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Gastroenteropancreatic Neuroendocrine Tumors

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Neuroendocrine tumors (NETs) represent a heterogeneous group of neoplasms with diverse biological and clinical behavior, and gastroenteropancreatic neuroendocrine tumors (GEP-NETs) are the most common subtype. This review provides an overview of GEP-NETs, with a focus on incidence trends, pathologic classification, diagnostic strategies, therapeutic advances, and the role of endoscopy in diagnosis and management of GEP-NETs. Incidence rates of GEP-NETs have significantly increased over recent decades, largely due to improved diagnostic modalities and increased use of endoscopy, although environmental factors may be at play as well. Pathologic grading and classification, based on the 2022 World Health Organization criteria, remain essential in defining prognosis and therapeutic options, and advanced imaging modalities like somatostatin receptor positron emission tomography scans enable precise localization and staging. Therapeutic approaches vary by tumor grade, stage, and localization, from an increasing role for endoscopic management of indolent tumors to surgical resection for certain higher-risk subtypes and for resectable metastatic disease. Novel treatments, including somatostatin analogs, radioligand therapy, mammalian target of rapamycin inhibitors, and antiangiogenic agents, have shown significant efficacy in advanced and metastatic disease. Future research is needed to identify molecular markers to refine diagnostic accuracy and personalize treatment strategies, thereby improving long-term outcomes for GEP-NET patients. Additionally, research is needed to better define GEP-NET subtypes that are appropriate for endoscopic therapy as well as to understand long-term outcomes after endoscopic resection. Given the important role that endoscopy has in the diagnosis and management of GEP-NETs, increased recognition of and knowledge about these tumors is critical for the gastroenterology community.

Keywords: Endoscopic Management; Recommendations; Gastroenteropancreatic Neuroendocrine Tumors; Neuroendocrine Tumors.

Neuroendocrine tumors (NETs) along with neuroendocrine carcinomas (NECs) are subtypes of the broader category of heterogenous tumors termed neuroendocrine neoplasms (NENs), originating from neuroendocrine cells found throughout the body. NETs are more common and typically more indolent than NECs, which usually demonstrate aggressive behavior.[1] Among NETs, gastroenteropancreatic neuroendocrine tumors (GEP-NETs) encompass a diverse group of tumors that occur across multiple locations in the gastrointestinal (GI) tract including the stomach, pancreas, small intestine, appendix, and colorectum. Differences in hormone production lead some GEP-NETs to be "functional" (ie, hormone producing with associated symptomatology) whereas others remain "nonfunctional."[2,3]

GEP-NETs are unique tumors that are increasingly encountered (see Epidemiology) in gastroenterology practice, which require heightened awareness by the gastroenterologist during endoscopic procedures. Unlike classic epithelial-derived GI tumors, GI tract NETs are typically subepithelial, which can make complete endoscopic resection more challenging. GEP-NETs are also heterogeneous lesions with, for example, management of gastric, rectal, and pancreatic NETs frequently dictated by size, although size does not correlate with behavior of more aggressive small intestinal NETs. Furthermore, most GEP-NETs overexpress somatostatin receptors (SSTR), which enables novel imaging and treatment options that take advantage of this characteristic. However, like other GI tumors, early diagnosis and treatment are important to improving long-term outcomes of GEP-NETs.[4] This review will focus on GEP-NETs and the critical role that gastroenterologists and endoscopic techniques play in their diagnosis and management. In-depth review of NECs and NETs outside the GI tract is beyond the scope of this manuscript and have been covered elsewhere.[5–7]

Epidemiology

Incidence of NETs has risen worldwide with a more than 6-fold increase in the United States between 1973 and 2012.[2,3] Increases in NET incidence were highest within the GI tract with incidence rate of 3.56 cases per 100,000

Abbreviations used in this paper: **CgA, chromogranin-A; CS, carcinoid syndrome; CT, computed tomography; dNET, duodenal neuroendocrine tumor; EFTR, endoscopic full-thickness resection; EMR, endoscopic mucosal resection; ENETS, European Neuroendocrine Tumor Society; ESD, endoscopic submucosal dissection; EUS, endoscopic ultrasound; FNA, fine-needle aspiration; FNB, fine-needle biopsy; GI, gastrointestinal; GEP-NET, gastroenteropancreatic neuroendocrine tumor; gNET, gastric neuroendocrine tumor; LAR, long-acting repeatable; MEN1, multiple endocrine neoplasia type 1; MRI, magnetic resonance imaging; NEC, neuroendocrine carcinoma; NEN, neuroendocrine neoplasm; NET, neuroendocrine tumor; OS, overall survival; PET, positron emission tomography; PFS, progression-free survival; pNET, pancreatic neuroendocrine tumor; PPI, proton pump inhibitor; RFA, radiofrequency ablation; RLT, radioligand therapy; rNET, rectal neuroendocrine tumor; siNET, small intestinal neuroendocrine tumor; SSA, somatostatin analogue; SSTR, somatostatin receptor; ZES, Zollinger-Ellison Syndrome.**

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followed by lung NETs with incidence rate of 1.49 cases per 100,000.[3] Among GEP-NETs, incidence has increased with each decade since the 1970s.[3,8] Furthermore, prevalence of NETs has also increased, with 20-year limited-duration prevalence increasing 8-fold between 1993 and 2012, and prevalence rate of nearly 0.05% (1 in 2000) in 2012 in the United States.[4] The highest prevalence amongst GEP-NETs are rectal NETs (rNETs) (approximately 1 in 7000) and small intestinal NETs (siNETs) (approximately 1 in 11,000).[3] Race may affect GEP-NET incidence, with Black individuals having higher incidence compared with non-Hispanic Whites and Hispanics in the United States.[9]

Of GEP-NETs, siNETs are most common followed by rNETs and pancreatic NETs (pNETs) (Figure 1*A*).[3] Geographic differences exist in GEP-NET prevalence: rNETs and siNETs are most common in North America, pNETs and siNETs in Europe, and rNETs and pNETs in Asia.[2] The rising incidence of GEP-NETs is likely due to increased incidental detection of early-stage disease with improvements in and increased use of endoscopy and abdominal imaging.[10] Environmental and genetic factors may also be contributing to increased incidence.[11]

Among all sites, appendiceal and rNETs have the highest median overall survival (OS) (over 30 years for appendiceal and 24.6 years for rectal).[3] OS depends on grade, stage, and location, and has been improving across all NETs, especially among metastatic GEP-NETs, likely reflecting both improved detection of early-stage disease and treatment options.[3] However disparities exist in survival based on race and ethnicity, which may in part result from socioeconomic and demographic factors.[9]

Pathology and Grading

Pathology remains the gold standard for diagnosing NENs, and the 2022 World Health Organization classification focuses on tumor differentiation and grade (Figure 1*B*).[12] Degree of differentiation (well or poorly) refers to how closely the cells resemble their endocrine cell counterpart.[13] Tumor grade refers to the biological aggressiveness of the lesion and is measured by Ki-67 index or mitotic count. Higher values connote more aggressive behavior regardless of stage.

Positive immunohistochemical staining for *INSM1*, synaptophysin, and chromogranin-A (CgA) supports the diagnosis of a NEN. CgA is highly specific but less sensitive and may be absent in rectal NETs.[14] *INSM1* is both highly sensitive and specific.[15] Well-differentiated cells stain strongly for neuroendocrine markers, hormones, and SSTR. On the other hand, poorly differentiated tumors infrequently express hormones or SSTR. Well-differentiated NETs were once considered only grade 1 or grade 2, but more recent identification of a higher-grade subset led to the addition of the well-differentiated grade 3 category. Survival rates fall between well-differentiated NETs and poorly differentiated NECs. Distinguishing between grade 3 NET and NEC may be challenging, and biomarkers may help: loss of ATRX, DAXX, menin, or p27 occurs in grade 3 NET whereas loss of retinoblastoma protein and SSTRs expression and/or abnormal p53 expression suggest NEC.[12]

Diagnostic Considerations

Clinical Features

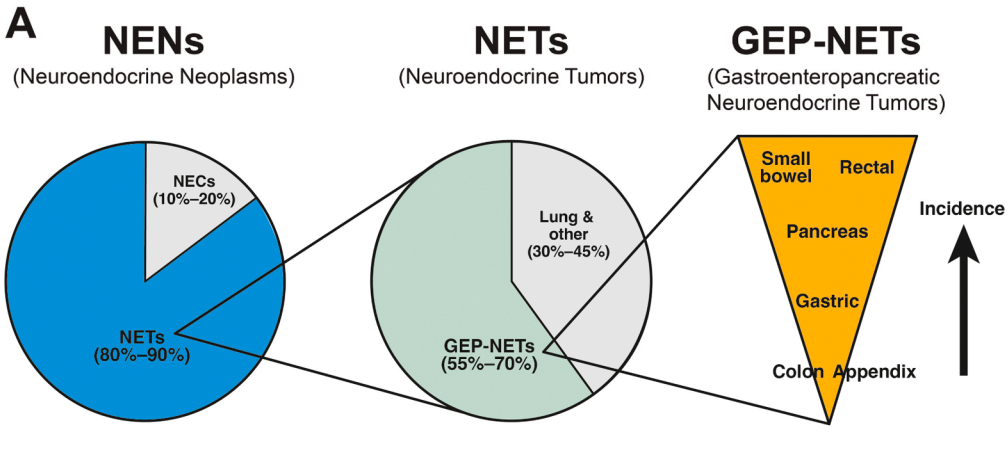
GEP-NETs can have vague and nonspecific symptoms related to tumor growth or bioactive amines secretion, which can result in substantial delays in diagnosis. The classic carcinoid syndrome (CS) results from hypersecretion of vasoactive amines (eg, serotonin, histamine, and prostaglandins) into the bloodstream, and occurs in about 30% of GI NETs, mainly from siNETs.[16] CS is typically characterized by flushing (85%), diarrhea (80%), abdominal cramps (75%), bronchospasm (20%), valvular heart disease (40%), and segmental intestinal ischemia with venous stasis, among other symptoms.[16] Diagnosing CS diarrhea is challenging due to its nonspecific presentation and broad differential, including pancreatic exocrine insufficiency, bile salt diarrhea, Si bacterial overgrowth, irritable bowel syndrome, and inflammatory bowel disease.[17] Notably, CS is rare in localized GI NETs, as it typically requires significant systemic amine elevation, usually due to liver metastases bypassing hepatic metabolism. In contrast, both localized and metastatic functional pancreatic NETs (pNETs) produce a myriad of syndromes related to the predominant hormone secreted by the tumors including the following: hypoglycemia in insulinoma; hyperglycemia in glucagonoma; Zollinger-Ellison Syndrome (ZES) with chronic diarrhea, gastroesophageal reflux disease, and recurrent peptic ulcers associated with gastrinomas; Verner-Morrison Syndrome with watery diarrhea, hypokalemia, and achlorhydria associated with vasoactive intestinal peptide tumors; and Cushing's syndrome in adrenocorticotropin hormone producing tumors.[18]

Laboratory Tests

The preferred initial screening for CS is the 24-hour urinary 5-HIAA test, with >90% sensitivity and specificity for siNETs.[19] Baseline assessment is recommended for all siNETs because elevated 5-HIAA levels may increase risk of carcinoid heart disease. Recently, measurement of plasma 5-HIAA levels was found to perform similarly to urine collection but is not yet widely available.[20] On the other hand, serum serotonin levels and CgA have limited value and are not recommended by guidelines for diagnosis of NETs.[21–24] Falsely elevated CgA occurs with specific food intake, exercise, drugs (proton pump inhibitors [PPI] and histamine type-2 receptor antagonists), and various comorbidities (atrophic gastritis, renal failure, cirrhosis among many others).[23,25] Its role as a marker of disease activity is also diminishing with improved imaging modalities. Markers like pancreastatin and pancreatic polypeptide have not been widely tested in clinical settings, and their utility remains low. However, evaluation of secreted hormone levels (insulin, glucagon, vasoactive intestinal peptide, gastrin, adrenocorticotropin hormone, etc) in functional pNETs is helpful in select cases to monitor disease response and recurrences. A detailed review of functional pNETs is beyond the scope of this review.[26]

Imaging

Anatomic imaging with computed tomography (CT) or magnetic resonance imaging (MRI) is essential for



B

Classification	Grade, type	Ki-67 index	Mitotic count mitoses/2 mm^2
Well-differentiated neuroendocrine tumor (NET)	1 (low)	<3%	<2
	2 (intermediate)	3%–20%	2-20
	3 (high)	>20%	>20
Poorly-differentiated neuroendocrine carcinoma (NEC)	Small cell NEC	>20%	>20
	Large cell NEC	>20%	>20

Figure 1. (*A*) Nomenclature and classification of neuroendocrine neoplasms. (*B*) Classification of gastroenteropancreatic neuroendocrine neoplasms.

diagnosing and staging GEP-NETs. Given their hypervascular nature, triple-phase abdominal CT is recommended to detect small vascular liver metastases.[27] MRI pancreas is optimal for assessing pNET resectability, whereas MRI liver, using hepatocyte-specific contrast and diffusion-weighted imaging, is best for detecting hepatic metastases.[28] CT limitations include radiation exposure, contrast use, and suboptimal performance for bony metastases.[28] The desmoplastic reaction around mesenteric metastases is a classic feature aiding in siNET diagnosis.

The widespread expression of SSTRs makes functional imaging with 68-Gallium or 64-Copper DOTA-TATE positron emission tomography (PET) (SSTR PET) the preferred modality for tumor localization, staging, and treatment assessment. SSTR PET has largely replaced octreotide scans given better image quality and studies showing its ability to detect significantly more lesions than octreotide scans (95% vs 31%) leading to improved staging, change of treatment plans, and identification of occult primaries (Figure 2*A* and *B*)[29] Prospective comparison of the 2 SSTR PETs (68-Gallium or 64-Copper), showed similar sensitivities, although ^{64}Cu-DOTA-TATE had substantially better lesion detection rate.[30] The Society of Nuclear Medicine and Molecular Imaging defined the following most compelling indications for SSTR PET: localizing an occult primary, staging (especially before surgery), selecting patients for radioligand therapy (RLT), and monitoring patients whose disease is predominantly seen on SSTR PET.[31,32]

Specific Subtypes of GEP-NETs

Gastric

Gastric NETs (gNETs) have a female predominance, represent 6.7% of all non-cardia gastric cancers, and are classified as 1 of 3 types with type 1 being by far the most common, followed by type 3, and then type 2 (Figure 3).[3,33,34] Type 1 gNETs typically present as multiple small tumors in a background of chronic atrophic gastritis resulting from either autoimmune gastritis or chronic *Helicobacter pylori* infection (Figure 2*C* and *D*). Tumor growth is driven by hypergastrinemia occurring in response to achlorhydria from gastric atrophy; therefore, recurrence is common given the underlying biology driving the hypergastrinemia. Type 2 gNETs arise in the setting of gastrinomas, which may be associated with multiple endocrine neoplasia type 1 (MEN1) syndrome and typically present as multiple tumors whose growth is gastrin driven. However, type 2 gNETs are differentiated from type 1 by the lack of gastric atrophy and presence of low gastric pH. Type 3 gNETs develop via a gastrin-independent mechanism, typically presenting as a single tumor, with normal fasting serum gastrin and normal gastric mucosal histology (Figure 2*E*). Although both type 1 and 2 gNETs are considered indolent with favorable prognosis, type 3 gNETs are more aggressive with distant metastases at diagnosis in over half the patients.[35] gNETs may also occur in individuals on long-term PPI therapy. Currently there is no separate classification for these presumed PPI-driven

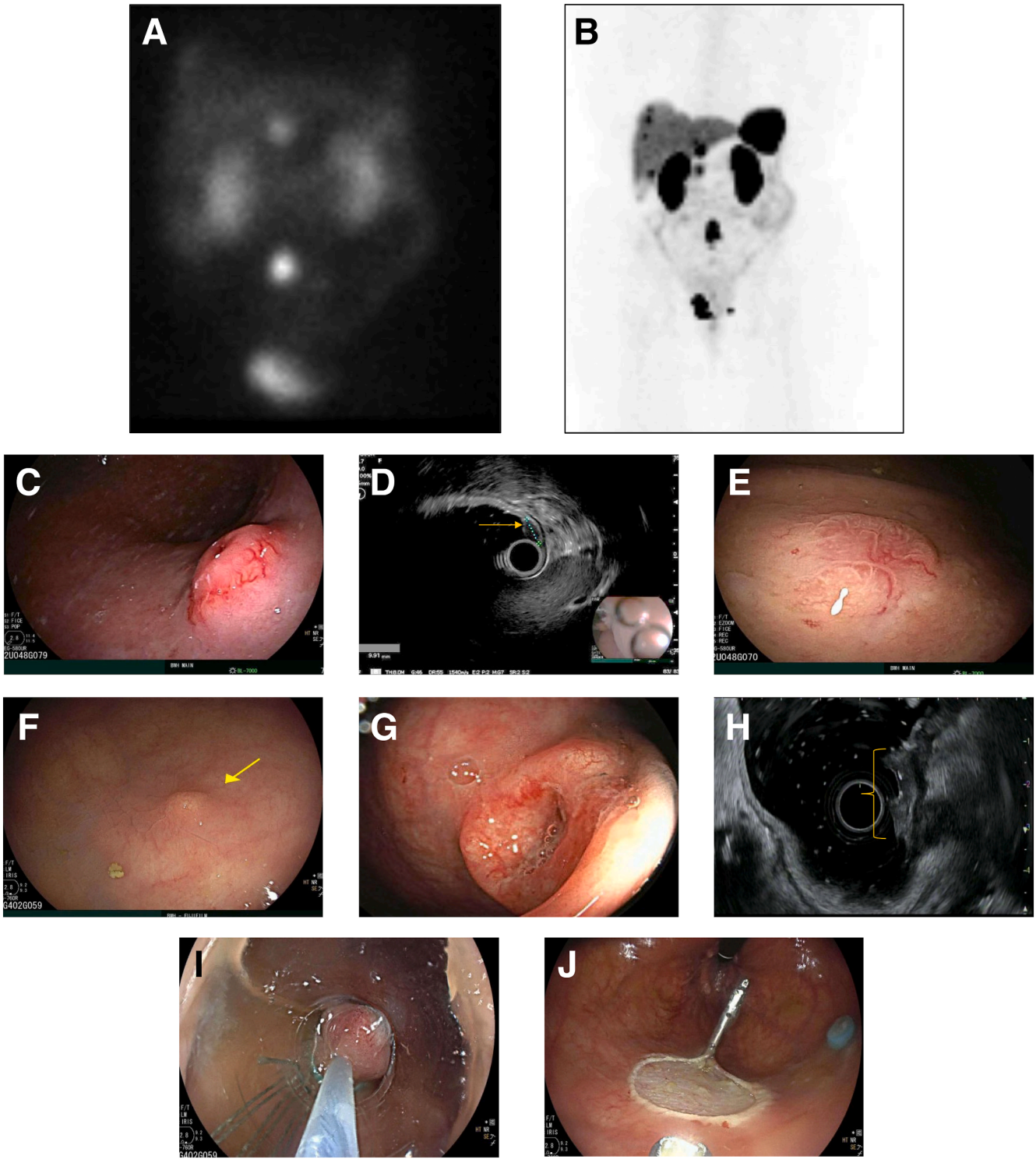


Figure 2. Functional and endoscopic imaging for NETs. (*A*) ^{111}In-pentetreotide SPECT scan and (*B*) ^{68}Ga-DOTA-TATE PET scan for the same patient taken 4 months apart. PET imaging provides significantly better image resolution and localization, and also shows many additional lesions not visualized on SPECT imaging. (*C*) Endoscopic image of type 1 gastric NET (grade 1, Ki-67 <3%) in a background of atrophic autoimmune gastritis. (*D*) EUS image of type 1 gastric NET. (*E*) Endoscopic image of type 3 gastric NET (grade 2). (*F*) Endoscopic image of rectal NET (grade 1, Ki-67 <3%). (*G*) Endoscopic image of rectal NET (grade 3, Ki-67 60.2%). (*H*) EUS image of rectal NET (between bracket). (*I*) Band ligator endoscopic mucosal resection. (*J*) Resection site after endoscopic mucosal resection. SPECT = single photon emission computed tomography.

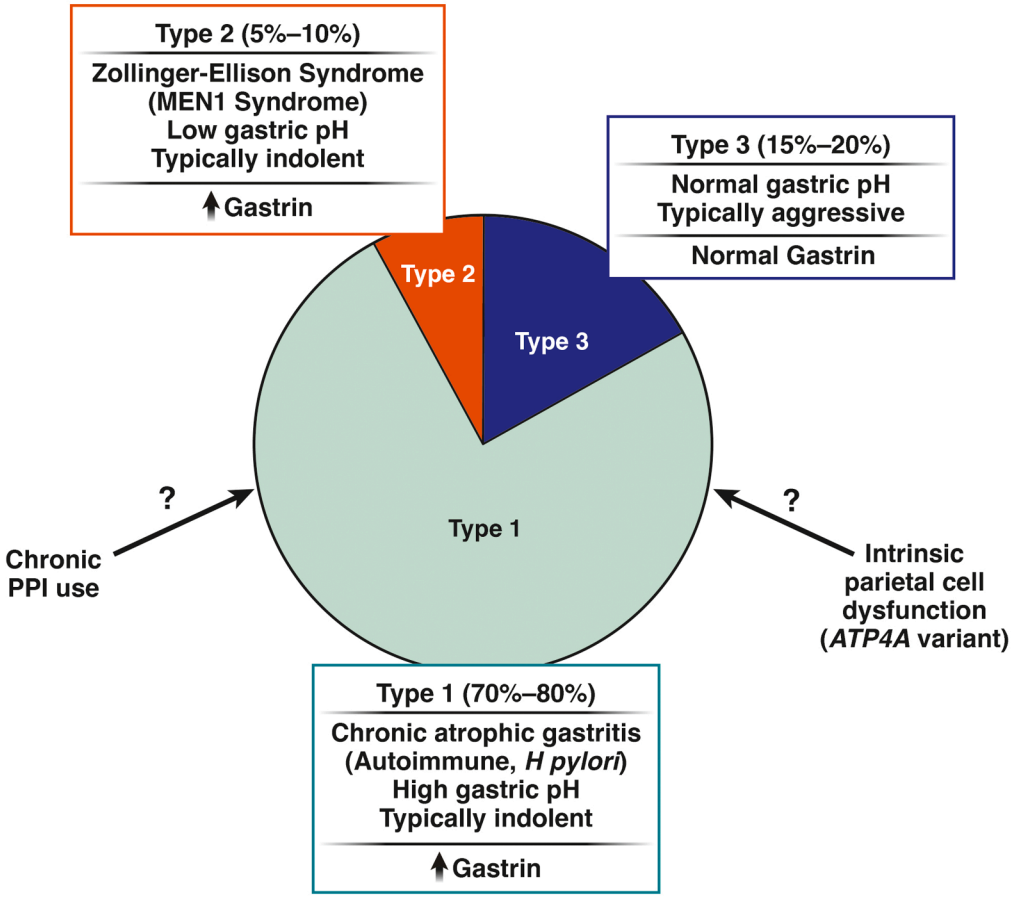


Figure 3. Classification of gNETs.

gNETs, although clinically they behave most similarly to type 1 gNETs.[36,37] Additionally, intrinsic parietal cell dysfunction with accompanying achlorhydria, including those related to germline variants in the H+/K+ ATPase coding gene *ATP4A*, can also predispose to gNET development.[38–40]

Most gNETs are asymptomatic and discovered incidentally, although some subtypes present with specific symptoms. Type 1 gNETs may develop in the setting of pernicious anemia with associated B12 deficiency, whereas type 2 gNETs linked to ZES may present with acid hypersecretion symptoms like reflux and diarrhea. Differentiating gNET subtypes requires gastric biopsies to assess for atrophic gastritis, gastric pH, and fasting serum gastrin level (off PPI if possible). However, once atrophic gastritis is diagnosed in the setting of gNET, this confirms diagnosis of type 1 gNET and further testing with pH and gastrin is not necessary.

Endoscopic management of gNETs depends on subtype, grade, and size (Figures 4 and 5*A*). However, endoscopic resection should not be considered when there is invasion beyond the submucosa, lymph node involvement, distant metastases and size >2 cm. For low-grade (grade 1/grade 2) type 1 gNETs, guidelines recommend removing all tumors 1 cm or larger.[21,35] Surgical resection is preferred for type 1 gNETs >2 cm. Endoscopic ultrasound (EUS) should be performed for gNETs 1–2 cm followed by endoscopic removal with endoscopic mucosal resection (EMR), endoscopic submucosal dissection (ESD), or less commonly endoscopic full-thickness resection (EFTR).[35] Although all these techniques are appropriate for type 1 gNET resection, data comparing them from randomized trials are lacking.[41] The most experience to date is with EMR although whether a specific EMR technique is superior remains uncertain. EMR may be performed with conventional saline lift and cautery resection, saline lift followed by precutting circumferentially several millimeters around the lesion and then snare cautery, or ligation-assisted using a band ligator. EMR may be associated with higher rates of incomplete resection compared with ESD and EFTR.[42,43] For incomplete resection, a step-up approach (eg, from EMR to ESD or EFTR) can be considered.

Management of low-grade type 1 gNETs <1 cm remains debated. Given the typical multiplicity of type 1 gNETs, endoscopic removal of all small tumors may not be feasible, and, indeed, endoscopic surveillance is safe for these subcentimeter grade 1/grade 2 NETs, with low progression rates.[44–46] Repeat endoscopy should be performed 1 year after initial diagnosis and then every 1–2 years.[35] Of note, given the gastric adenocarcinoma risk associated with atrophic gastritis, a 3-year surveillance interval is recommended

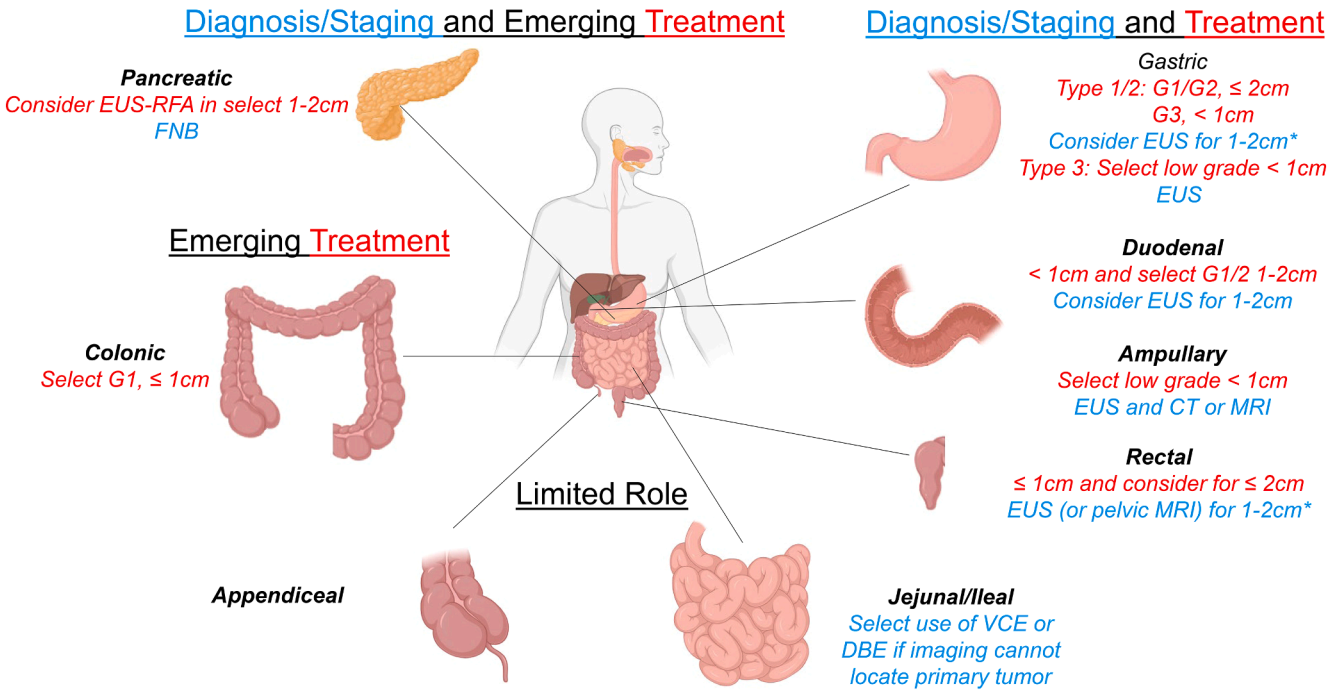


Figure 4. Overview of role of endoscopy in diagnosis and treatment of GEP-NETs. *Blue font* = diagnostic procedure; *red font* = therapeutic procedure. *If invasion deeper than submucosa, consider surgery.

in atrophic gastritis regardless of the presence of gNETs. Surveillance should be performed with Sydney protocol biopsies to assess the presence and extent of gastric intestinal metaplasia, and targeted biopsies of any areas concerning for dysplasia or gastric adenocarcinoma.[47]

Given the increased aggressiveness of grade 3 type 1 gNETs, CT or MRI and potentially SSTR PET should be performed followed by surgery for lesions 1 cm or larger, with EUS followed by endoscopic resection for superficial subcentimeter lesions.[35] The European Neuroendocrine Tumor Society (ENETS) recommends annual surveillance endoscopy after endoscopic resection of type 1 gNETs.[35] In addition, PPI discontinuation should be encouraged if possible.[48]

For type 2 gNETs, endoscopic management is governed by whether the gastrinoma driving tumorigenesis is removed. If gastrinoma location is unknown, anatomic and functional imaging should be performed to identify the primary. Surgical resection of the primary gastrinoma may obviate the need for endoscopic surveillance. Apart from primary tumor removal, endoscopic management of type 2 gNETs is similar to type 1 gNETs.

Given the aggressive nature of type 3 gNETs, surgery is typically recommended. However, endoscopic resection with EMR, ESD, or EFTR can be considered for select low-grade, superficial, subcentimeter lesions.[21] Similar recurrence-free survival has been observed for endoscopic and surgical resection of small (1 cm or smaller) grade 1 type 3 gNETs, adding support to this selective strategy.[49] However, regardless of the treatment modality, all type 3 gNETs should undergo full staging with anatomic and functional imaging to assess for metastatic disease and, if none present, EUS.[35] After endoscopic resection, repeat endoscopy is performed about 3 months later followed by ongoing surveillance anatomic imaging and endoscopy/EUS.[35]

Duodenal and Ampullary

Nearly 90% of duodenal NETs (dNETs) are nonfunctioning. Functional duodenal gastrinoma and duodenal somatostatinoma are rare.[22] Gastrinomas produce extragastric gastrin, which leads to clinical ZES and cannot be diagnosed by positive gastrin staining on pathology alone. Presence of multiple dNETs occurs about 10% of the time, and should raise concern for MEN1.[50] When symptoms occur rarely with nonfunctioning dNETs, they typically result from the large size causing gastric outlet obstruction or location near the ampulla causing jaundice, abdominal pain, or bleeding.

The typical endoscopic appearance of a dNET is a small, firm subepithelial lesion in the duodenal bulb through D2. Overlying mucosa may be erythematous, yellow, or pale. With smaller lesions, biopsies may resect most of the lesion, making it challenging to identify the resection site during follow-up endoscopy in cases of R1 resection. Careful description of the location, photodocumentation, and tattoo away from the lesion may help with subsequent identification. Although EUS, anatomic imaging, and functional imaging are important for staging, it remains unclear when and which studies are most beneficial. The 2023 ENETS guideline suggests EUS for dNETs >1 cm.[35]

Optimal management of nonfunctioning dNETs remains uncertain due to paucity of data (Figure 5*B*). Previous data suggested tumor size correlated with survival, presumably due to association with lymph node metastasis (eg, <5% of duodenal NETs <1 cm had local lymph node involvement).[51]

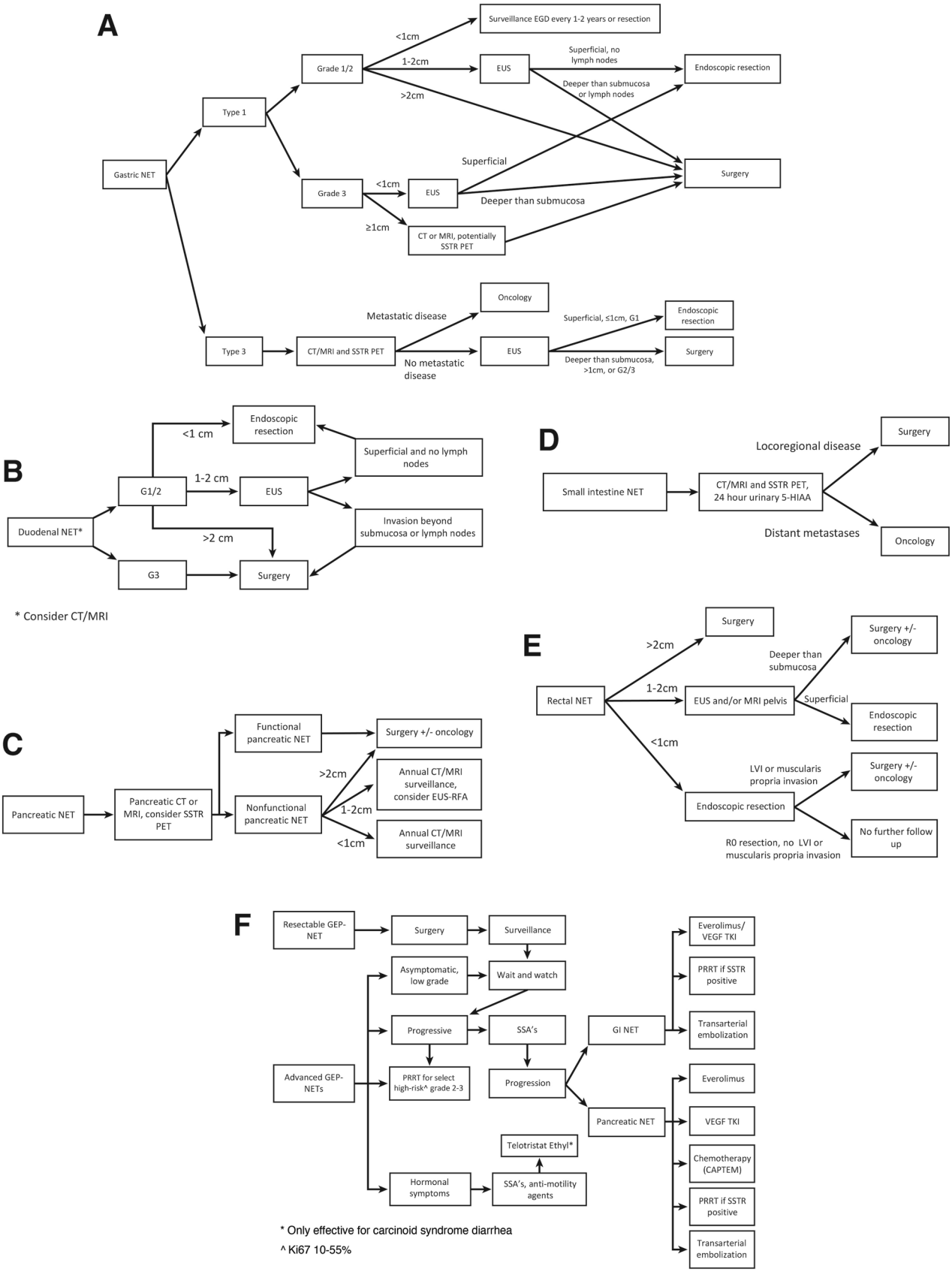


Figure 5. Clinical algorithms. (*A*) Overview of management of type 1 and type 3 gNETs. (*B*) Overview of management of dNETs. (*C*) Overview of management of pNETs. (*D*) Overview of management of SiNETs. (*E*) Overview of management of rNETs. (*F*) Management of advanced GEP-NETs. CAPTEM, capecitabine temozolomide; PRRT, peptide receptor radio therapy; VEGK TKI, vascular endothelial growth factor tyrosine kinase inhibitor.

However, other studies indicated that size may not predict regional lymphadenopathy and even the relationship of lymph node metastasis with survival has been questioned recently.[52–54] A Surveillance, Epidemiology, and End Results (SEER) database study suggested comparable survival after endoscopic or surgical resection of dNETs even after stratifying by tumor size.[52] In recognition of the success of endoscopic resection for small dNETs with survival comparable to T1N0M0 lesions, the American Joint Committee on Cancer added T1NXM0 to stage 1.[22,55]

Most small (<1 cm) dNETs may be managed endoscopically with snare polypectomy, EMR, ESD, or EFTR (Figure 4).[35,55,56] Cold biopsy forceps are not ideal and typically used when lesions are found incidentally before diagnosis of dNET. A less-studied EMR approach is band ligation without resection, which had 100% technical success and no long-term recurrence in small series.[57,58] Its safety profile makes it attractive for carefully selected patients although resection margins cannot be assessed due to lack of pathology specimen. For larger dNETs between 1 and 2 cm without invasion into muscularis propria or lymphadenopathy, whether endoscopic or surgical resection is optimal remains unclear although endoscopic resection is increasingly performed.[55,56] If margins are positive, residual tissue may be resected endoscopically or surgically while biopsies should be taken from scars.[56,59] For lesions >2 cm, higher grade (grade 2/grade 3), invading into the muscularis propria, or with regional lymphadenopathy, surgical resection is indicated.[35,55] Endoscopic surveillance may be appropriate for nonfunctional grade 1 dNETs <5 mm in patients who are not fit for endoscopic or surgical resection as per the recent ENETS guidance paper.[35]

Similar to gNETs, data suggests lower R0 resection with EMR compared with ESD or EFTR, although whether this translates into worse long-term outcomes after EMR remains unclear.[60–62] More complications occur with endoscopic resection in the duodenum including bleeding in up to 20% of patients and perforation in up to 13%–67% after ESD although most were managed endoscopically.

There is even less data to guide management of ampullary NETs, which are typically more aggressive with higher-grade pathology, greater incidence of lymph node metastases, and worse survival compared with dNETs and frequently occur in neurofibromatosis-1.[63,64] EUS and CT or MRI are recommended for staging, although EUS alone has very low accuracy for both T and N stage.[65] For lesions without distant metastases, pancreaticoduodenectomy is recommended, although its morbidity and mortality make endoscopic resection an attractive option. Tumor size >1 cm is predictive of R1 endoscopic resection. Therefore, endoscopic ampullectomy may be reasonable in nonsurgical candidates with small, low-grade lesions and no regional lymphadenopathy or invasion beyond the submucosa on EUS (Figure 4).[66]

Appropriate surveillance after endoscopic resection of duodenal and ampullary NETs remains unclear. One approach is to perform endoscopic surveillance every 1–2 years.[56,59]

Pancreatic. Although some pNETs are functional, the majority (65%–90%) are nonfunctional.[67–69] Multiple nonfunctioning pNETs should raise concern for genetic syndromes including MEN1, Von Hippel Lindau, tuberous sclerosis, and neurofibromatosis-1. In addition to anatomic and functional imaging, EUS is particularly useful for identifying suspected small pNETs not visualized on CT or MRI and increases pNET detection by >25%.[70] EUS also allows assessment of regional lymph nodes and the relationship of the pNET with the main pancreatic duct. Solid pNETs classically appear well-defined, hypoechoic, and may be hypervascular on EUS. Cystic pNETs account for at most 35% of all pNETs and often have a thick wall. EUS–fine-needle aspiration (FNA) cytology yield is lower (73%–83%) for cystic pNETs compared with solid pNETs.

Although adjuncts including elastography, contrast-enhanced harmonic EUS, and confocal endomicroscopy may help, ultimately pathology is important and necessary for diagnosis. EUS-FNA or fine-needle biopsy (FNB) provide pathologic diagnosis with 73%–100% sensitivity and 83%–93% specificity.[71] When available, FNB is favored over FNA due to its ability to obtain histology with greater cellularity and using fewer passes (Figure 4).[72]

Accuracy of grading from EUS-FNA samples seems to depend on tumor grade with one retrospective pooled analysis demonstrating superior sensitivity (91%) for identifying grade 1 tumors vs 56% for grade 2 and 60% for grade 3.[71] Whether EUS-FNB significantly improves grading remains uncertain although FNB samples are more frequently adequate to assess Ki-67 in pNETs ≤20 mm (96.1% vs 88.2%; $P = .04$).[73]

For functional pNETs without distant metastases or with resectable metastatic disease (for example, isolated liver metastasis), surgical resection is recommended regardless of tumor size. Surgery is also the treatment of choice for localized nonfunctioning pNETs >2 cm or those with main pancreatic duct dilation.[74] Small nonfunctioning pNETs <1 cm should undergo surveillance. For nonfunctioning pNETs <1 cm, no difference in mortality or disease progression was reported between surveillance and surgical resection over median 45-month follow-up although high morbidity (46%) was noted postoperatively.[75]

Optimal management of nonfunctioning pNETs between 1 and 2 cm remains controversial, although the pendulum is swinging toward surveillance (Figure 5*C*).[76] Two large ongoing prospective observational studies both published interim analyses supportive of surveillance. The PANDORA study is following patients with pNETs <2 cm sent to surgery when concern for tumor progression arose.[77] Results showed no change in 89% of pNETs and growth by >0.5 cm/y in 11% with 1 patient having a peritoneal lesion and postoperative recurrence after median 17-month follow up. The ASPEN study is following patients with pNETs <2 cm and allowing the physician to select surveillance or surgery; to date, 81% patients are undergoing surveillance with only 1.7% converted to surgical resection due to tumor growth or pancreatic duct dilation.[78] Therefore, close surveillance with at least annual CT or MRI may

be safe although management should be individualized based on patient's age, comorbidities, and tumor grade.[76]

With the relatively high morbidity associated with surgical resection and some unease over surveillance of 1- to 2-cm pNETs, EUS-guided radiofrequency ablation (RFA) may offer an attractive minimally invasive treatment option for patients who are not surgical candidates or refuse surgery. Compared with surgery, EUS-RFA was safer (adverse event rate 18% vs 61.8%; $P < .001$) with decreased length of stay although relapse rate was higher (16.9% vs 0%; $P < .001$).[79] This is a relatively simple technique using a special internally cooled 19G EUS-RFA needle (EUSRA, Taewoong Medical, South Korea) with a specific generator (VIVA RF generator, Taewoong Medical, South Korea). Although early findings are encouraging, especially for functional pNETs like insulinomas, long-term clinical efficacy results are necessary to understand the role EUS-RFA may play in managing modestly sized pNETs. In addition, with the small risk of pancreatitis and pancreatic duct stricture, the decision to pursue EUS-RFA should be made by a multidisciplinary team.

Small Intestine (Jejunal and Ileal)

Unlike other GEP-NETs, siNETs are less frequently diagnosed incidentally (except ileal NETs if the terminal ileum is intubated during colonoscopy), often present with metastatic disease although they still have a median 56-month survival, and thus are most commonly associated with CS.[3,80–82] Diagnosis is typically delayed, ranging from less than 5 months at academic centers to as long as 9 years in the community.[83] Although primary siNETs are small, they are known to cause a strong desmoplastic reaction in the mesentery and are associated with large mesenteric masses representing enlarged lymph nodes. These can present with abdominal cramping, postprandial pain, and partial or even complete small-bowel obstructions.[84]

Improved anatomic and functional imaging has enhanced the diagnostic landscape of siNETs dramatically and SSTR PETs routinely identify unknown primaries and multifocal disease in the small intestine (Figure 5*D*). Hence endoscopic techniques like capsule endoscopy and double-balloon enteroscopy are not routinely endorsed by guidelines but can be used when other imaging tests cannot identify a primary (Figure 4).[85,86] In patients with NETs and unknown primary tumors, capsule endoscopy had 75% sensitivity and 38% specificity compared with exploratory surgery, whereas double-balloon enteroscopy had 33% sensitivity with low diagnostic yield in the general population.[87,88]

In patients with loco-regional disease, surgical resection remains the mainstay of therapy for siNETs. The rate of lymph node metastases is very high and hence optimal surgical management includes segmental small-bowel resection with resection of regional lymph nodes. Given the multifocal nature of these tumors, it is important for surgeons to palpate the entire small bowel to detect multifocal tumors, which often are subcentimeter in size.[89] Similarly, inspecting the abdomen and liver for metastatic disease is routinely done given the high rate of metastatic disease at diagnosis. Studies suggest that 77% of patients with siNETs will require treatment with somatostatin analogues (SSAs), increasing the risk of developing gallstones.[90] If there is high likelihood that the patient will require SSAs (such as those with liver metastases, peritoneal disease, or significant nodal involvement), prophylactic cholecystectomy should be performed during the initial resection.[91]

The risk of recurrence after complete resection of siNETs has not been prospectively studied given the need for prolonged follow-up. In one observational study of patients with stage I–III siNETs (majority stage III), the rate of metastatic recurrence was 31% after median follow-up of 7.5 years.[92] Interestingly, the rate of recurrence was highest between years 3 and 8. Guidelines recommend radiographic and clinical surveillance every 6–12 months for the first year and then every 1–2 years for up to 10 years.[21,85]

Appendiceal

Most appendiceal NETs are found incidentally after appendectomy or laparotomy performed for acute appendicitis or unrelated reasons. The majority (70%) of these NETs are localized in the tip of the appendix with no or minimal symptoms.[93] Diagnostic testing is rarely performed due to their incidental nature and identification during pathologic evaluation after appendectomy. Some guidelines recommend staging CT, MRI, and possibly SSTR PET for tumors at least 2 cm or any tumor size with incomplete resection or positive nodes, which is reported in 2.5% of tumors <1 cm, 31% of tumors between 1 and 2 cm, and 64% of tumors >2 cm. Some important pathologic features that help determine the course of treatment include size, lymphovascular invasion, depth of invasion into mesoappendix, and grade.[94]

Localized appendiceal NETs are primarily treated with surgical resection—either appendectomy or right hemicolectomy. Incidental diagnosis after appendectomy complicates decisions on re-exploration. Generally, tumors >2 cm warrant right hemicolectomy, whereas those <1 cm with negative margins require only appendectomy. Management of 1- to 2-cm tumors remains controversial. A retrospective study of 278 patients found a 1% rate of synchronous and no metachronous metastases after median follow-up of 13 years, regardless of further surgery.[95] Regional lymph node metastases were found in 22 of 112 (20%) patients with right hemicolectomy and, based on histopathologic risk factors, authors estimated a 12.8% rate of lymph node metastases in the appendectomy group. Despite its retrospective nature and limited follow-up, this study represents the largest cohort to date. Notably, right hemicolectomy did not improve overall survival in this study. Current guidelines recommend considering right hemicolectomy for 1- to 2-cm tumors with high-risk features (positive margin, mesoappendiceal invasion >3 mm, or lymphovascular invasion).[21,94] Surveillance after resection is recommended for tumors where hemicolectomy was initially performed due to risk factors or those with

positive margins after appendectomy and no completion surgery. Guidelines recommend anatomic imaging and clinical surveillance every 6–12 months for the first year and then every 1–2 years for up to 10 years.[21]

Colorectal

The majority of colorectal NETs are asymptomatic and identified incidentally.[2,3,8] Colorectal NETs can be subdivided into colonic NETs and rNETs because the clinical features and management of these 2 subgroups are distinct. Although rNETs (Figure 2*F*–*H*) are more common than colonic NETs, colonic NETs are considered more aggressive.[96] A large study of nearly 20,000 colorectal NETs in the National Cancer Database showed that 5-year OS was 69% for colonic NETs compared with 92% for rNETs.[97] Among rNETs, nearly 80% presented as 1 cm or smaller with 5-year OS of 94.1%.[98] Lymph node metastases was associated with worse survival (53.3% vs 91.4% without lymph nodes).[98] Similar results were observed in the SEER database, where only 1.1% of rNETs 1 cm or smaller had metastatic disease at diagnosis compared with 6.6% of tumors 11–19 mm.[99] Apart from size, higher grade is also associated with increased risk of distant disease for rNETs.[100]

Management of colonic NETs is quite different from rNETs. On identification of a colonic NET, both anatomic and SSTR PET imaging should be performed to assess disease burden. Classically, management of colonic NETs has involved surgery given their increased aggressiveness.[21,101] There is evidence that small (<1 cm), mucosa-confined, colonic NETs have lymph node metastases in only 4% of cases, which led to recent ENETS guidelines allowing for endoscopic resection of select grade 1 colonic NETs that are 1 cm or smaller with EMR, ESD, or EFTR.[102] However, the C-NET Study, currently ongoing in Japan showed 29.2% of colorectal NETs had lymphovascular involvement, including 26.4% of lesions <5 mm.[103] Notably, long-term data comparing endoscopically to surgically resected colonic NETs is lacking.

Management of rNETs depends on size, grade, and depth of invasion (Figure 5*E*).[21,101] For rNETs <1 cm, endoscopic removal with EMR, ESD, or EFTR can typically be performed. A systematic review and meta-analysis showed that for rNETs, EMR, using circumferential precutting or band ligator, and ESD had higher rates of complete resection compared with conventional saline lift EMR, however, currently all these techniques are considered appropriate.[104] For completely resected incidental grade 1 rNETs <1 cm, additional imaging and follow-up are not recommended given the very good prognosis with low recurrence rates.[105] However, for tumors between 5 and 10 mm with lymphovascular or muscularis propria invasion, MRI pelvis should be considered.[101]

For rNETs 1 cm or greater in size, EUS and/or pelvic MRI should be performed to assess for local invasion. With invasion beyond the submucosa, more extensive anatomic and SSTR PET imaging should be performed to rule out metastatic disease.[21] Endoscopic resection (Figure 2*I* and *J*) can be considered for localized rNETs between 1 and 2 cm. As seen with gastric and duodenal NETs, complete resection rates appear higher with ESD compared with EMR.[106] For rNETs >2 cm, surgical excision is preferred.

Size, grade, and depth of invasion are all important predictors of recurrence. In a study of surgically resected grade 2 rNETs, 60% had positive lymph nodes, although for tumors 1.5 cm or smaller, recurrence and survival outcomes were similar after endoscopic or transanal excision compared with surgical resection.[107] A large study of resected rNETs showed overall 5.4% recurrence with significantly higher rates associated with invasion beyond the submucosa, Ki-67 >2%, and positive resection margins.[108]

Incomplete endoscopic resection may occur, and repeat endoscopic removal of residual rNET with EMR, ESD, or EFTR should be considered. EUS may have a role after incomplete resection as it had 94% sensitivity, 71% specificity, and 87% overall accuracy for detecting residual rNET after incomplete resection.[109] In another study, scar resection of incompletely resected rNETs using EMR, ESD, or EFTR revealed residual NET in 43% of cases although the majority of initial resections were performed with improper technique (forceps or cold snare).[110] Similar to gastric and duodenal NETs, there is continued debate about whether positive resection margins after rNET resection are associated with negative outcomes. In a study of 436 individuals with rNET removed via ESD, the presence of a positive resection margin did not impact progression-free survival (PFS) or OS.[111] Similarly in another study of 326 individuals with rNETs, 25.5% had incomplete resection, with no recurrence reported after a median of 30.9 months.[112]

Therapy for Advanced GEP-NETs

There are currently multiple systemic options for GEP-NETs, however sequencing of therapy remains a challenging question. Treatment should be guided by a shared decision-making approach, considering the risks and patient characteristics. For asymptomatic patients with low-volume disease and favorable grade, watchful waiting is a widely accepted treatment strategy. Figure 5*F* provides a simplified algorithm for management of advanced GEP-NETs.

Management of Hormonal Symptoms

Short-acting SSA (octreotide) has long been used for acute management of hormonal symptoms. Octreotide long-acting repeatable (LAR) and lanreotide both improve CS symptoms.[113,114] Serotonin is a well-established essential mediator of CS symptoms. Telotristat ethyl, a peripherally active tryptophan hydroxylase inhibitor, reduces peripheral serotonin and significantly improved octreotide-refractory CS diarrhea in 2 phase 3, randomized, placebo-controlled trials.[115,116] However, the effect of this medication on flushing is modest at best. Tumor-directed therapies, especially loco-regional therapies and peptide receptor radionuclide, also known as RLT, indirectly improve hormonal symptoms.

Carcinoid crisis is a life-threatening condition resulting from massive release of vasoactive compounds. Opinions differ on whether prophylactic octreotide must be administered before endoscopic procedures in patients with CS to prevent carcinoid crisis especially in patients already on SSAs. A prospective study eliminating perioperative octreotide resulted in neither increased rate nor duration of crisis.[117] Intravenous fluids and vasopressors should be provided with intravenous octreotide if hemodynamic instability occurs.

Locoregional Options

For patients with liver-dominant disease that is potentially resectable, surgical debulking can provide durable control of symptoms and tumor growth with improved survival.[118] Resection of primary tumors in selected patients with metastatic disease is sometimes considered when feasible to relieve symptoms, avoid future symptoms, and for its potential survival advantage but only if associated with very low morbidity.[91]

For patients with liver-dominant but unresectable disease, transarterial bland, chemo-, or radio-embolization, are potential therapeutic options. The potential risk of radiation-induced liver injury from radioembolization must be considered especially in NETs given their favorable prognosis. Nonetheless, most patients respond well to transarterial therapy with studies showing objective response rate of >50% decrease in size.[119–122] Significant improvement in hormonal symptoms is also observed, making transarterial therapy an attractive option for functional tumors. Currently, there are no studies suggesting superiority of one transarterial modality over another. The RETNET study (NCT02724540), comparing bland vs chemoembolization in patients with liver metastases from NETs, was recently presented at the Society of Interventional Oncology 2025 meeting and showed no difference in hepatic PFS between the 2 arms. The objective response rate was higher in bland embolization (60% vs 40%) but was less durable.

Somatostatin Analogues

Guidelines recommend first-line SSA therapy for metastatic well-differentiated GEP-NETs with progressive disease or high-risk features.[21,123] The PROMID trial showed octreotide LAR improved median PFS (14.3 vs 6 months; $P = .000072$), whereas the CLARINET trial found lanreotide increased 2-year PFS rates (65% vs 33%; $P < .001$) compared with placebo.[124,125] Common side effects include hyperglycemia, biliary complications, pancreatic insufficiency, diarrhea, and flatulence. Researchers are exploring oral and self-administered SSA alternatives (NCT05361668 and NCT05050942). Importantly, there is limited to no role for long acting SSAs in managing localized nonfunctional GEP-NETs that are being observed or undergoing endoscopic resection.

Radioligand Therapy

^{177}Lu-DOTA-TATE is a novel radioligand that allows targeted delivery of radioisotope to SSTR-expressing tumors. In the NETTER-1 trial, it reduced risk of progression or death by 79% compared with high-dose octreotide LAR (hazard ratio, 0.21; $P < .001$), with median PFS of 28.4 vs 8.4 months and an objective response rate of 18% vs 3%. The follow up NETTER-2 trial in newly diagnosed patients with high-risk grade 2–grade 3 GEP-NETs also demonstrated improved PFS for ^{177}Lu-DOTA-TATE compared with SSAs (median PFS 23 vs 9 months).[126,127] Long-term toxicities of RLT may include renal insufficiency and leukemia/myelodysplastic syndromes (<3% risk).[128] Small-bowel obstruction and abdominal pain are also emerging as distinct side effects. Ongoing research aims to identify better radioisotopes.

Everolimus

Everolimus, a mammalian target of rapamycin inhibitor, is approved for well-differentiated NETs regardless of primary site. In the phase 3 RADIANT-3 trial, everolimus improved median PFS compared with placebo in advanced pNETs (11 vs 4.6 months; $P < .001$).[129] Subsequently, the RADIANT-4 randomized trial of nonfunctional GI and lung NETs demonstrated improved median PFS for everolimus vs placebo (11 vs 3.9 months; $P = .00001$).[130] Side effects of everolimus include stomatitis, diarrhea, rash, hyperglycemia, cytopenias, and pneumonitis.

Antiangiogenic Drugs

Sunitinib improved PFS over placebo (11 vs 5.5 months; $P < .001$) in a phase 3 trial of 171 patients with grade 1–2 pNETs.[131] The CABINET trial similarly showed cabozantinib extended PFS in progressive, pretreated NETs compared with placebo for pNETs at 11 vs 3 months and extrapancreatic NETs at 8 vs 3 months.[132] Common side effects include fatigue, hypertension, hand-foot syndrome, and diarrhea.

Chemotherapy

Alkylating agents have shown activity in pNETs. The E2211 trial demonstrated improved PFS in pNET patients who received temozolomide with capecitabine compared with temozolomide alone (22.7 vs 14.4 months).[133] This combination is typically used in patients with high-risk pNETs (higher Ki67, bulky symptomatic tumors). Of note, cytotoxic chemotherapy has negligible activity in midgut NETs and is typically not used in this setting.

Conclusions

In conclusion, GEP-NETs present diverse challenges in diagnosis and management due to their variable biological behavior and often indolent clinical course. Gastroenterologists are frequently the first to diagnose GEP-NETs, often as incidental findings on endoscopic procedures. Therefore, improving awareness and understanding of GEP-NETs among gastroenterologists is essential. Additionally, endoscopy is increasingly important in managing GEP-NETs with advanced endoscopic resection techniques,

providing definitive therapy in select localized GEP-NETs. Outcomes have improved for advanced-stage tumors with recent strides in targeted therapies, including somatostatin analogs, RLT, antiangiogenic drugs, and mammalian target of rapamycin inhibitors, but identifying the appropriate sequence of agents needs refining. Future research of these complex and heterogeneous neoplasms should aim to identify improved diagnostics and therapeutics to foster personalized treatment strategies, ultimately enhancing patient outcomes and quality of life.

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Conflicts of interest
The authors disclose the following: Namrata Vijayvergia was a consultant for Exelixis, Novartis, Pfizer, and RayzeBio. Linda S. Lee was a consultant for Boston Scientific, Fujifilm Healthcare Americas Corporation, and Cook Medical. Bryson W. Katona was on the Advisory Board of Immunovia.

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Data Availability
This review article summarizes the latest research in the field. For access to specific data, researchers will need to directly contact corresponding authors of works cited in this article.