, double blind placebo trial, provided support for lanreotide in preventing disease progression in advanced well to moderately differentiated nonfunctioning pancreatic NETs (prolonged progression-free survival 65% vs 33% at 24 mo)[160]. Short-acting octreotide may be used and if effective, changed to long-acting depot with monthly injections.

Chemotherapy is particularly helpful in aggressive disease with rapidly growing metastases[10]. Compared to temozolomide, the use of combination chemotherapy with capecitabine and temozolomide (CAPTEM) demonstrated high response, progression free survival, and manageable toxicity in patients with well-differentiated intermediate to high grade pancreatic NETs[161,162]. Given its favorable toxicity profile as an oral regimen, CAPTEM is typically favored over streptozocin-containing regimens. Expression of methylguanine DNA methyltransferase (MGMT) may predict response to alkylating chemotherapeutics as studies suggested that patients without MGMT had better response[163]. However, prospective studies are necessary.
Molecular targeted therapy has a role in patients with disease progression on SSAs by inhibiting the mammalian target of rapamycin or tyrosine kinase with everolimus and sunitinib, respectively [164]. Compared to placebo, everolimus was able to prolong progression free survival (11 mo vs 4.6 mo) in a cohort of 410 patients with advanced, progressive low and intermediate grade pancreatic NETs [165]. Sunitinib has also demonstrated safe and reliable results in progressive, well-differentiated pancreatic NETs where progression free survival was double placebo (11.4 mo vs 5.5 mo) [161]. with a response rate of 24.5% [166]. Other promising agents include tyrosine kinase inhibitors sorafenib, pazopanib, vascular endothelial growth factor receptor inhibitor cabozantinib and lenvatinib, which all require further prospective study.

PRRT uses radiolabeled SSAs (90Yttrium or 177Lutetium) to bind somatostatin receptors as a means to emit localized radiation in advanced pancreatic NETs [164]. Therefore, it is an option in patients who have progressed through SSAs. A phase III trial compared 177Lu-Dotatate (116 patients) to long acting octreotide (113 patients) and found longer progression free survival (65.2% vs 10.8%) and higher response rates (18% vs 3%) with 177Lu-Dotatate [167]. A larger study of 610 patients (which included bronchial NETs) also reported a favorable survival and response rate, especially in the pancreatic NET group [168]. Despite encouraging results, concern remains over potential long-term toxicity including acute leukemia (0.7%) and myelodysplastic syndrome (1.5%) [168]. As such, risk and benefits of treatment should be carefully discussed with patients before embarking on PRRT. Further studies are needed to understand the role and safety of PRRT as well as whether combination therapy with SSAs is more efficacious.

Although immunotherapy has revolutionized oncology, its utility in treating pancreatic NETs remains unclear. Early trials evaluating anti-programmed cell death 1 antibodies including spartalizumab and pembrolizumab have not been encouraging with minimal response in pancreatic NETs. Further studies are certainly needed.

CONCLUSION

GEP-NENs represent a complex and diverse physiologic and pathologic spectrum of neoplasms with varying disease activity that benefit from multidisciplinary care. With advancements in functional imaging, serum biomarkers, and endoscopic techniques for diagnosis including EUS as well as therapy with EMR, ESD and EUS-RFA, identification and management of these protean lesions continue to improve and allow for tailored treatment plans based on prognostic information and location throughout the gastrointestinal tract.

FOOTNOTES

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