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VOLUME 18

SURGERY

Roshan Lall Gupta's

Recent Advances in SURGERY

Editor

Puneet



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CHAPTER 5

Neuroendocrine Tumors of the Gastroenteropancreatic System

Gurudutt P Varty, Vikram A Chaudhari, Manish S Bhandare, Shailesh V Shrikhande

INTRODUCTION

Neuroendocrine tumors (NETs) arise from the diffuse neuroendocrine cell system. Most frequently, these neoplasms occur in the gastrointestinal system followed by the lung.[1] Historically, these tumors were described by various terms such as APUDomas, Kulchitsky cell tumors, argentaffinomas, carcinoid tumors, and pancreatic islet tumors. In the year 2000, the World Health Organization (WHO) developed a universal nomenclature and classification system labeling them as neuroendocrine tumors. Currently, the 2019 WHO classification is widely accepted for classifying NETs and guiding management. Gastroenteropancreatic neuroendocrine tumors (GEP-NETs) are a group of tumors originating from enterochromaffin (neuroendocrine) cells of the gut.[2]

EPIDEMIOLOGY

Annual incidence and prevalence of GEP-NETs are rising steadily around the world in recent years. According to the Surveillance, Epidemiology, and End Results (SEER) data, the age-adjusted incidence of GEP-NETs has increased from 1.05 to 5.45 cases/100,000 population in the USA between 1975 and 2015 with an annual percentage change of 4.98%.[3] In Europe, the incidence of GEP-NETs currently ranges between 1.33 and 2.33/100,000 population; however, this data is heterogeneous and retrospective.[1] Multicenter longitudinal NET registry from India reported 407 GEP-NET patients in 2017 wherein data was collected from 2001 to 2016 from six tertiary care centers. Even though the exact incidence was not reported, the rising incidence of GEP-NETs was noted since the initiation of the registry.[4] Widespread use of cross-sectional imaging, availability of sensitive diagnostic tools, and higher awareness among clinicians seem to contribute to the rise in GEP-NETs incidence.

Men are affected marginally more frequently than women.[1] GEP-NETs usually occur sporadically. Around 5–25% of the cases are associated with some familial or genetic predisposition. Familial syndromes associated with GEP-NETs [particularly pancreatic neuroendocrine tumors (Pan-NETs)] are described in **Table 1**.

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TABLE 1: Hereditary syndromes associated with NETs.

Syndrome	*Gene associated*	*NET manifestation*
MEN1 (Werner syndrome)	*MENIN*	Parathyroid hyperplasia, pituitary adenoma, and gastroenteropancreatic NETs [Zollinger–Ellison syndrome, insulinoma, VIPoma, thymic, and/or bronchial tube endocrine tumors (foregut carcinoid tumors)]
MEN2 (2A, 2B)	*RET*	Medullary thyroid carcinoma (MEN2A and 2B), pheochromocytoma (MEN2A and 2B), primary hyperparathyroidism (MEN2A), neuromas of the tongue, ganglioneuromas of the intestine, and a marfanoid habitus (MEN2B)
MEN4	*CDKN1B*	Parathyroid adenoma/ hyperplasia, pituitary adenoma, gastroenteropancreatic NETs
von Hippel–Lindau (VHL)	*VHL*	Pheochromocytoma/paraganglioma, pancreatic NETs
Neurofibromatosis type I (Recklinghausen disease)	*NF1*	Pheochromocytoma, duodenal NETs
Tuberous sclerosis	*TSC1, TSC2*	Pancreatic NETs

(MEN1: multiple endocrine neoplasia type 1; MEN2A: multiple endocrine neoplasia type 2A; MEN2B: multiple endocrine neoplasia type 2B; MEN4: multiple endocrine neoplasia type 4; NET: neuroendocrine tumor)

PATHOLOGY AND CLASSIFICATION

Histological diagnosis can be obtained from either the resected specimen or core biopsies. Fine-needle aspiration may not provide sufficient tissue for accurate diagnosis and calculation of the proliferation index. The neuroendocrine nature of the tumor is confirmed by the immunohistochemical detection of neuroendocrine markers such as synaptophysin and chromogranin A (CgA). Tumor grade and differentiation are the key factors to determine the clinical behavior of GEP-NETs. The grade refers to the proliferative activity of neoplastic cells, which is measured by the Ki-67 (MIB1) index and the mitotic rate, whereas the differentiation refers to the extent to which tumor cells resemble their normal counterparts. Neuron-specific enolase (NSE) and CD56 are other nonspecific markers that are often positive in GEP-NETs.

Gastroenteropancreatic neuroendocrine tumors are currently classified according to the WHO Classification of Digestive System Tumors, 2019, and staged according to the Union for International Cancer Control/American Joint Committee on Cancer (UICC/AJCC) tumor, node, and metastasis (TNM)

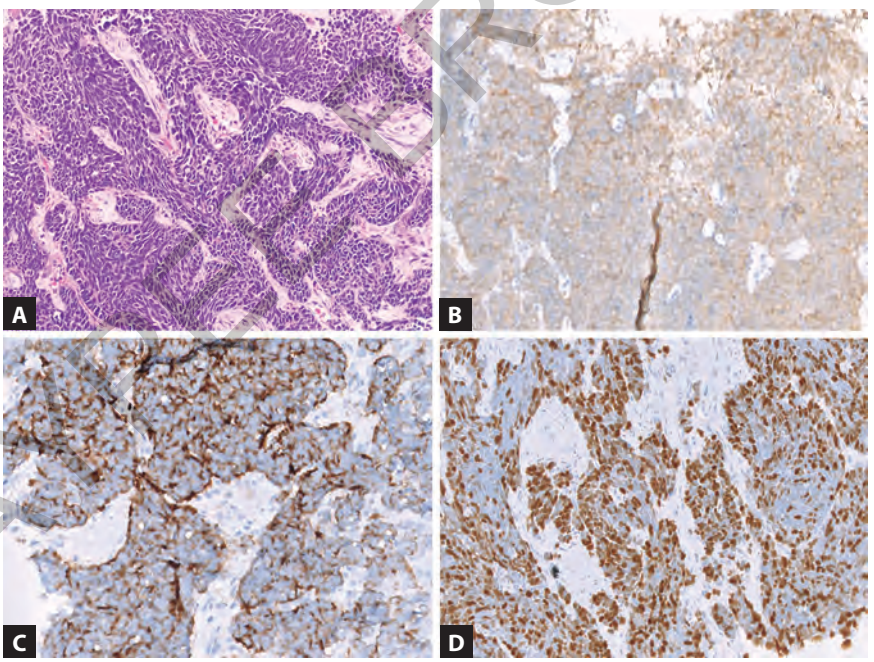
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staging system or the European Neuroendocrine Tumor Society (ENETS) TNM classification. As per the 2019 WHO classification, GEP-NETs are divided into well-differentiated (WD) NETs grades 1, 2, and 3 and poorly differentiated neuroendocrine carcinomas (NECs) **(Table 2 and Figs. 1A to D)**.

TABLE 2: The WHO 2019 classification for gastroenteropancreatic NETs.

Morphology	*Grade*	*Mitotic count/2 mm²*	*Ki-67 index (%)*
Well-differentiated NET	G1	<2	<3
Well-differentiated NET	G2	2–20	3–20
Well-differentiated NET	G3	>20	>20
Poorly-differentiated NET • Small cell • Large cell	G3	>20	>20
MiNEN Tumor-like lesions			

(MiNEN: mixed neuroendocrine non-neuroendocrine neoplasm; NET: neuroendocrine tumor; WHO: World Health Organization)



Figs. 1A to D: *Neuroendocrine carcinoma*. Histology shows a tumor arranged in the interconnected thick fascicles with intervening fibrous stroma. The tumor cells are spindle to epithelioid with hyperchromatic nuclei and scant cytoplasm. Tumor molding is seen (A). By immunohistochemistry, the tumor cells are diffusely and strongly positive for synaptophysin (B) and chromogranin (C). The MIB1 labeling index is 85–90% in the highest proliferating areas (D).

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Poorly differentiated NECs are further classified into small-cell and large-cell NECs. Another notable change was the introduction of the term mixed neuroendocrine non-neuroendocrine neoplasms (MiNENs) to include other non-neuroendocrine histological variants apart from adenocarcinoma. MiNENs comprise both neuroendocrine and non-neuroendocrine components (>30% of either one). These were earlier classified as mixed adenoneuroendocrine carcinoma (MANEC). For staging, the TNM staging system proposed by ENETS was recently widely adopted by the eighth edition of the UICC/AJCC staging system for various types of GEP-NETs.[5] For all NECs, the staging system of adenocarcinomas is applicable.[5]

CLINICAL EVALUATION, DIAGNOSIS, AND WORKUP

Evaluation for GEP-NETs can be broadly divided into:

- History and physical examination
- Biochemical testing
- Imaging
- Biopsy

History and Physical Examination

The incidence of carcinoid syndrome is around 19% in patients with NETs.[6] Intestinal NETs with carcinoid syndrome present with flushing, diarrhea, wheezing or fatigue, and shortness of breath secondary to heart failure, whereas those without carcinoid syndrome present with nonspecific vague abdominal pain. Similarly, functioning Pan-NETs usually have symptoms that fit into one of the syndromes such as Zollinger–Ellison syndrome (ZES), WDHA (watery diarrhea, hypokalemia, and achlorhydria), and Cushing's syndrome, whereas nonfunctional (NF) Pan-NETs present with nonspecific abdominal pain or, rarely, jaundice and weight loss. NETs of the gastroduodenal region can present with gastric outlet obstruction or bleeding (hematemesis, melena). Thus, the symptoms related to GEP-NETs mainly depend on the size and location of the tumor apart from its functional status. A detailed family history needs to be elucidated, especially in <40-year-old patients, to rule out familial syndromes such as multiple endocrine neoplasia type 1 (MEN1), multiple endocrine neoplasia type 2 (MEN2), neurofibromatosis type 1 (NF1), von Hippel–Lindau (VHL), and tuberous sclerosis.

Biochemical Testing

Twenty-four-hour urinary 5-hydroxy indoleacetic acid (5-HIAA) is the gold standard biochemical test for small intestinal neuroendocrine tumors (SI-NETs) (sensitivity—73%, specificity—100%).[7] An acceptable alternative is plasma 5-HIAA levels (sensitivity—89%, specificity—97%). Serum CgA is commonly found to be elevated in the majority of patients of GEP-NETs.

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However, it is not an ideal biomarker for screening as its specificity is affected by various other factors such as the use of proton-pump inhibitors (PPIs), chronic atrophic gastritis, kidney, liver, and heart failure, and several other non-neuroendocrine malignancies. Furthermore, normal serum CgA levels can also be found in GEP-NETs. However, serum CgA is specific and sensitive for tumor progression, and basal levels of serum CgA can predict overall survival (OS). It is important to note that serum CgA alone is inadequate to predict tumor progression and on follow-up, it must always be used in conjunction with imaging. Serum measurements of insulin, gastrin, glucagon, cholecystokinin, cortisol, vasoactive intestinal peptide (VIP), and insulin-like growth factor-1 (IGF-1) need to be done in the appropriate clinical setting. N-terminal pro-brain natriuretic peptide (NT-proBNP) is a useful biomarker in the diagnosis of carcinoid heart disease secondary to carcinoid syndrome. Another tumor marker elevated in 30–50% of GEP-NETs is NSE (sensitivity—38%, specificity—73%).[8] Elevated preoperative NSE does have prognostic implications but is currently not widely favored because of low sensitivity.

Imaging

Indications of radiological imaging in GEP-NETs are:

- Localization and characterization of primary tumor
- Assessment of locoregional spread of primary tumor
- Staging and evaluation of metastatic disease
- Treatment planning
- Follow-up

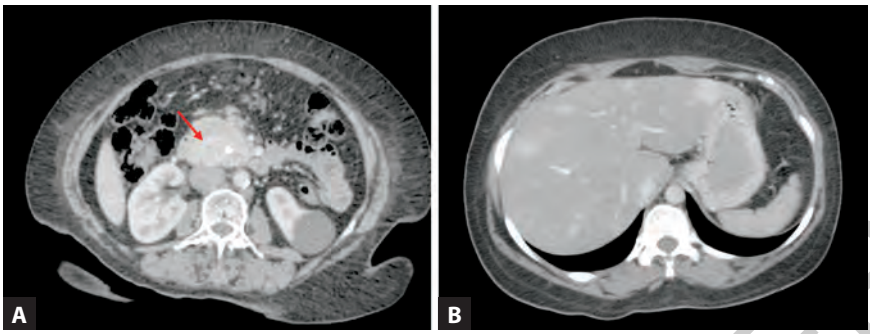
Contrast-enhanced Computed Tomography

Contrast-enhanced computed tomography (CECT) is the first investigation of choice for the assessment, staging, and surgical planning of GEP-NETs. GEP-NETs intensely enhance in the arterial phase on CECT scan as they are hypervascular tumors **(Figs. 2A and B)**.[9] The tumor size, presence of calcification and necrosis along with the pattern of enhancement are important radiological features that differentiate malignant from benign tumors. CECT scan has a sensitivity of 70–80% in the detection of a primary tumor.[9] Poor soft-tissue resolution making it difficult to differentiate between reactive and metastatic nodal tissue and exposure to ionizing radiation are the main disadvantages of CT scan.

Magnetic Resonance Imaging

Gastroenteropancreatic neuroendocrine tumors are T1 hypointense, T2 hyperintense, and brightly enhancing on postcontrast sequences **(Figs. 3A and B)**. Diffusion-weighted imaging assigns an apparent diffusion

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Figs. 2A and B: *Pancreatic neuroendocrine tumor (NET) with liver metastasis*. (A) Contrast-enhanced computed tomography (CECT) axial image showing a hyperenhancing mass (red arrow) arising from the pancreatic head and uncinate process with internal calcification; (B) CECT axial image showing hyperenhancing multiple bilobar liver metastasis.

coefficient (ADC), which helps to differentiate between well- and poorly-differentiated lesions.[10] Magnetic resonance imaging (MRI) is generally used when other imaging findings are equivocal. It is somewhat superior when compared to CECT in the evaluation of neuroendocrine liver metastasis (NELM) and subcentimetric liver lesions and also plays an important role in differentiating liver metastasis from other benign hepatic lesions.[9]

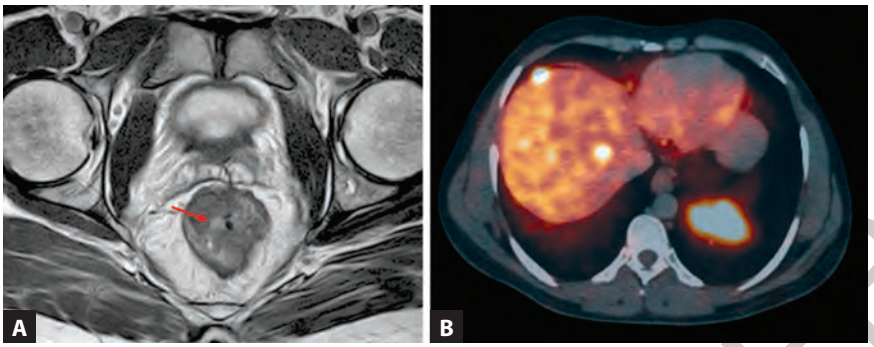
Endoscopic Ultrasound

A high-frequency ultrasound (US) probe (7.5–10 mHz) can be used taking advantage of the close proximity of the transducer to the pancreas. This results in improved image resolution and increased sensitivity (79–100%) for the detection of small and multiple Pan-NETs.[11] A major advantage of endoscopic ultrasound (EUS) is obtaining tissue biopsy during the same setting. EUS is an operator-dependent test. It is technically challenging and it requires specialized training. It may increase the cost of evaluation and may not be widely available.

Nuclear Medicine-based Functional Imaging

Somatostatin-based nuclear imaging has a very important role in the primary diagnosis as well as staging of GEP-NETs. They are equally important in the post-treatment follow-up and response evaluation after therapy.[12] One of the main characteristics inherent to the NETs is the overexpression of somatostatin receptors (SSTRs) on its cell surface, which enables imaging with somatostatin analogs labeled with different radionuclides. Functional imaging utilizes various compounds tagged with another radioactive substance that emits radiation, which, in turn, is captured by either a gamma camera or a positron emission tomography (PET) machine.

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Figs. 3A and B: *Rectal neuroendocrine tumor (NET) with liver metastasis.* (A) Magnetic resonance imaging (MRI) T2-weighted (T2W) axial image showing circumferential growth (red arrow) in the lower rectum; (B) DOTA computed tomography (CT) showing two metastatic lesions in segments VIII and IVA of the liver.

Somatostatin Receptor—Single Photon Emission Computed Tomography

^{111}Indium (^{111}In)-labeled or ^{99m}technetium (^{99m}Tc)-labeled somatostatin analogs (SSAs) are commonly used radiotracer agents. ^{111}In-pentetreotide is the most commonly used radiotracer agent. ^{99m}Tc-depreotide and ^{99m}Tc-EDDA/HYNIC-Tyr3-octreotide (^{99m}Tc-EDDA/HYNIC-TOC) are the most commonly used ^{99m}Tc-labeled SSAs.[12] ^{111}In- and ^{99m}Tc-labeled SSTR analogs have similar sensitivity in the detection of GEP-NETs due to the nonspecific abdominal tracer accumulation.[13] Their usage has decreased after the widespread availability of gallium-68 (^{68}Ga) DOTA-PET scan.

Somatostatin Receptor—Positron Emission Tomography-computed Tomography (SSTR PET-CT)

Image quality with a positron-emitting radionuclide labeled compound is superior as compared to the image quality with a gamma camera including single photon emission computed tomography (SPECT) in the diagnosis and staging of the primary lesion, as well as nodal, bone, and liver metastasis. Furthermore, PET has the capability to quantify the tracer uptake, which is expressed as the standardized uptake value (SUV). This plays an important role in the planning of peptide receptor radionuclide therapy (PRRT). SSAs are labeled with the positron emitter ^{68}Ga for PET imaging.[12] ^{68}Ga-DOTATOC, ^{68}Ga-DOTANOC, and ^{68}Ga-DOTATATE are the most commonly used SSAs labeled with ^{68}Ga.[12] Geijer and Breimer reported a sensitivity of 93% and a specificity of 95% of SSTR-PET in their meta-analysis.[14] SSTR PET-CT imaging is the current "gold standard" for the diagnosis and staging of WD grade 1 and grade 2 GEP-NETs. It also plays a key role in directing the choice of systemic therapy (e.g., appropriate patient selection for PRRT) in grade 3 NETs **(Fig. 4)**.

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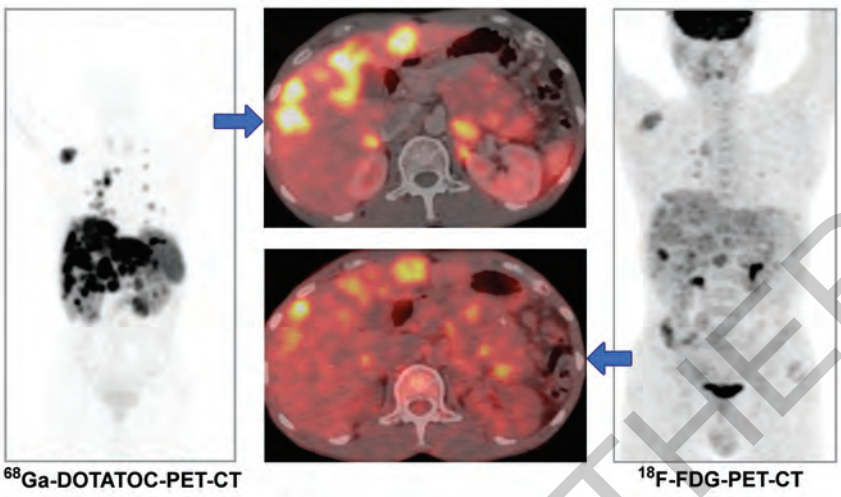


Fig. 4: *Dual-tracer imaging (*^{68}*Ga-DOTANOC and* ^{18}*FDG).* A 47-year-old gentleman presented with pain in the abdomen associated with generalized weakness and weight loss. Biopsy—WHO well-differentiated grade 2 NET, MIB1 index—8–10%. DOTA PET—MIP image shows multiple foci of tracer uptake in the region of liver, lungs, and right axillary nodes, which on fused PET/CT image corresponds to multiple DOTANOC avid liver metastases. MIP image of FDG-PET shows multiple foci of tracer uptake in liver, lungs, and right axillary nodes. Axial fused PET/CT image shows FDG avid liver metastatic lesions. *Thus, there is dual-tracer uptake on* ^{68}*Ga-DOTANOC PET/CT and FDG-PET/CT images*. This patient was managed by PRRT along with chemotherapy (capecitabine + temozolomide). (CT: computed tomography; FDG: fluorodeoxyglucose; ^{68}Ga: gallium-68; MIP: maximum intensity projection; NET: neuroendocrine tumor; PET: positron emission tomography; PRRT: peptide receptor radionuclide therapy; WHO: World Health Organization)

There is a direct correlation between the degree of SSTR expression and the SUV on DOTA-PET imaging. As a result, this can be used as an accurate imaging marker for measuring the treatment response following chemotherapy or PRRT. A modified Krenning scale scoring system is used for uptake interpretation, which compares SSTR expression at the disease site with physiological tracer uptake in the liver and spleen as follows:

- *Grade 1*: Uptake less than normal liver uptake
- *Grade 2*: Uptake equal to normal liver uptake
- *Grade 3*: Uptake greater than normal liver uptake
- *Grade 4*: Uptake more than spleen

As we progress through the spectrum of the grade of GEP-NETs (well differentiated to poorly differentiated), tumors lose their differentiation, which leads to a substantially increased expression of glucose transporter (GLUT). Thus, combined dual imaging with SSTR-PET and fluorodeoxyglucose (FDG)-PET is beneficial for metastatic WD NETs, especially in patients with Ki-67

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index between 5 and 20% or those with Ki-67 <5% and have progressed in a short span of <6 months. Also, in cases of metastatic GEP-NETs, dual imaging is important to understand the tumor heterogeneity and characterization of metastatic disease, which has important treatment implications. The utility of dual PET imaging as a baseline imaging modality in metastatic GEP-NETs provides exciting prospect as a prognostic marker as well as establishing treatment protocols. The "NETPET" score combines the complexity of dual PET imaging and combines it into a single parameter.[15] PET using other radiotracers such as ^{18}F-DOPA has a role in high serotonin production and SSTR-negative lesions, whereas ^{68}Ga-Exendin-4 PET has shown superiority in the detection of insulinomas.

PRINCIPLES OF MANAGEMENT OF GASTROENTEROPANCREATIC NEUROENDOCRINE TUMORS

It is recommended that GEP-NET cases be managed in a high-volume center with adequate experience in dealing with GEP-NETs. Management options available range from observation to liver transplantation and should be discussed and agreed upon in a multidisciplinary team comprising specialties regularly dealing with the management of GEP-NETs. Various modalities available for NETs in the armamentarium are surgery, SSAs, cytotoxic chemotherapy, molecular targeted therapy, and PRRT.

Surgery

Surgery remains the mainstay of the treatment for localized or locoregional GEP-NETs. The type and extent of surgery depend on the organ involved and the disease burden. In general, oncological resection with regional lymphadenectomy is recommended. Resection of the primary tumor and/or debulking surgery is beneficial for the local control as well as for mitigating the endocrine symptoms even when R0 resection cannot be achieved. Chemotherapy or PRRT can also be used as a neoadjuvant strategy in a few cases for downstaging the tumor to attain resectability.[16] Surgical management of site-specific GEP-NETs will be considered in the respective sections.

Somatostatin Analogs

Majority of GEP-NETs (>90%) express SSTRs. SSAs—octreotide and lanreotide—are used for symptomatic as well as in the antiproliferative treatment of GEP-NETs. Although SSAs were developed primarily for symptomatic control of NETs because of their antisecretory effect, the results of the PROMID, CLARINET, and CLARINET OLE studies confirm that SSAs do have a positive impact on the progression-free survival (PFS) as well as

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with their antiproliferative effects.[17-19] In the PROMID study, median PFS was significantly longer in the octreotide long-acting repeatable (LAR) arm as compared to the placebo (14.3 months vs. 6 months). Similarly, in the CLARINET study, which included nonfunctioning NETs, median PFS was found to be significantly longer with the lanreotide as compared to placebo (38.5 months vs. 18 months). Thus, SSA treatment is recommended in metastatic GEP-NETs with a low Ki-67 index (<10%). In the NETTER-1 study, patients with SI-NET who progressed on standard SSA dose were randomized to either PRRT or SSA dose escalation. Although PRRT was found to be superior, the higher dose of SSA did result in an additional 9 months of stabilization of the disease.[20] Abdominal pain, flatulence, diarrhea, injection site subcutaneous nodules, nausea, and development of cholelithiasis are the common side effects of SSAs. Short-acting formulations are especially useful in preventing and treating perioperative carcinoid crisis and in the management of carcinoid syndrome, and may also have a role as rescue medication in refractory carcinoid syndrome.

Peptide Receptor Radionuclide Therapy

Peptide receptor radionuclide therapy is a targeted radionuclide therapy that involves systemic administration of therapeutic peptides labeled with radionuclides that selectively target cancer cells. The preferred choice for PRRT is radiolabeled SSAs. The primary indication for PRRT is locally advanced or metastatic GEP-NETs that demonstrate a high tumor uptake on somatostatin receptor imaging (SSI) **(Fig. 5)**. Yttrium-90 (^{90}Y) and lutetium-177 (^{177}Lu) are the most commonly used radioisotopes with ^{177}Lu preferred over ^{90}Y due to a better toxicity profile. The NETTER-1 study compared PRRT versus high dose of SSA therapy in SI-NETs. At the end of 20 months, 65% of patients in the PRRT arm were without progression compared to 11% in the SSA arm.[20] Currently, PRRT is mainly used for advanced SSTR positive, WD GEP-NETs. PRRT is indicated not only in grades 1 and 2 NETs but also in grade 3 tumors having high SSTR uptake. However, careful patient selection and prospective trials are needed to further elucidate the role of PRRT in grade 3 GEP-NETs. The NETTER-2 trial is currently underway to address this issue. PRRT is administered as three to four cycles of ^{177}Lu-DOTATATE/DOTATOC with an 8-week interval between two cycles. In order to keep the SSTRs unblocked, long-acting SSAs are stopped 4–6 weeks prior to the initiation of PRRT. Side effects of PRRT include nausea, vomiting, pain, marrow depression, and renal impairment, which is usually reversible. Some of the future perspectives in PRRT are as follows:

- Role of PRRT as first-line therapy as explored by NETTER-2 trial. The NETTER-2 trial, which is currently underway, compares PRRT with SSAs versus high-dose SSAs in metastatic or locally advanced inoperable G2

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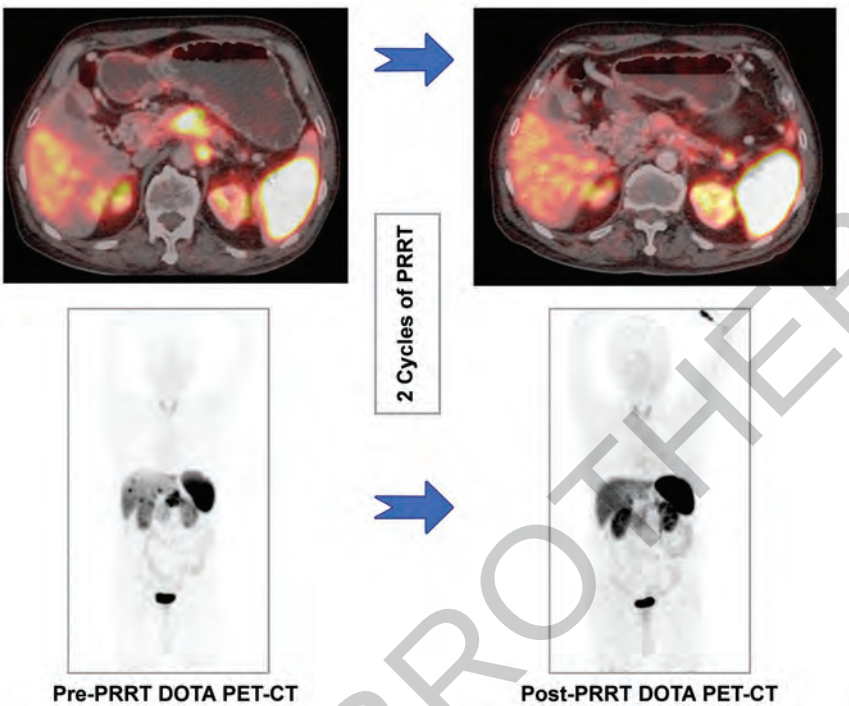


Fig. 5: *Response to PRRT*. A 63-year-old gentleman presented with decreased appetite and weight loss. Pretreatment DOTA PET-CT (MIP and axial fused) showing DOTA avid pancreatic body lesion with multiple liver metastasis. Biopsy from liver lesions was a well-differentiated grade 2 NET with MIB1 of 10%. After two sessions of PRRT, the liver lesions as well as the primary tumor have responded with no DOTA uptake seen on MIP or axial fused PET/CT images. (CT: computed tomography; MIP: maximum intensity projection; NET: neuroendocrine tumor; PET: positron emission tomography; PRRT: peptide receptor radionuclide therapy)

and G3 GEP-NETs with Ki-67 index between 10 and 55% as a first-line therapy.

- Role of PRRT in the neoadjuvant setting in Pan-NETs
- Role of retreatment with PRRT as a salvage therapy
- Role of "Tandem PRRT," which is the combination of ^{90}Y and ^{177}Lu PRRT
- Role of ^{225}actinium/^{213}bismuth/^{211}astatine-based alpha PRRT. Targeted α-particle therapy offers a therapeutic option for patients resistant to the conventional β-irradiation treatments (^{90}Y and ^{177}Lu based).
- Role of intra-arterial PRRT for NET liver metastasis. Intra-arterial PRRT involves the direct administration of radiopharmaceutical agents into the common hepatic artery to increase the site-specific concentration of the drug and avoid the first-pass metabolism due to intravenous administration in standard PRRT.

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Chemotherapy

The primary role of systemic chemotherapy is in the management of advanced Pan-NETs and grade 3 GEP-NETs or NECs of any site. Commonly used first-line chemotherapeutic drugs for advanced Pan-NETs are streptozocin/5-fluorouracil (5-FU) or capecitabine (CAP)/temozolomide (TEM). PFS and OS of 23 and 52 months, respectively, have been reported in the treatment of Pan-NETs with streptozocin/5-FU.[21] Similarly, a PFS of 11–20 months but with a slightly higher tumor size response rate is shown by treatment with CAP/TEM.[22] Thus, the combination of capecitabine and temozolomide (CAPTEM) is indicated in progressive WD GEP-NETs, primarily Pan-NETs. The toxicity profile includes nausea and hematological toxicity. Platinum-based chemotherapy with cisplatin/carboplatin plus etoposide is used in the treatment of metastases from high-grade small- or large-cell NEC G3 regardless of the primary tumor origin.

Molecular Targeted Therapy

Everolimus, a mammalian target of rapamycin (mTOR) pathway inhibitor, is approved for advanced, progressive, WD, and nonfunctioning GEP-NETs. In the RADIANT 3 trial, 410 patients with low-intermediate-grade Pan-NETs were randomized to 10 mg everolimus versus placebo. A significant improvement in PFS with everolimus (11 months vs. 4.6 months; p <0.001) was noted.[23] Similar results in other studies (RADIANT 2, RADIANT 4) were also observed with everolimus.[24,25] In the RADIANT 4 study, which included lung and GEP-NET patients, the median PFS was significantly longer in the everolimus arm as compared to the placebo arm (11.0 months vs. 3.9 months).[25]

Because of the significant adverse effects (neutropenia, infections, rash, diarrhea, and hyperglycemia), everolimus is currently reserved for patients who have significant progression of disease on other modalities. Sunitinib, a tyrosine kinase inhibitor, is also approved for use in advanced Pan-NETs. Usually, both everolimus and sunitinib are used after the progression on SSA and chemotherapy.

SITE-SPECIFIC GASTROENTEROPANCREATIC NEUROENDOCRINE TUMORS

Gastroduodenal Neuroendocrine Tumors

Gastric NETs

The origin of gastric NETs is from the enterochromaffin-like cells present in the gastric mucosa. Most gastric NETs are indolent slow-growing tumors; however, some of them can be aggressive resulting in early metastasis. They are classified as types I, II, and III **(Table 3)**. Types I and II gastric

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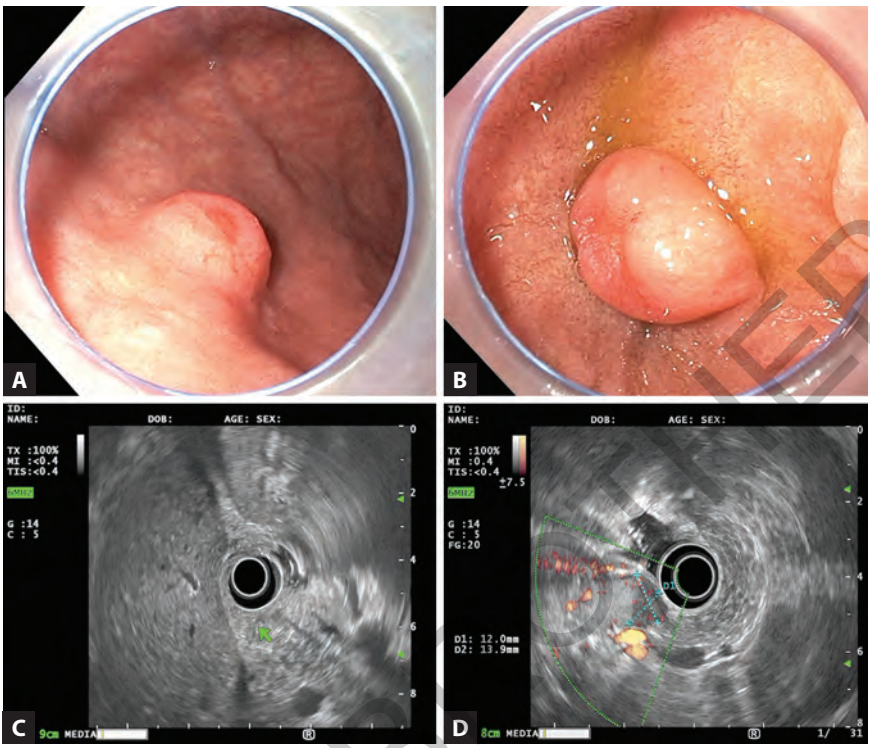
TABLE 3: Classification of gastric NETs.

	Type I	*Type II*	*Type III*
Proportion among NETs	70–80	5–6	14–25
Tumor characteristics	Often small (<1–2 cm), multiple in 65% of cases, and polypoid in 78% of cases	Often small (<1–2 cm), multiple, and polypoid	Unique, often large (>2 cm), polypoid, and ulcerated
Associated conditions	Atrophic body gastritis	Gastrinoma/MEN1	None
Pathology	G1–G2 NET	G1–G2 NET	G3 NEC
Serum gastrin levels	↑	↑	Normal
Gastric pH	↑↑	↓↓	Normal
Metastases, %	2–5	10–30	50–100
Tumor-related deaths, %	0	<10	25–30

(MEN1: multiple endocrine neoplasia type 1; NEC: neuroendocrine carcinoma; NET: neuroendocrine tumor)

NETs are usually incidentally found on upper gastrointestinal endoscopy. Type I gastric NETs arise secondary to chronic atrophic gastritis, whereas type II gastric NETs develop in patients with gastrinomas. Gastric NETs are usually <2 cm in size, multiple, and have a Ki-67 index <5%. Tissue diagnosis is achieved by endoscopic biopsy **(Figs. 6A to D)**. Serum CgA and serum gastrin are usually elevated. Gastric acid secretion is low (high pH) in type I tumors, while in type II tumors, acid secretion is high (low pH). For treatment planning, EUS evaluation of the depth of tumor invasion and regional lymph node status is recommended. Single or multiple tumors that are <1 cm can undergo close surveillance as such lesions do not exhibit malignant behavior. A large proportion of these can be kept on surveillance for a prolonged period spanning years owing to their indolent nature. For lesions >1 cm, local excision by endoscopic resection techniques can be performed. However, surgical management is indicated for those with multiple tumors, large lesions, or those invading into and beyond the muscularis propria. Type III gastric NET patients have a propensity for metastasis, usually at the time of diagnosis, and thus warrant systemic therapy. However, type III gastric NET patients with localized disease warrant surgical management, which proceeds in the same manner as for gastric adenocarcinoma (subtotal/total gastrectomy with D2 lymphadenectomy)[26] **(Flowchart 1)**. The 5-year OS in type I and type II gastric NETs is 100 and 95%, respectively, which suggests a favorable overall prognosis, whereas 5-year OS is 50% in type III NETs.

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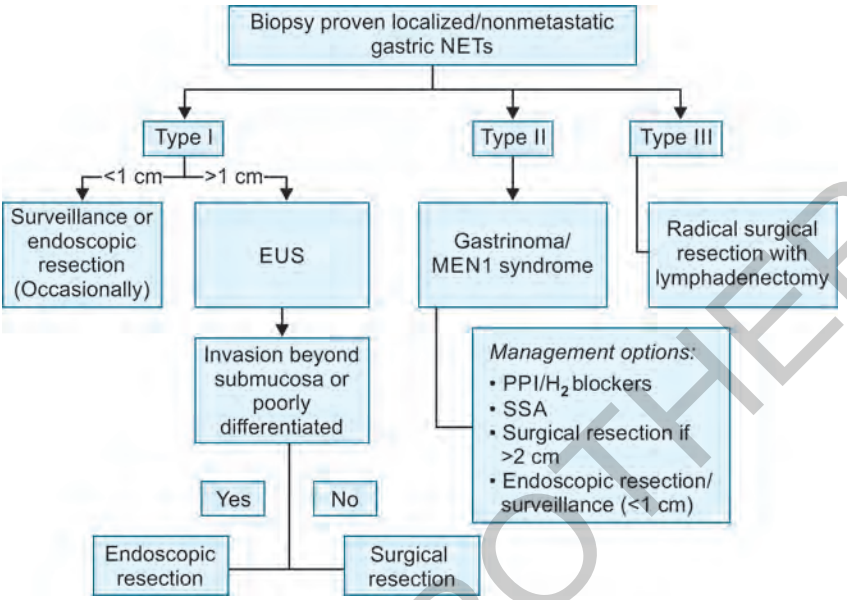
Figs. 6A to D: A 49-year-old lady presented with dyspepsia and diarrhea (six to eight times/day) with serum gastrin levels of 1,200 pg/mL. (A) Endoscopic image of a 1.1 × 1.4 cm nodule along the greater curvature of the stomach in the region of the distal body; (B) Endoscopic image of a 1.2 × 1.2 cm nodule at the D1–D2 junction with central umbilication; (C and D) EUS images of the gastric and duodenal lesion, respectively. The lesion was not found to be invading the submucosa. Biopsy of both the lesions was a well-differentiated grade 1 NET. DOTA CECT scan shows no evidence of metastasis. Patient was managed by endoscopic resection in view of persistent symptoms. (CECT: contrast-enhanced computed tomography; EUS: endoscopic ultrasound; NET: neuroendocrine tumor)

Duodenal NETs

Duodenal NETs are generally diagnosed as an incidental finding during endoscopy, and considerable heterogeneity exists in the presentation, treatment, and outcomes[27] **(Flowchart 2)**. Duodenal NETs can be divided into functioning and nonfunctioning. Nonfunctioning tumors are more common. More than 50% of the patients may have metastatic disease at the time of presentation. Histological diagnosis is achieved by endoscopic biopsy and serum gastrin and CgA may be elevated. Measurement of urinary and serum 5-HIAA levels and serum calcitonin is needed as indicated by the symptoms. CECT/MRI, EUS, and SSI are recommended for staging. As per the ENETS guidelines,[26] endoscopic resection is recommended for duodenal NETs

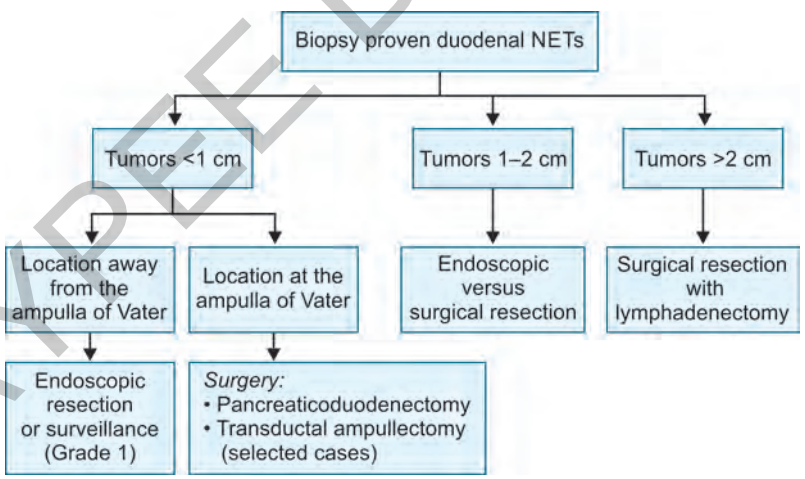
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Flowchart 1: Management algorithm for gastric NETs.



(EUS: endoscopic ultrasound; MEN: multiple endocrine neoplasia; NET: neuroendocrine tumor; PPI: proton-pump inhibitor; SSA: somatostatin analog)

Flowchart 2: Management algorithm for duodenal neuroendocrine tumors (NETs).



≤1 cm in size, confined to the submucosa (T1), and without the evidence of spread to the adjacent lymph nodes or organs. There is no consensus regarding treatment for tumors between 1 and 2 cm without worrisome features, and either surgical or endoscopic approach is justified. Formal staging workup is recommended followed by surgical resection with standard regional lymphadenectomy for tumors >2 cm in size. Another

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Puneet MS DNB (Surgery) MNAMS FACS has competed his graduation and postgraduation from Institute of Medical Sciences, Banaras Hindu University, Varanasi, Uttar Pradesh, India. He has obtained DNB in Surgery from National Board of Examination and worked as Senior Registrar in Dr Ram Manohar Lohia Hospital, New Delhi, India. Thereafter, he has worked in different hospitals in various capacities. He was appointed as Assistant Professor in King George Medical College (KGMC), UP State Colleges and Institute of Medical Sciences, Banaras Hindu University, Varanasi, Uttar Pradesh, India. However, he decided to join his alma mater. He has been elevated to Associate Professor and then Professor in the Department of Surgery, Institute of Medical Sciences, Banaras Hindu University, Varanasi, Uttar Pradesh, India.

Professor Puneet has presented various papers and delivered lectures in India and abroad. He has best paper award and travelling fellowships to his credit. He has done his Fellowship in Hepatobiliary and Pancreatic Surgery from Queen Elizabeth Hospital, Birmingham, UK. He has published more than 120 national and international papers, authored/edited 6 books and written 22 chapters in various publications. He has been Investigator to various research projects and Reviewer to journals. He is also Fellow of American College of Surgeons, Chicago and Recipient of Citation from Oklahoma, USA.

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