Article published online: 2025-08-26

Clinical Insights into Duodenal Neuroendocrine Tumors: A Case Series

Debasmita Pal[1] Adesh Kumar[1] Vijith Shetty[1] Kishan Prasad H.L.[2]

[1] Department of Medical Oncology, K.S. Hegde Medical Academy of NITTE (Deemed to be University), Mangalore, Karnataka, India
[2] Department of Pathology, K.S. Hegde Medical Academy of NITTE (Deemed to be University), Mangalore, Karnataka, India

Address for correspondence Debasmita Pal, MBBS intern, Department of Medical Oncology, K S Hegde Medical Academy of NITTE (Deemed to be University), Mangaluru, 575018, Karnataka, India (e-mail: barsha_pal@yahoo.in).

Ind J Med Paediatr Oncol

Abstract

Duodenal neuroendocrine tumors (d-NETs) are rare neoplasms representing a small subset of gastrointestinal NETs. Due to their nonspecific symptoms, such as abdominal pain, vomiting, and weight loss, diagnosis is often delayed. This case series analyzes six patients with well-differentiated d-NETs, highlighting their clinical presentation, diagnostic evaluation, treatment strategies, and follow-up. Diagnosis was established through endoscopic biopsy, imaging modalities including computed tomography (CT) and positron emission tomography-CT, and confirmed by histopathology and immunohistochemistry. Tumors were graded using the World Health Organization/European Neuroendocrine Tumor Society classification, with Ki-67 indices ranging from 1 to 6%, corresponding to grade 1 or 2 NETs. Treatment included endoscopic or surgical resection in localized cases, while somatostatin analog therapy and peptide receptor radionuclide therapy were used in multifocal or metastatic disease. All patients were managed with an individualized, multidisciplinary approach, and demonstrated stable disease on follow-up. This study emphasizes the importance of early detection, accurate grading, and personalized management to optimize outcomes in patients with d-NETs.

Keywords
- case series
- duodenal neuroendocrine tumors
- diagnosis
- octreotide therapy
- surgical resection

Introduction

Neuroendocrine tumors (NETs) are rare neoplasms originating from peptide-producing neuroendocrine cells and represent less than 1% of all malignancies.[1] Within the gastrointestinal (GI) tract, NETs account for approximately 0.4 to 1.8% of all GI malignancies, with duodenal neuroendocrine neoplasms being particularly uncommon, showing an incidence of 0.17 per 100,000.[2]

Duodenal NETs (d-NETs) comprise 1 to 3% of all GI NETs and are more prevalent in men. They are typically sporadic but may be associated with multiple endocrine neoplasia type 1 (MEN1). Most are well-differentiated, low-grade tumors, characterized histologically by uniform round nuclei, eosinophilic cytoplasm, and organoid nesting patterns.[2]

Histologically, d-NETs are classified into five types: nonfunctioning, functioning (e.g., gastrinomas, somatostatinomas), carcinoids (serotonin-secreting), duodenal paragangliomas, and poorly differentiated neuroendocrine carcinomas (NECs).[2] They often present with nonspecific symptoms such as abdominal pain, diarrhea, or GI bleeding; functional tumors may exhibit hormonal syndromes.

Diagnosis involves endoscopy with biopsy, cross-sectional imaging (computed tomography [CT] or magnetic resonance imaging [MRI]), and somatostatin receptor (SSTR)-based functional imaging (e.g., somatostatin receptor scintigraphy or Ga-68 DOTANOC positron emission tomography

DOI https://doi.org/10.1055/s-0045-1811554.
ISSN 0971-5851.

Thieme Medical and Scientific Publishers Pvt. Ltd., A-12, 2nd Floor, Sector 2, Noida-201301 UP, India

[PET]-CT).[3] NETs are graded per the World Health Organization (WHO)/European Neuroendocrine Tumor Society (ENETS) classification into grade 1 (Ki-67 $\leq$ 2%), grade 2 (Ki-67 3–20%), and grade 3 (Ki-67 $>$ 20%). NECs, in contrast, are poorly differentiated, high-grade tumors with high Ki-67 indices (usually $>$ 55%) and are not assigned grades G1 to G3.[3]

Management depends on tumor size, grade, and extent. Localized tumors $<$ 1 cm may be amenable to endoscopic resection, while larger or higher-grade lesions often require surgical resection. Advanced or unresectable cases are managed with somatostatin analogs (SSAs), peptide receptor radionuclide therapy (PRRT), chemotherapy, or targeted therapy, depending on receptor expression and tumor biology.

While well-differentiated d-NETs generally have a favorable 5-year survival of 60 to 80%, NECs are associated with poorer outcomes due to their aggressive behavior and limited treatment responsiveness.[3] Accurate histopathological classification is therefore crucial to guide individualized management as per staging and protocol.

Case Series

Case 1

A 55-year-old female presented with complaints of abdominal pain. An esophageal-gastroduodenoscopy (EGD) was performed, which revealed a 2 $\times$ 2 cm polypoidal lesion with central umbilication at the first and second part of the duodenum (D1-D2) junction. A PET scan was planned, which showed a localized tumor. Serum chromogranin levels were normal. Upon presentation, there was suspicion of solitary, enhancing fluorodeoxyglucose (FDG)-avid celiac lymph nodes, so a triple-phase CT scan was performed. The CT results suggested possible locoregional metastasis. An oncology consultation was obtained, and the patient was started on injection octreotide long-acting release (LAR). A total of three doses were planned, and she has tolerated the therapy well. Two months later, a repeat EGD was performed (►**Fig. 1**).

The findings revealed a 1.5 $\times$ 2 cm sessile polypoidal lesion with central umbilication and ulceration at the D1-D2 junction, corresponding to the previous NET site. The lesion appeared smaller than the initial endoscopic findings, suggesting mild interval regression of the d-NET. Four months later, another EGD was conducted, and a biopsy was taken from the stomach. The endoscopy showed a 1.5 $\times$ 2 cm sessile polypoidal lesion with central umbilication and ulceration at the D1-D2 junction, which appeared to have remained stable in size. Pangastritis was also noted. The biopsy report indicated features of mild chronic gastritis in the fundus/body region. The patient continued to follow-up regularly and presented for an assessment of the feasibility of resecting the NET tumor. Diagnostic endoscopic ultrasound (EUS) revealed no significant celiac adenopathy, and EUS of the NET showed no evidence of serosal involvement. Her serum chromogranin A level was 1000 ng/mL. The patient was advised about the option of full-thickness resection device (FTRD) using the Ovesco endoscopy technique for the NET. Status postresection serum chromogranin A values normalized to 90 ng/mL. She was advised to follow-up every 3 months.

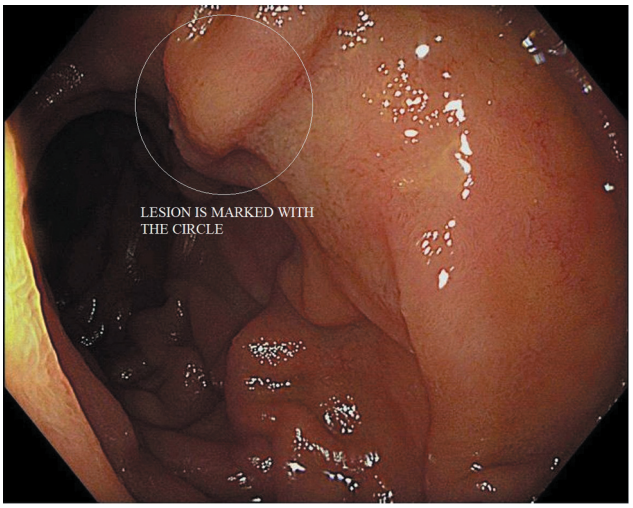

Fig. 1 Case 1: 1.5 $\times$ 2 cm sessile polypoid lesion with central umbilication and ulceration noted at the D1-D2 junction corresponding to previous neuroendocrine tumor (NET) site, comparatively decreased in size with previous endoscopic findings.

Case 2

A 63-year-old female presented with a burning sensation in the chest for 1 month. The symptoms were insidious in onset, gradually progressive, and were associated with vomiting after consuming food and liquids. She also had intermittent loose stools over the past month, with no blood in the stools.

The patient underwent clinical and radiological evaluation, which led to a diagnosis of *Helicobacter pylori*-induced antral gastritis, multiple polypoidal lesions in the first part of the duodenum (D1), multiple healed ulcers in the duodenum (D1), and grade III hiatus hernia (according to Hill classification), as per the upper GI endoscopy report. Histopathological examination (►**Fig. 2**) of the D1 polyp suggested features consistent with a NET, grade 1. The patient was regularly followed up and planned to undergo six cycles of octreotide therapy, which she tolerated well. She continued to attend follow-up appointments as scheduled.

Case 3

A 65-year-old male patient presented with severe abdominal pain and vomiting. An EUS was performed, which revealed duodenal submucosal lesions measuring 15 $\times$ 10 mm. Three hypoechoic lesions were identified within the submucosal layer, without involvement of the muscularis propria. Histopathological evaluation of the biopsy was consistent with a well-differentiated NET. Immunohistochemistry (IHC) showed positive staining for synaptophysin and chromogranin, with a Ki-67 index of 3 to 4%, classifying the tumor as WHO grade 2 (►**Fig. 3**).

Given the lesion's size, submucosal depth, and intermediate proliferative activity, surgical management was advised. A distal gastrectomy with gastrojejunostomy and

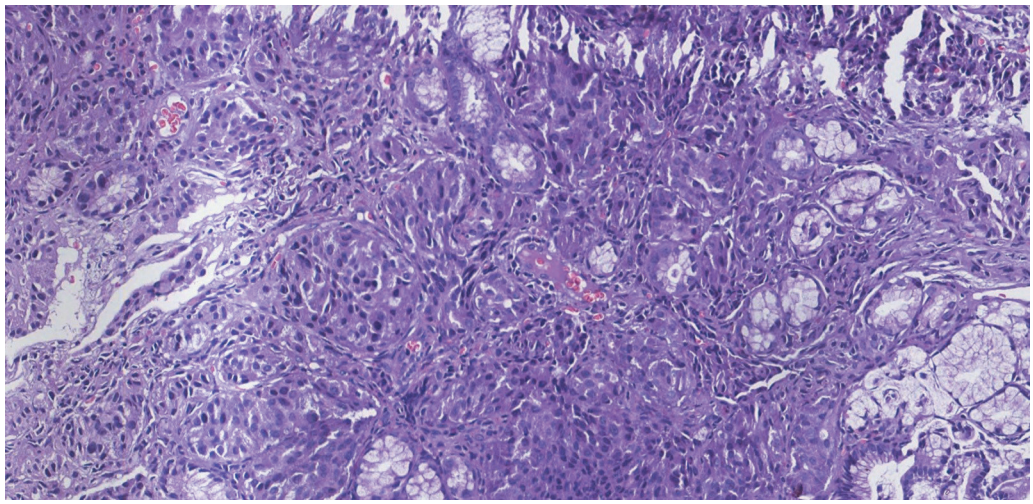

Fig. 2 Case 2: Histopathology showing clusters of tumor cells in the lamina propria of the duodenum (hematoxylin and eosin [H&E], ×100).

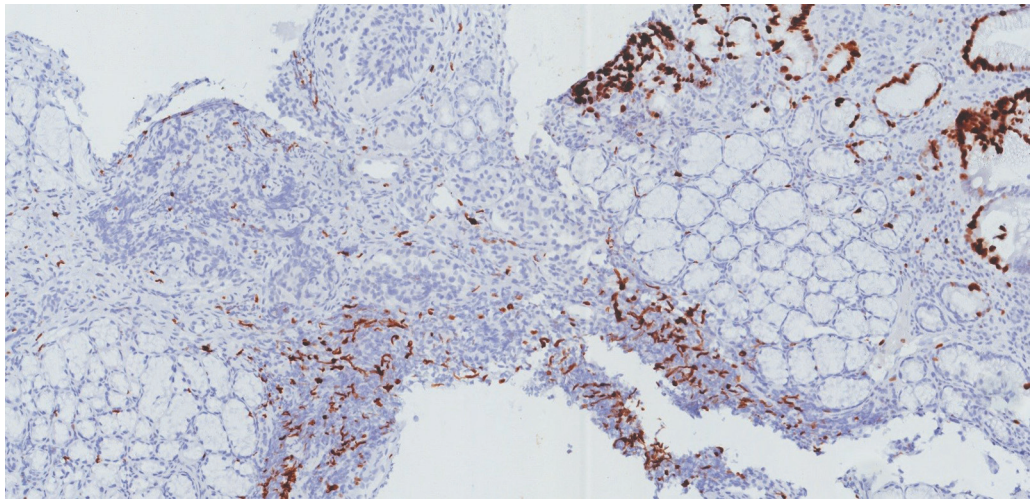

Fig. 3 Case 3: Immunohistochemistry (IHC) with Ki-67 showing 3–4% positivity.

jejunojejunostomy was performed. Analysis of the resected specimen reconfirmed a well-differentiated NET, with IHC positive for synaptophysin, chromogranin, and cluster-of-differentiation 56 (CD56), and a Ki-67 index of 6%, maintaining its classification as a grade 2 tumor. Although CD56 expression was observed, the tumor lacked morphologic features of poor differentiation and remained consistent with a NET rather than a NEC.

The patient remained clinically stable. Follow-up ultrasound showed no postoperative collections, and serial CT scans demonstrated no abnormalities.

Case 4

A 63-year-old male patient presented to the surgery department with complaints of abdominal pain for the past 4 months. The pain was insidious in onset, gradually progressive, and intermittent, associated with a burning sensation in the upper abdomen. An upper GI endoscopy was performed (►**Fig. 4**), which revealed multiple polypoid growths in the first part of the duodenum, *H. pylori*-associated antral gastritis, and several hyperplastic polyps in the first part of the duodenum. A colonoscopy was also performed, which was reported as usual. A biopsy was taken from the upper GI lesions during endoscopy. The histopathology report suggested features consistent with a NET, specifically a D1 polyp with chronic *H. pylori*-induced duodenitis. IHC markers for synaptophysin and chromogranin were positive (►**Figs. 5** and **6**) in the tumor cells, while Ki67 was 1 to 2%, classifying the tumor as WHO grade 1. A contrast-enhanced CT (CECT) scan was performed, which showed multiple well-defined, enhancing intramural polyps in the first and second parts of the duodenum, indicating primary lesions.

Additionally, the possibility of liver metastasis was noted. A gallium-68 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid (DOTA)-1-Nal^3-octreotide (DOTANOC) PET-CT scan was done to evaluate further, utilizing a SSTR radiotracer (►**Fig. 7**).

The scan revealed active somatostatin-expressing disease in multiple well-defined intramural-enhancing lesions involving the first and second parts of the duodenum,

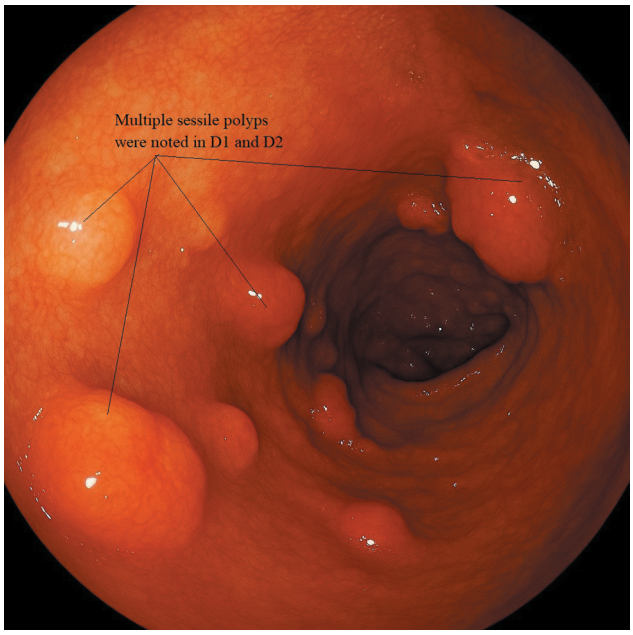

Fig. 4 Case 4: Endoscopic image of duodenum showing multiple sessile polyps, noted in D1 and D2.

confirming the known primary site—the largest lesion measured 1 × 1.9 cm. Additionally, several small non-DOTANOC-avid-enhancing lesions were observed in segments VI, VII, and VIII of the liver, with the largest measuring 8 mm. These lesions were isodense with hepatic parenchyma in the portal and venous phases. A medical oncology consultation was obtained on follow-up, and the patient was planned for DOTA therapy.

Case 5

A 64-year-old male presented with complaints of epigastric pain for the past 2 months, accompanied by early satiety, loss of appetite, and paraparesis. Blood investigations revealed mild hyponatremia. Upper GI endoscopy showed an ulcerated lesion in the gastric fundus, atrophic gastric mucosa, and a lesion in the first part of the duodenum. Biopsies were taken from both sites. Histopathology confirmed a moderately differentiated adenocarcinoma in the stomach and a well-differentiated NET, grade 2, in the duodenum. IHC was positive for synaptophysin and chromogranin, with a Ki-67 index of 5 to 6%.

A PET-CT scan revealed:

- Mild hypermetabolic thickening at the gastric cardia
- A small, non-FDG-avid duodenal nodule
- Hypermetabolic thickening in the ileal loops is suggestive of neoplastic involvement
- Low-grade activity in retroperitoneal nodes
- Mediastinal and hilar lymphadenopathy
- A lytic, hypermetabolic lesion at the fifth vertebra (D5) compressing the spinal canal, along with additional lytic lesions in the axial and appendicular skeleton

Given the multifocal disease and spinal involvement, the case was deemed systemic and advanced. Surgery was deferred, and the patient was initiated on long-acting SSA therapy (octreotide-LAR) for disease stabilization. A total of six cycles were planned, with ongoing clinical and radiological follow-up.

Case 6

A 66-year-old male presented to the outpatient department with a 3-month history of epigastric pain and vomiting. Over the past month, he also reported decreased appetite and significant weight loss. Upper GI endoscopy revealed two lesions in the first part of the duodenum. A serum chromogranin A test was positive. A PET-CT scan confirmed the presence of lesions in the first part of the duodenum, with no other abnormalities observed in the body. The patient was informed of the need for surgical intervention, and a plan for duodenectomy with gastrojejunostomy and jejunojejunostomy was made. The procedure was successfully performed later, and tissue samples were sent for histopathological examination. The report indicated a well-differentiated NET, grade 2. On follow-up, a DOTANOC PET-CT scan was repeated.

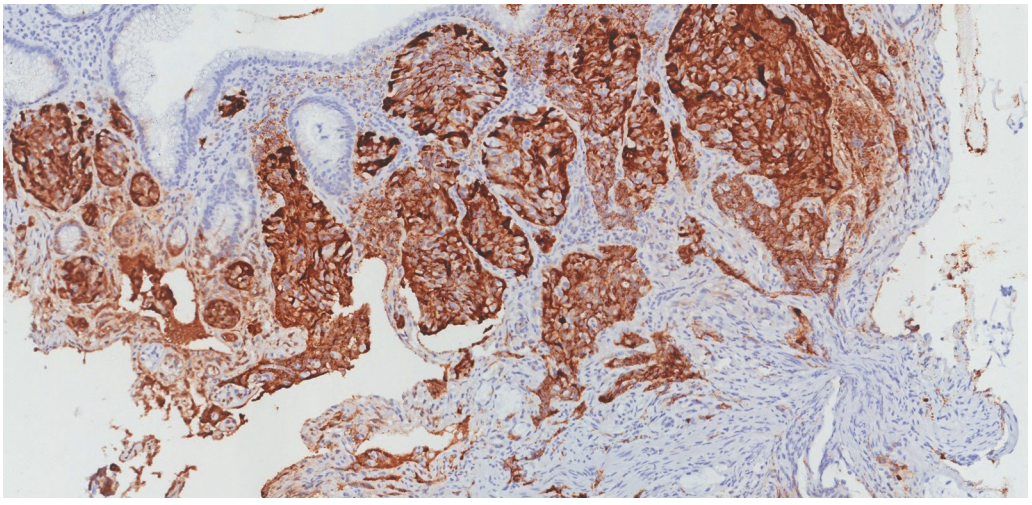

Fig. 5 Immunohistochemistry (IHC) showing chromogranin membranous positivity.

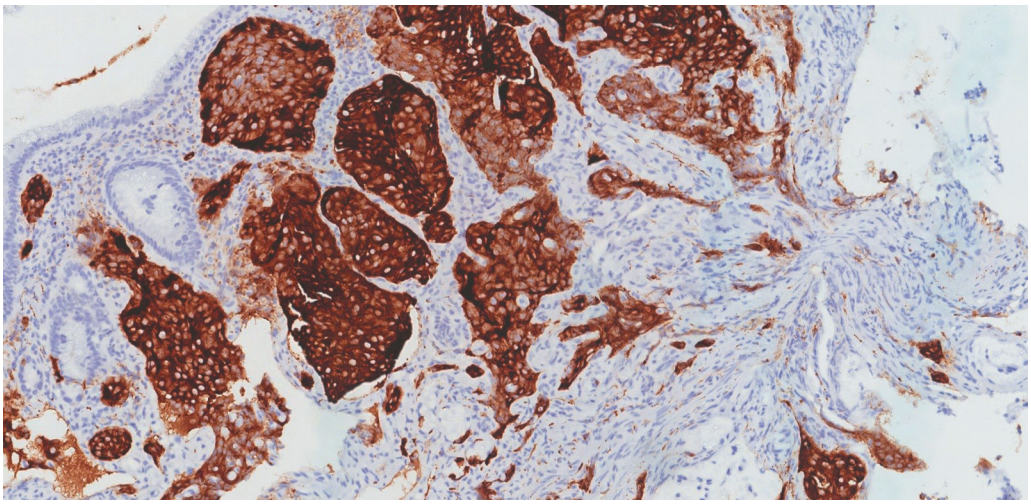

Fig. 6 Immunohistochemistry (IHC) showing tumor cells positive for synaptophysin.

The results showed the status post-duodenectomy with gastrojejunostomy and jejunojejunostomy. Mild soft tissue thickening was observed at the anastomotic site, with low-grade somatostatin expression, which could indicate postoperative inflammatory changes or potential recurrent disease. Additionally, faint somatostatin expression was noted in small perigastric, celiac axis, aortocaval, and left para-aortic nodes, likely due to reactive inflammation. No active somatostatin-expressing disease was detected elsewhere in the body. An oncology consultation was obtained, and the recommendation was to initiate therapy with octreotide-LAR, with a planned course of six cycles, as per case 2 protocol.

Summarizing all the cases, ►**Table 1** has been added.

Discussion

Epidemiology and Presentation

d-NETs represent nearly 2% of all gastroenteropancreatic (GEP) neoplasms, most sporadic and nonfunctional.[2,4] Notably, 90% of d-NETs are not associated with a functional clinical syndrome, and more than 90% are located in the first or second part of the duodenum.[2,4] These tumors are primarily nonfunctional and may remain asymptomatic in the early stages. Symptoms typically emerge as the tumor grows and invades surrounding tissues. Early symptoms can be nonspecific, which makes the diagnosis of NETs challenging. These tumors most commonly present in the 6th decade of life, with a higher incidence in males. The majority of GEP-NETs are nonfunctional and are clinically presented with symptoms such as abdominal pain, upper GI bleeding, anemia, or jaundice. In our series, there were six cases, four male and two female patients, aged between 55 and 66 years. All patients presented with nonspecific symptoms, including prolonged abdominal pain, nausea, and vomiting. Other signs, such as early satiety and reduced appetite, were also observed.

Diagnosis

CT scans are typically the first imaging modality when a patient presents with symptoms suggestive of a NET.[5] However, according to the ENETS guidelines, MRI is considered superior for detecting and following primary tumors and liver metastases compared to CT. In some of our cases, a Ga-68 DOTANOC PET-CT scan was performed, which proved helpful in better staging the disease. Ga-68 DOTANOC PET-CT was used in our case to assess SSTR expression, enabling accurate staging and therapeutic planning, particularly in the context of suspected multifocal or metastatic well-differentiated NETs. A study on Ga-68 DOTANOC PET/CT imaging for detecting the primary site in patients with metastatic NETs of unknown origin highlights the promising role of this modality. Ga-68 DOTANOC PET/CT should be considered a first-line investigation in such cases.[6] Studies by Ambrosini et al[7] and Naswa et al[8] evaluating the role of Ga-68 DOTANOC PET/CT in initial staging found a sensitivity range of 78 to 92% and a specificity between 92.5 and 98% for detecting NETs. The increasing use of Ga-68-labeled SSAs in PET/CT imaging emphasizes the need to assess their appropriate role in managing these tumors.[6]

Upper GI endoscopy with biopsies remains the gold standard for diagnosing d-NETs.[5] Surgical resection is recommended for all sporadic d-NETs unless contraindicated by medical comorbidities or the presence of distant metastases. Endoscopic resection is an option for minor, non-gastrinoma d-NETs after excluding lymph node metastases via EUS or other localization studies. Surgery, such as local resection with lymphadenectomy or pancreaticoduodenectomy, is typically performed for patients with duodenal gastrinomas, large d-NETs (> 2 cm), tumors extending beyond the submucosa, lymph node metastases, or d-NETs in the periampullary region. Correlation with the case series has been done in the treatment section.

Histology

The histological characteristics of GI-NETs are critically important in guiding diagnosis, prognosis, and therapeutic strategies. These tumors are classified according to the WHO and ENETS criteria based on tumor differentiation and proliferative activity, specifically the Ki-67 index and mitotic count. Well-

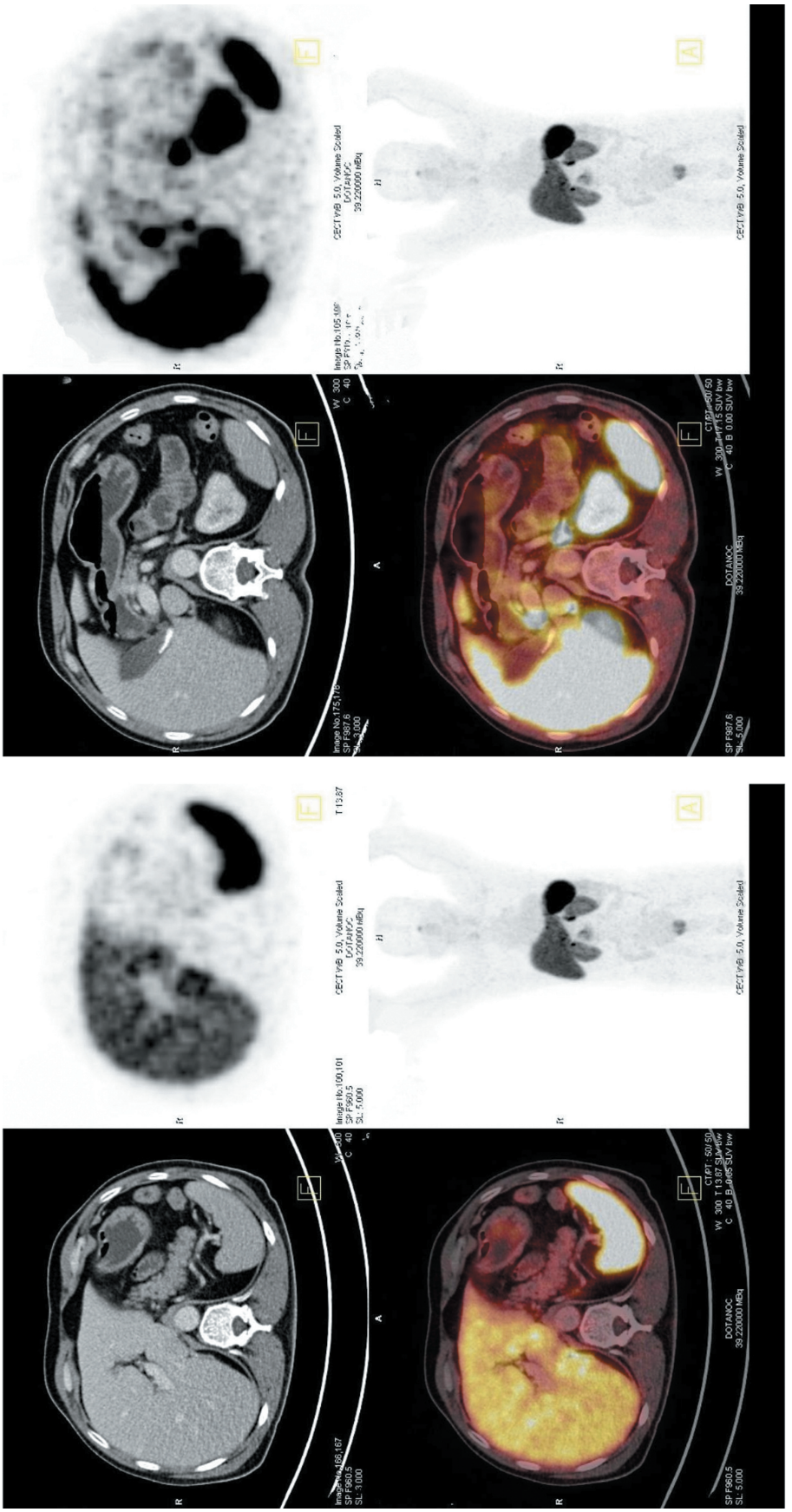

Fig. 7 Active somatostatin-expressing disease in multiple well-defined intramural-enhancing lesions involving the first and second parts of the duodenum, confirming the known primary site. The largest lesion measured 1 × 1.9 cm. Additionally, several small non-DOTA-1-Nal^3-octreotide (DOTANOC)-avid-enhancing lesions were observed in segments VI, VII, and VIII of the liver, with the largest measuring 8 mm.

Table 1 Summary of cases

Case	Age/Sex	Symptoms	Location	Grade (WHO)	Ki-67 index	IHC markers (Pos.)	Treatment	Outcome/Status
1	55/F	Abdominal pain	D1–D2 junction	G2	Not stated	Chromogranin, synaptophysin	Octreotide LAR → FTRD resection	Stable, biochemical response
2	63/F	Epigastric pain, vomiting	D1	G1	1–2%	Chromogranin, synaptophysin	Octreotide LAR (6 cycles)	Stable
3	65/M	Severe pain, vomiting	D1 submucosa	G2	3–6%	Chromogranin, synaptophysin, CD56	Distal gastrectomy + bypass	No recurrence on follow-up
4	63/M	Epigastric pain, multiple polyps	D1–D2	G1	1–2%	Chromogranin, synaptophysin	PRRT planned (Ga-68 DOTANOC + liver mets)	On systemic therapy
5	64/M	Epigastric pain, paraparesis	D1	G2	5–6%	Chromogranin, synaptophysin	Octreotide LAR (6 cycles)	Advanced, systemic disease
6	66/M	Epigastric pain, weight loss	D1	G2	Not stated	Chromogranin, synaptophysin	Duodenectomy + octreotide LAR (6 cycles)	Stable, follow-up ongoing

Abbreviations: F, female; FTRD, full-thickness resection device; IHC, immunohistochemistry; LAR, long-acting release; M, male; PRRT, peptide receptor radionuclide therapy; WHO, World Health Organization.

differentiated NETs are categorized into grade 1 (Ki-67 < 3%), grade 2 (Ki-67 3–20%), and grade 3 (Ki-67 > 20%), with higher grades indicating increased tumor aggressiveness, rapid progression, and poorer prognosis. Functionality—whether the tumor secretes bioactive hormones—further impacts clinical presentation and biochemical monitoring. Poorly differentiated NECs, which may histologically resemble small cell carcinoma, are aggressive and typically require systemic cytotoxic chemotherapy. IHC plays a pivotal role in diagnosis, with chromogranin A, synaptophysin, and CD56 serving as key markers for neuroendocrine lineage, while the Ki-67 index provides grading information.

In the present case series, all six tumors were classified according to the WHO/ENETS grading system as well-differentiated NETs, ranging from grade 1 to 2. No tumors demonstrated features consistent with poorly differentiated NEC. Although CD56 expression was observed in one case (case 3), this was not accompanied by cytological atypia, necrosis, or a high proliferative index typically required to classify a tumor as NEC. While CD56 is more commonly associated with NEC, it may also be expressed in well-differentiated NETs and is not a sole criterion for classification. Although Ki-67 indices ranged from 1 to 6%, all tumors retained well-differentiated morphology. The slight increase in Ki-67 in some postoperative specimens (e.g., case 3) likely reflects intratumoral proliferative heterogeneity, a recognized feature in NETs that does not alter the classification when morphology remains consistent. Immunohistochemical staining demonstrated uniform positivity for chromogranin A and synaptophysin in all cases, confirming neuroendocrine origin. The tumors also exhibited typical NET architecture, including organoid nesting, eosinophilic cytoplasm, and uniform round nuclei. These histopathological and immunohistochemical findings were central to accurate grading, prognostication, and formulation of individualized treatment strategies across the spectrum of disease presentations.

Current guidelines for management (2024–2025): The current management guidelines as suggested by authoritative sources such as ENETS, the National Comprehensive Cancer Network, European Society for Medical Oncology, and the North American Neuroendocrine Tumor Society emphasize a comprehensive, stepwise protocol based on tumor location, grade (as determined by Ki-67 index and mitotic rate), differentiation, functionality, and extent of disease. Initial workup includes biochemical markers such as chromogranin A and 24-hour urinary 5-hydroxyindoleacetic acid (5-HIAA) for functional tumors, along with imaging via CECT/MRI and 68Ga-DOTATATE PET/CT for staging and SSTR status. For localized, well-differentiated (grade 1 or 2) tumors, complete surgical resection is the treatment of choice, including lymphadenectomy in small bowel NETs due to high metastatic risk. Rectal NETs under 1 cm may be removed endoscopically, while larger or invasive lesions require transanal or radical excision. For metastatic or unresectable well-differentiated NETs, long-acting SSAs such as octreotide LAR or lanreotide are first-line to control hormone-related symptoms and slow tumor progression. Patients with disease progression on SSAs or high tumor burden and positive

Table 2 NET type and management guidelines

NET type	Grade	First-line treatment	Advanced treatment
Gastric NET	Type I/II	Endoscopic/Surgical resection	SSA (if functional)
Small bowel NET	G1/G2	Surgical resection	SSA → PRRT → Targeted therapy
Pancreatic NET	G1–G2	Resection if possible	Everolimus/Sunitinib/SSA → PRRT
High-grade NEC (G3)	Poorly diff.	Chemotherapy (Platinum-based)	Second-line chemo or clinical trials

Abbreviations: NEC, neuroendocrine carcinoma; NET, neuroendocrine tumor; PRRT, peptide receptor radionuclide therapy; SSA, somatostatin analog.

SSTR imaging are eligible for PRRT using 177Lu-DOTATATE. For pancreatic NETs, targeted therapies like everolimus, a mechanistic target of rapamycin (mTOR) inhibitor, or sunitinib (tyrosine kinase inhibitor) are indicated in progressive, advanced disease. Liver-directed therapies, including embolization or ablation, are considered in hepatic-dominant disease. High-grade (grade 3), poorly differentiated NECs are managed with systemic chemotherapy, typically a platinum-etoposide regimen. Regular surveillance with imaging every 3 to 12 months, along with monitoring of biomarkers, is essential for detecting recurrence or treatment response. A multidisciplinary team including oncology, surgery, radiology, pathology, and nuclear medicine is central to optimizing individualized patient care (►**Table 2**).

Treatment Reasoning

Case 1: The lesion was identified as sessile, centrally umbilicated, and ulcerated, located at the D1–D2 junction—an anatomically complex region that poses significant challenges for standard endoscopic mucosal resection or surgical wedge resection. Its proximity to the ampulla of Vater increases the risk of iatrogenic injury to the common bile duct or pancreatic duct during conventional resection. Initial imaging revealed FDG-avid celiac lymph nodes, and a triple-phase CT scan raised the possibility of locoregional metastasis, suggesting disease extension beyond the scope of local resection. Given these findings and the patient's clinically stable status, the multidisciplinary team initiated medical management with long-acting SSA (octreotide LAR) and opted for close surveillance. Follow-up EUS demonstrated lesion stability and no evidence of serosal invasion or nodal enlargement. Based on this favorable reassessment, FTRD using the Ovesco FTRD system was performed. This approach offers en bloc excision with secure closure in anatomically difficult areas, making it increasingly preferred for d-NETs larger than 1 cm or those located near critical structures. The intervention was successful, with postresection serum chromogranin A levels declining from 1000 to 90 ng/mL, indicating both biochemical response and likely curative resection.

Case 2: The patient presented with upper GI symptoms including epigastric discomfort, vomiting, and intermittent loose stools. Endoscopic evaluation revealed multiple duodenal lesions along with *H. pylori*-induced gastritis and a large hiatal hernia, complicating the clinical picture. Histopathology confirmed a grade 1 well-differentiated NET in the first part of the duodenum (D1). While grade 1 NETs are typically indolent and may be amenable to local resection, the presence of multiple polypoidal lesions suggested multifocal disease, making endoscopic or surgical resection technically challenging and potentially incomplete. Moreover, her coexisting GI conditions (healed duodenal ulcers, severe reflux, and grade III hiatus hernia) may have further increased procedural risks. Considering these factors, a noninvasive, systemic approach using long-acting SSA (octreotide LAR) was selected. This decision aligns with current guidelines for managing low-grade, nonresectable, or multifocal d-NETs, where medical therapy serves to both stabilize the disease and manage any occult hormone-related activity. The patient tolerated the octreotide therapy well and remained stable on follow-up.

Case 3: Surgical resection was chosen due to the lesion's size (15×10 mm), submucosal depth, and intermediate proliferative index (Ki-67 up to 6%), which increased the risk of progression. The presence of multiple submucosal lesions and the technically challenging duodenal location made endoscopic resection less feasible. Surgery also allowed for complete staging and ensured clear margins in a well-differentiated grade 2 NET.

Case 4: Despite the tumor being classified as a grade 1 well-differentiated NET based on Ki-67 index (1–2%) and immunohistochemical positivity for synaptophysin and chromogranin, the presence of multiple primary lesions in both the first and second parts of the duodenum, as well as suspicious liver lesions on imaging, indicated multifocal disease with possible metastasis. The Ga-68 DOTANOC PET-CT scan confirmed SSTR-positive disease in the duodenum and revealed nonavid hepatic lesions suggestive of early metastatic spread. Given this systemic disease burden, localized surgical or endoscopic resection was not considered sufficient. Therefore, the patient was appropriately referred for PRRT with a DOTA-conjugated radiolabeled SSA, which is in line with the current guidelines for treating unresectable, metastatic, SSTR-positive NETs. This approach offers targeted cytoreduction while preserving liver function and overall systemic control.

Case 5: Given the presence of advanced systemic disease, including bone metastases with spinal involvement, retroperitoneal and mediastinal lymphadenopathy, and possible multifocal intestinal disease, curative surgery would not be appropriate. The duodenal lesion, confirmed as a well-differentiated grade 2 NET with Ki-67 of 5 to 6%, showed SSTR expression. Therefore, the patient was initiated on long-acting SSA therapy (octreotide-LAR) to control tumor progression, alleviate potential hormonal symptoms, and stabilize systemic disease, in accordance with the current guidelines for unresectable or metastatic NETs.

Table 3 Summarizing treatment reasoning

Case	Key clinical features	NET grade / Ki-67	Main treatment	Treatment rationale
1	Solitary D1–D2 lesion, centrally umbilicated, FDG-avid node, no serosal involvement	G2 / Not stated	Octreotide-LAR → FTRD resection	Anatomically complex location near ampulla, initial suspicion of nodal spread, lesion stabilized with SSA; FTRD enabled safe en bloc removal
2	Multifocal duodenal lesions, large hiatal hernia, *H. pylori* gastritis	G1 / 1–2%	Octreotide-LAR	Multifocal disease and poor surgical candidacy due to comorbidities; SSA chosen for stabilization and symptom control
3	3 submucosal lesions (15 × 10 mm), technically challenging location	G2 / 3–6%	Distal gastrectomy + bypass	Intermediate grade, multifocal deep submucosal lesions not amenable to EMR; surgery ensured margin clearance and staging
4	Multifocal D1–D2 lesions, non-avid liver lesions on DOTANOC PET	G1 / 1–2%	PRRT	Evidence of systemic spread; SSA and surgery insufficient; PRRT initiated for receptor-positive metastatic NET
5	Gastric adenocarcinoma + D1 NET, bone and spinal metastases, hilar/mediastinal lymphadenopathy	G2 / 5–6%	Octreotide-LAR (6 cycles)	Advanced systemic disease; SSA used to control progression and stabilize hormone activity
6	D1 lesion surgically resected, low-grade nodal uptake post-op on DOTANOC	G2 / Not stated	Duodenectomy + Octreotide-LAR (6 cycles)	Postop scan showed mild residual/recurrent uptake; SSA started as adjuvant therapy to reduce recurrence risk

Abbreviations: EMR, endoscopic mucosal resection; FDG, fluorodeoxyglucose; FTRD, full-thickness resection device; LAR, long-acting release; NET, neuroendocrine tumor; PRRT, peptide receptor radionuclide therapy; SSA, somatostatin analog.

Case 6: The patient was diagnosed with a grade 2 well-differentiated d-NET, confirmed histologically following successful surgical resection via duodenectomy with gastrojejunostomy and jejunojejunostomy. Although the initial PET-CT scan showed no distant disease, postoperative DOTANOC imaging revealed mild somatostatin expression at the anastomotic site and in a few regional lymph nodes. While these findings may reflect postsurgical inflammatory changes, the possibility of microscopic residual disease or early recurrence could not be completely excluded, especially in the context of a grade 2 tumor, which carries an intermediate risk of progression.

Given this background, a prophylactic or adjuvant approach with long-acting SSA therapy (octreotide-LAR) was recommended. This aligns with current guidelines for managing resected, intermediate-grade NETs with uncertain residual activity, where SSAs are used to delay recurrence, stabilize residual disease, and improve progression-free survival (PFS). The decision to proceed with six planned cycles of therapy, as per the institutional protocol used in similar cases, was based on both the histological grade and functional imaging findings, despite the absence of overt SSTR-positive metastatic disease.

Summarizing the treatment selection in ►**Table 3**.

Discussing Recent Advances

Recent clinical trial data from 2025 have expanded the therapeutic options for patients with GEP NETs. The phase III COMPETE trial (NCT03049189) demonstrated that lutetium-177 (^177Lu)-edotreotide (ITM-11), an investigational radiolabeled peptide conjugate, significantly improved PFS compared to everolimus (Afinitor) among patients with grade 1 or 2 GEP NETs. ITM-11 not only reached its primary endpoint but also exhibited a favorable safety profile in this population, marking it as a promising therapeutic alternative to mTOR inhibition with everolimus.[9] In another advancement, the phase III CABINET trial (NCT03375320) evaluated cabozantinib (Cabometyx) versus placebo in patients with previously treated extrapancreatic NETs of GI origin. Among the GI NET subgroup ($n = 116$), those treated with cabozantinib ($n = 70$) achieved a median PFS of 8.5 months compared to 5.6 months in the placebo group ($n = 46$), a statistically significant difference (hazard ratio = 0.50; $p = 0.007$). Additionally, 69% of patients in the cabozantinib group had stable disease, with only 9% showing progression, compared to 26% in the placebo group.[10] The STARTER-NET trial (phase III) tested the combination of everolimus and lanreotide versus everolimus alone in patients with advanced or recurrent GEP NETs. The combination therapy nearly doubled median PFS (29.7 vs. 11.5 months), prompting early termination of the trial due to clear efficacy.[11] Furthermore, the ongoing Retreatment PRRT Trial (Phase II) is assessing the benefits of repeat 177Lu-DOTATATE therapy versus standard care in patients with progressive NETs after initial PRRT, representing another effort to refine personalized treatment strategies.

Survival rate: In our series of cases, at the time of follow-up, all patients were clinically stable with no mortality reported, and imaging showed no evidence of progression

or recurrence, suggesting favorable short- to mid-term outcomes. This aligns with existing literature, which reports 5-year overall survival (OS) rates of 75 to 90% for well-differentiated, nonfunctional d-NETs treated surgically.[12] In contrast, poorly differentiated NECs, which were absent in this cohort, are associated with much poorer prognosis, with median survival under 2 years and 5-year OS below 20%.[13] Quality of life (QoL) in patients with d-NETs is influenced by tumor-related symptoms, treatment side effects, and long-term functional outcomes. Many d-NETs are nonfunctional, but advanced disease or therapy (e.g., SSA-induced GI effects) may impair daily well-being. Surgical or endoscopic resection often restores QoL by reducing tumor burden. Ongoing surveillance and patient-centered symptom management are essential to maintain health-related QoL over time.

Conclusion

d-NETs are rare, biologically diverse, and often diagnostically elusive. While the WHO and ENETS classifications guide clinical decisions, uncertainties persist for multifocal, intermediate-grade, or anatomically complex cases. Although global advances in imaging and therapies have improved outcomes, d-NETs remain underrepresented in prospective studies—particularly in India.

This series—one of the most detailed Indian contributions in recent years—highlights six histologically confirmed cases managed with DOTANOC PET-CT, FTRD, SSAs, and adherence to updated 2024 to 2025 guidelines. Favorable short-term outcomes underscore the value of individualized, multidisciplinary care.

Limitations include its retrospective design, small sample size, brief follow-up, lack of QoL data, and absence of molecular profiling. Nonetheless, this work adds important context to real-world Indian NET management and reinforces the need for multicentric research and national registries to advance care for these rare tumors.

Authors' Contributions

V.S., K.P.H.L.: Concepts. D.P., A.K.: Design; D.P., V.S., K.P.H.L.: Definition of intellectual content; D.P.: Literature search; D.P., A.K., V.S.: Clinical studies; A.K., K.P.H.L.: Data analysis; D.P., K.P.H.L.: Manuscript preparation; A.K.: Manuscript editing; D.P., A.K., V.S., K.P.H.L.: Manuscript review; A.K.: Guarantor.

Ethical Approval

Institutional ethical committee approval was obtained.

Patient's Consent

Informed consent was obtained from the patient or the patient's party for the publication of the cases. No patient information was used without consent. The identity of the patients and the patient party has been kept confidential.

Funding

None.

Conflict of Interest

None declared.

Acknowledgments

The authors would like to thank the Departments of Medical Oncology, Pathology, Medical Gastroenterology, and General Surgery of K.S. Hegde Medical Academy, Mangalore, and the Department of Nuclear Medicine of A.J. Medical College, Mangalore, for providing the information and resources to go forward with the case series.

References

1 Wang X, Wu Y, Cao X, Zhang X, Cheng Y, Kong L. Duodenal neuroendocrine tumor: a rare case report. Medicine (Baltimore) 2021;100(06):e24635
2 Sultana Q, Kar J, Verma A, et al. A comprehensive review on neuroendocrine neoplasms: presentation, pathophysiology and management. J Clin Med 2023;12(15):5138
3 Rindi G, Mete O, Uccella S, et al. Overview of the 2022 WHO classification of neuroendocrine neoplasms. Endocr Pathol 2022; 33(01):115–154
4 Yao TJ, Shah MH, Shia J, et al. What every gastroenterologist should know about gastrointestinal neuroendocrine tumors. Am J Gastroenterol 2023;118(04):606–609
5 Yao JC, Shah MH, Ito T, et al. Neuroendocrine tumors of the pancreas and gastrointestinal tract: a clinical practice guideline. J Natl Compr Canc Netw 2021;19(07):839–868
6 Pruthi A, Pankaj P, Verma R, Jain A, Belho ES, Mahajan H. Gallium-68-DOTA-NOC PET/CT in neuroendocrine tumors: a prospective single-centre study. J Gastrointest Oncol 2016;7(03):449–461
7 Ambrosini V, Campana D, Tomassetti P, Fanti S. ^{68}Ga-labelled peptides for diagnosis of gastroenteropancreatic NET. Eur J Nucl Med Mol Imaging 2012;39(Suppl 1):S52–S60
8 Naswa N, Sharma P, Kumar A, et al. Gallium-68-DOTA-NOC PET/CT in gastroenteropancreatic NETs: a prospective single-centre study. AJR Am J Roentgenol 2011;197(05):1221–1228
9 Capdevila J, Borbath I, Pavel M, et al. COMPETE: a phase III trial of 177Lu-edotreotide vs everolimus in patients with progressive, SSTR-positive GEP-NETs. Presented at: ENETS 2025 Annual Conference; March 6, 2025; Krakow, Poland
10 Chan JA, Yao JC, Pavel M, et al. CABINET: a phase III trial of cabozantinib vs placebo in advanced pancreatic and extra-pancreatic NETs. N Engl J Med 2024;391(12):1123–1134
11 Hijioka S, Honma Y, Machida N, et al. STARTER-NET: a phase III study of everolimus plus lanreotide vs everolimus alone in unresectable or recurrent GEP-NETs. J Clin Oncol 2025;43 (4_suppl):Abstract 652. Doi: 10.1200/JCO.2025.43.4_suppl.652
12 Mandair D, Kamieniarz L, Pizanias M, et al. Diagnostic features and management options for duodenal neuroendocrine neoplasms: a retrospective, multi-centre study. Sci Rep 2022;12(01):15762
13 Basturk O, Tang L, Hruban RH, et al. Poorly differentiated neuroendocrine carcinomas of the pancreas: a clinicopathologic analysis of 44 cases. Am J Surg Pathol 2014;38(04):437–447

