Neuroendocrine Tumors (Gastroenteropancreatic)

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Introduction

An increasing incidence (per 100,000 population per year) has been reported in multiple recent population-based studies throughout the world. In the USA, the prevalence of neuroendocrine tumors (NETs) is 3.5 per 100,000 [1]. In Ontario, Canada, the incidence of NETs went from 2.48 (1994) to 5.86 (2009) [2]. This increase is likely explained by better detection, diagnosis, and classification [2]. Combined with prolonged survival, this explains that NETs are now more prevalent than esophageal, gastric, and pancreatic carcinoma combined [2–4]. Distribution and survival of various NETs are summarized in Table 18.1.

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Table 18.1 Distribution, presentation, and survival of neuroendocrine tumors [2]

Site	Proportion of all NETs (%)	Metastases at presentation (%)	Metachronous metastases (%)	10-year overall survival (%)
Stomach	5.0	10.6	23	49.7
Small intestine	18.1	34	42.3	51.2
Colon[a]	12.9	22.6	37.6	48.3
Rectum	12.3	3.3	13.3	84.0
Pancreas	9.4	23.4	57.8	30.2
Broncho-pulmonary	25.0	14.3	33.9	49.7
Others	17.3	28.8	50.7	23.1

[a]This group includes appendiceal NET

For the purpose of this chapter, we focus on well-differentiated gastroenteropancreatic (GEP) NETs. Primary pulmonary, thyroid, or thymic NETs and gynecological and poorly differentiated NETs are beyond the scope of this chapter.

Pathological Classification and Grading

- If the histology is suggestive of NET, confirmation of GEP-NET requires immunohistochemistry (IHC) for low molecular keratin and chromogranin, as well as synaptophysin (optional). The neuroendocrine granules contained in the cells stain strongly for chromogranin and most often synaptophysin [5, 6].
- The histological grading system of NETs is determined by both the proliferation index (using the Ki-67 labeling index or the mitotic index) and differentiation. It is most commonly classified according to the World Health Organization (WHO) and UICC/AJCC, which is endorsed by the European Neuroendocrine Tumor Society (ENETS) and the North American Neuroendocrine Tumor Society (NANETS) [7]. This grading system is independent of tumor stage.
- Ki-67 labeling index requires automated or manual counting of 1000 cells. The grade is assigned based on the region with most intensive labeling ("hotspot") [6].
- The most recent WHO grading classification of NETs was updated in 2017 [3] and is summarized in Table 18.2. It includes a new distinction between poorly-differentiated G3 (G3 neuroendocrine *cancers*) and well-differentiated G3. NENs (G3 neuroendocrine *tumors*) recognizes different biology, response to treatment, and prognosis, and was initially developed for pancreatic tumors [30].
- In case of metastatic disease without identified primary tumor, additional IHC can support identification of the primary tumor site (see Table 18.3) [6].

Table 18.2 Derived from 2017 World Health Organization neuroendocrine neoplasm classification [8]

	Differentiation		Criteria
Grade 1 (G1)	Well differentiated (called neuroendocrine tumor)		<2 mitosis/10 HPF <3% Ki-67 index
Grade 2 (G2)	Well differentiated (called neuroendocrine tumor)		3–20% Ki-67 index 2–20 mitosis/10 HPF
Grade 3 (G3)	**Well differentiated** (neuroendocrine tumor)		>20 mitosis/10 HPF >30% Ki-67 index
	Poorly differentiated (neuroendocrine cancer)	Small cells	>20 mitosis/10 HPF >30% Ki-67 index
		Large cells	
Mixed neuroendocrine non-neuroendocrine neoplasms **(MiNEN)**		Combination of neuroendocrine histology with another histology, each accounting for ≥30% of the specimen	Grade is assigned based on grading of the most aggressive histological component

GEP gastroentropancreatic, *NET* neuroendocrine tumor, *GI* gastrointestinal, *Panc* pancreatic, *HPF* high power field

Table 18.3 IHC differential diagnosis of suspected NET

IHC stains	Primary tumor site	Confirmation IHC stains
TTF-1	Thyroid (medullary thyroid carcinoma) Broncho-pulmonary	CEA and calcitonin + in thyroid NET
CDX-2	Small intestine Pancreas	Serotonin + in small intestine. Pancreatic hormones + in pancreas
ISL-1 PDX-1	Pancreas	Pancreatic hormones +
PSAP	Rectum	
Tyrosine hydroxylase (and keratin negative)	Pheochromocytoma Paraganglioma	

Adapted from [6]

Staging

Two TNM staging systems are currently available, the American Joint Committee on Cancer/Union for International Cancer Control (AJCC/UICC) and ENETS [9, 10]. Staging systems are specific to each primary tumor site. The College of American Pathologists (CAP) has based their protocol on the AJCC classification. Neither staging system includes patient-level variables or information on associated endocrinopathy.

- Given the variability in staging systems, it is essential that pathology reports clearly identify the system that was used to classify, grade, and stage the tumor.
- Survival for GEP-NETs is dictated by (1) grade and (2) primary tumor localization, and (3) metastases [1, 2].
- Minimal dataset for pathology reporting of NET include: anatomic site of primary tumor, presence of multicentric disease, immunohistochemistry (IHC) for chromogranin and synaptophysin, grade (proliferation rate assessed by Ki-67 and mitotic rate), presence of other non-neuroendocrine components, lymph node metastases, and their characteristics [11].

Workup

The workup of NETs can be divided into the following:

1. *Primary tumor site and extent of disease*
   (a) Primary tumor site:
      - Cross-sectional imaging:
      - CT C/A/P for pancreas and lungs
      - CT-enterogram for small intestine
      - MRI for pancreas if further assessment required after CT
      - Upper and lower gastrointestinal endoscopy for stomach, colon, and rectum
      - Endoscopic ultrasound for pancreas if further assessment and tissue diagnosis require

   (b) Extent disease
      - Cross-sectional imaging with arterial and venous phases – NETs are typically hypervascular hyperenhancing tumors that require an arterial phase for identification. Liver metastases can be isointense to the normal parenchyma on venous phase and thus overlooked.
      - CT scan C/A/P
      - MRI liver if further assessment of liver metastases required for surgery-Functional imaging (see below)
2. *Grading*
   (a) Tissue diagnosis for histological grade classification
   (b) Functional imaging for biology behavior classification (see below)
3. *Endocrinopathy* (hormonal status)
   (a) Clinical evaluation for functional syndromes
   (b) Biochemical assessment, based on primary tumor site (see below)
   (c) Echo if serotonin secretion

Primary Tumor and Extent of Disease

Imaging and Endoscopy

Initial investigations in the workup of NETs are summarized in Table 18.4.

Table 18.4 Initial workup for NETs

Tumor site	Endoscopy	CT chest	CT triphasic abdo-pelvis	CT enterogram	Biochemical markers	Other
Stomach	Gastroscopy	X	X		Gastrin (off PPI)	Biopsy of antrum to document the presence of atrophic gastritis
Small intestine	Colonoscopy	X	X	X	24 h-u5HIAA	
Appendix	Colonoscopy	X		X	24 h-u5HIAA	Role of video capsule is limited due to risk of obstruction and small luminal size of small intestine NETs
Colon	Colonoscopy	X	X		24 h-u5HIAA	
Rectum	Colonoscopy	X	X		Targeted by symptoms (see below)	If >2 cm or high risk signs[a]: local staging with ERUS or MRI pelvis
Pancreas		X	X		Targeted by symptoms (see below)	MRI pancreas if additional information required after CT scan
Metastases with unknown primary	Gastroscopy Colonoscopy	X	X	X	24 h-u-5HIAA Targeted by symptoms (see below)	MRI pancreas if other investigations negative

[a]High risk sign for rectum NET: ulceration, umbilication, hyperaemia, semi-pedunculated

Special Notes

- CT-enterogram is an important imaging modality to identify primary small bowel NET and synchronous tumors. It should be performed and interpreted in specialized centers, as sensitivity and specificity of the test is related to expertise and volume.
- Over 50% of small bowel NETs are multifocal. Identification of multiple sites of intestinal NETs is important in planning therapy. CT-enterogram is therefore useful for workup of small intestine NETs.
- Unknown primary has been reported in up to 46% of NETs diagnosed initially by identification of distant metastases. Detailed preoperative workup can identify the primary tumor in the majority of those cases. With preoperative workup, 10% of metastatic NETs may not have a primary tumor identified. Surgical exploration, including staging laparoscopy, can identify the primary tumor in half of those cases. It is indicated if identification of the primary tumor will alter surgical or medical management [12, 13].
- MRI of the liver can further define the extent of metastatic disease. It is most useful for: (1) identification of occult metastases when suspected based on endocrinopathy or other clinical signs and (2) detailing number and localization of metastases in planning for maximal surgical cytoreduction.
- The risk of synchronous or metachronous neoplasia in patients with GEP-NETs is 20–25% in contemporary studies [14–16]. It has been suggested that this association could be related to higher detection rate of NET in patients with other cancers as a result of surveillance strategies.

Functional/Somatostatin Receptor-Based Imaging Techniques

- Given many well-differentiated NETs express somatostatin receptors, radiolabeled somatostatin analog can be utilized to produce functional images. The most commonly used somatostatin receptor analog imaging (SRI) techniques are indium-111 pentetreotide scan (OctreoScan) and somatostatin receptor positron emission tomography (SSTR-PET, e.g., 68-Ga DOTATATE PET/CT).
- With improvement in cross-sectional imaging and introduction of new functional imaging modalities (such as SSTR-PET), the role of Octreoscan is limited. SSTR-PET should replace Octreoscan [17].
- Use of SSTR-PET can be useful in the following situations [17]:
  - Staging after initial histologic diagnosis of NET, if the identification of additional disease sites will change management
  - Evaluation of a mass suggestive of NET but not amenable to endoscopic or percutaneous biopsy
  - Staging prior to planned surgery, if the identification of additional disease sites will change the indication or extent of surgery

  - Evaluation of unknown primary (after completing other workup)
  - Evaluation of patients with biochemical evidence of NET without evidence on conventional imaging, or re-staging of patients with biochemical or clinical evidence of progression without progression on conventional imaging
  - New indeterminate lesion on conventional imaging with unclear etiology and not amenable to biopsy
- The avidity of NETs on functional imaging can help assess the tumor biology:
  - As the grade of NENs increases, their somatostatin receptor expression decreases, making grade 3 well-differentiated NETs less likely to be avid on SSTR-PET than their grade counterparts [18].
  - Grade 3 and/or poorly differentiated NENs are more likely to be avid on FDG-PET [18–20].

Grading

- Histology confirmation and grading is necessary for classification and therapeutic decision-making.
- Fine needle aspiration (FNA) can obtain adequate cells for establishing the diagnosis of NENs via performing specific staining and/or IHC.
- Morphological assessment can also be performed on the FNA samples to try to distinguish poorly-differentiated NEC from well-differentiated NETs [5].
- Larger amount of material through core biopsies are usually required for more accurate grading assessment and calculation of mitotic rate or Ki-67 index as analysis on the FNA can underestimate the grade [5, 21, 22].
- IHC profile can be used to identify the primary tumor site and orient workup for patients with distant metastases with unknown primary (see section "Pathological Classification and Grading")

Endocrinopathy

Tumor site		Hormone	Clinical syndrome	Diagnosis
Stomach	Type I	None		
	Type II	Gastrin		
	Type III	Serotonin Histamine	Atypical carcinoid syndrome	Elevated 24-hour u5HIAA Elevated 24-hour urinary N-methyl histamine
	Type IV	Rare		
Small intestine		Serotonin	Carcinoid syndrome	Elevated 24-hour u5HIAA

Tumor site		Hormone	Clinical syndrome	Diagnosis
Pancreas	Insulinoma	Insulin	Whipple's triad: Documented hypoglycemia (BG <3.0 mmol/L) associated with symptoms of hypoglycemia (confusion, sweating, weakness, unconsciousness), and immediate relief with administration of glucose Weight gain	Inappropriately elevated insulin (>20 pmol/L) and C-peptide (>200 pmol/L) when hypoglycemic (<3.0) 48–72 hours supervised fasting test: glucose, insulin, c-peptide, pro-insulin, beta-hydroxybutyrate, sulfonylurea screen, drawn at the time of hypoglycemia(<3.0 mmol/L) Can also assess response to glucagon
	Gastrinoma	Gastrin	Zollinger-Ellison syndrome (ZES): Multiple ulcers Diarrhea (may resolve with PPI)	Elevated fasting serum gastrin (off PPI for 1 week, can use H2 blockers during this period) Usually >200 pg/mL If >1000 pg/mL: diagnostic of ZES unless hypochlorhydria present If <1000 pg/mL: confirm with secretin or calcium simulated gastrin or acidic gastric acid Gastroscopy: Gastric pH <2 (perform off PPI to avoid false negatives) Document peptic ulcer disease
	Glucagonoma	Glucagon	"Sweet" syndrome: 4Ds: Dermatosis (necrolytic migratory erythema) Depression Deep venous thrombosis Diabetes: 40–90% will have glucose intolerance Weight loss	Fasting serum glucagon >500 pg/ml (normal≤50) (check with a blood glucose to rule out a physiologic response to hypoglycemia)
	VIPoma	Vasoactive intestinal peptide (VIP)	Verner-Morrison syndrome: Watery, secretory diarrhea (>700 ml/day) Hypokalemia Hypochlorhydria Hypercalcemia	Elevated serum VIP
	Somatostatinoma	Somatostatin	Secretory diarrhea that persists with fasting Possible steatorrhea (secondary to somatostatin inhibition of digestive enzymes) Cholelithiasis Diabetes Hypochlorhydria	Elevated fasting serum somatostatin
Colon		Serotonin	Carcinoid syndrome	Elevated 24-hour u5HIAA
Rectum		Very rare Histamine		Elevated 24-hour urinary N-methyl histamine

u5HIAA urinary 5-hydroxyindoleacetic acid [23, 24]

Biochemical Testing for Endocrinopathy

- *24-Hour urinary 5-HIAA (U5-HIAA):* 5-Hydroxyindoleacetic acid is an end product of serotonin metabolism and may be elevated in well-differentiated NETs that produce serotonin, most commonly in midgut primary NETs versus rarely in foregut, hindgut, or pancreatic NETs [25].
  - Its levels can be falsely elevated by a variety of foods and medications, which should be avoided when possible before testing [25].
  - In patients with elevated U5-HIAA at diagnosis, this marker can be followed as a marker after treatment [21].
  - All patients with symptoms suggestive of carcinoid syndrome should have U5-HIAA levels checked as the marker to confirm serotonin excess [6] and to monitor effective serotonin inhibition after treatment.
- *Functional pancreatic NETs hormones:* 10% of pancreatic NETs are functional.
  - Routine testing for hypersecretion of pancreatic hormones is not recommended. Biochemical testing should be performed in the presence of clinical signs and symptoms suggestive of a pancreatic endocrine syndrome [6, 21].
  - Hormones should be checked at a fasting state, as secretion is stimulated postprandially
  - Hormone testing needs to be interpreted in the context of the clinical situation. An elevated value is not always pathologic, if it is an appropriate physiologic response.

Carcinoid Syndrome

- *Constellation of symptoms including secretary diarrhea, dry flushing (no sweating), and/or bronchospasm, as a result of excess serotonin in the systemic circulation* [6, 26].
- *Most common primary tumor sites* [6, 26].:
  - *Small intestine*
  - *Colon*
  - *Pancreatic: rarely*
  - *Rectal: rarely*
- *As serotonin is inactivated in the liver, carcinoid syndrome usually occurs in the context of liver metastasis or when the portal circulation is bypassed if there is disease in sites not drained by the portal system (such as retroperitoneum)* [6, 27].
- *20–30% of patients with liver metastases will present clinical carcinoid syndrome* [27].
- *Fibrosis: desmoplastic reaction and fibrosis can develop as a complication of serotonin excess, with or without clinical manifestations of carcinoid syndrome* [28].
  - *Mesenteric and retroperitoneal fibrosis: 50% of patients with midgut NETs and can lead to:*

Intestinal obstruction
Mesenteric angina or ischemia
Mesenteric venous ischemia
Ureteral obstruction

- *Cardiac valvulopathy: 40% of patients with carcinoid syndrome and is due to fibrosis in the right-heart leading to:*
  Pulmonic insufficiency in 50%
  Tricuspid insufficiency in 90%
  *Left ventricular dysfunction, if the left heart exposed to serotonin (*e.g., *lung secretion of serotonin), in 10%*
- *All patients with elevated 24 h-u5HIAA should have an echocardiogram to rule out carcinoid heart disease upon diagnosis, and yearly thereafter for follow-up.*

- *Biochemical workup: 24-hour urinary 5-HIAA acid*
  - *24-Hour urinary collection.*
  - *Diet restrictions with a low-amine diet should be followed in days prior and during the collection to ensure accuracy.*
- *Diagnosis:*
  - *Carcinoid syndrome symptoms with elevated 24 h-u5HIAA.*
  - *Patients may have endocrinopathy and functional tumors with hypersecretion of serotonin (elevated 24 h-u5HIAA) without reporting typical symptoms.*

Other Biochemical Markers

- *Serum chromogranin A (CgA)*: It is a protein that is stored in neuroendocrine tissue. Elevated serum CgA levels can be associated with functional or nonfunctional well-differentiated GEP NETs [29].
  - CgA is nonspecific and can be falsely elevated by different medications, foods, and medical conditions [29, 30].
  - CgA alone should not be used for diagnosis of NETs, but with caution, its levels can be used as one of the tools in assessing disease progression, response to treatment, or as a sign of disease recurrence in surveillance [21, 29].
  - CgA level changes should not be used alone as the reason to modify treatment [21, 25].

Management of Gastroenteropancreatic NETs with Locoregional Disease

Goals of Therapy

Incidental Finding

When an NET is identified incidentally, the management should be tailored to the risk of nodal and distant metastases, the morbidity of therapy, and the acceptability/feasibility of monitoring. Clinical observation can be indicated.

Curative Intent

When the disease is localized (local or locoregional), curative intent management can be undertaken. The risk of recurrence is however high, and recurrence can occur over a prolonged period of time [31]. See section below for details regarding recommended surveillance protocols.

Noncurative Intent

Patients with NETs have prolonged survival even with active metastatic disease and can experience complications and deteriorating quality of life from hormonal hypersecretion. It can be considered a "chronic cancer [1].

With metastatic disease, curative intent management is unlikely. Half of liver metastases are not detectable on preoperative imaging and measure <2 mm [32].

Considering the unique characteristics of NETs, the goals of therapy are:

1. Control of tumor burden
2. Control of endocrinopathy/hormonal hypersecretion
3. Prevention of locoregional complications from primary tumor site

Gastric NETs

Characteristics, workup, and management of gastric NET subtypes are summarized in Table 18.5.

Duodenal NETs

Characteristics, workup, and management of duodenal NETs are summarized in Table 18.6.

Special Notes

- Although liver metastases are rare in duodenal NETs, lymph node dissection (LND) is advised if imaging suggests lymph node involvement.
- Duodenal/ampullary NETs are classified separately from jejunal in the eighth edition of AJCC TNM staging (2017)
- Ampullary NETs appear to have a higher nodal metastasis rate even in smaller than 2 cm lesions [38, 39] and may need to be treated more aggressively even when small [36].

Ileal/Jejunal NETs

Characteristics, workup, and management of small bowel NETs are summarized in Table 18.7.

Table 18.5 Characteristics and management of locoregional gastric NETs [21, 33–35]

Type	I	II	III	IV
Frequency	75%	4%	20%	1%
Associated conditions	Atrophic gastritis Pernicious anemia (50%)	ZES MEN-1	Sporadic Atypical carcinoid syndrome	Sporadic
Size and number	<1 cm Multifocal	<2 cm Multifocal	>2 cm Solitary	4-5 cm Solitary
Grade	G1-G2	G1-G2	G3	G3 Poorly differentiated Small cells
Gastrin (off PPI)	Elevated	Elevated	Normal	Normal
Gastric pH (off PPI)	Elevated	Low	Normal	Normal
Nodal metastases	<2%	30%	70%	>75%
Distant metastases	<2%	10–30%	25–75%	50–100%
5-year OS	100%	90%	50%	<10%
Workup	Gastroscopy with biopsy of polyps and *antrum* Fasting serum gastrin (off PPI[a])			
	CT chest-abdo-pelvis	CT chest-abdo-pelvis MRI pancreas +/− EUS Genetics (MEN-1)	CT chest-abdo-pelvis U5HIAA	CT chest-abdo-pelvis
Management	Monitoring: gastroscopy q 1–2 years Lesion ≥1 cm on monitoring: Endoscopic resection Surgical wedge resection if endoscopic not feasible Anemia refractory to medical management: can consider antrectomy (very rare indication)	Management of the gastrinoma	Locoregional: gastrectomy with LND Metastatic: systemic therapy (regimen based on Ki67 and differentiation)	Systemic therapy: cytotoxic chemotherapy (cisplatin-etoposide)

PPI proton pump inhibitors, *ZES* Zollinger–Ellison syndrome, *MEN-1* multiple endocrine neoplasia type 1, *OS* overall survival. *EUS* endoscopic ultrasound

[a]PPI should be stopped at least 7 days prior to measuring serum gastrin

Table 18.6 Characteristics and management of locoregional duodenal NET [2, 36, 37]

Types		**5 types**: Sporadic or gastrinoma occurring in the setting of MEN-1/ZES (most common) Somatostatinomas occurring near ampulla, associated with NF-1 (~18%) Gangliocytic paraganglioma Nonfunctional NET containing serotonin, gastrin, or calcitonin positive cells Neuroendocrine carcinoma
Associated conditions		MEN-1/ZES (40%) NF-1
Nodal metastases		40% Increases with grade, larger tumor size, and higher grade
Distant metastases		Rare
Workup	Lab	24 h u5HIAA Serum gastrin (off PPI) or somatostatin if suggestive clinical manifestations
	Endoscopy	Gastro-duodenoscopy with biopsy: localization and grading
	Imaging	CT chest-abdo-pelvis EUS (define depth of invasion)[a] Consider SSTR-PET if identification of additional disease will alter management
Management	<2 cm Confined to mucosa or submucosa No nodal disease on imaging REF	Endoscopic resection If endoscopic not feasible: Wedge duodenal resection Transduodenal resection if D2/periampullary
	≥2 cm Or when endoscopic criteria not met	Segmental resection with LND Avoid aggressive resection with pancreaticoduodenectomy by performing transduodenal or segmental duodenal resection with LND if possible
	Metastases	Limited role for resection of primary tumor and liver cytoreduction (exception: functional tumors, for palliation of endocrinopathy) See section below on metastatic disease

U5HIAA urinary 5-hydroxyindoleacetic acid, *ZES* Zollinger–Ellison syndrome, *MEN-1* multiple endocrine neoplasia type 1, *NF-1* neurofibromatosis type 1, *LND* lymph node dissection

[a]Gastrinomas can be submucosal, making detection difficult on upper GI endoscopy/EUS

Table 18.7 Characteristics and management of locoregional ileal/jejunal NETs [2, 36, 40]

Nodal metastases		70%
Distant metastases		76%
Workup	Labs	24 h u5HIAA
	Endoscopy	Colonoscopy to rule out synchronous neoplasm
	Imaging	CT chest-abdo-pelvis CT-enterogram, to assess the number and localization of multifocal primary tumors Consider SSTR-PET if identification of additional disease will alter management
Management	Localized (no lymphadenopathy on imaging)	Segmental resection with LND[a]
	Locoregional (mesenteric lymphadenopathy on imaging)	Segmental resection with LND Avoid aggressive extensive small bowel resection to achieve resection of mesenteric mass[a]
	Distant metastases	See section below on metastatic disease

U5HIAA urinary 5-hydroxyindoleacetic, *LND* lymph node dissection
[a]See special notes below

Special Notes

- Consider resection of primary and lymph nodes even if clearly metastatic, for locoregional control, symptom management, and possibly survival benefit [40–42].
- Inspect and palpate the entire small bowel looking for additional tumors:
  - Multifocal tumors are most often located within 100 cm of the ileocecal valve.
  - Tumors are rarely located in the first 100 cm from angle of Treitz [43].
- After initial resection performed in an emergency setting (e.g., for small bowel obstruction), re-image with CT scan to rule out residual/unresected mesenteric nodal disease. Consider resection of residual/unresected mesenteric nodal disease to prevent complications from mesenteric fibrosis.
- Cross-sectional imaging should be used to carefully assess the relationship of mesenteric bulky nodal disease to the superior mesenteric artery/vein in the assessment of resectability. Desmoplasia/fibrosis can make resection of bulky nodal disease more challenging. Mesenteric lymph node metastases are divided into four stages [44]:
  - Stage 1: close to the edge of small bowel NET
  - Stage 2: involve the distal branches of the mesenteric arteries
  - Stage 3: extend proximally on the SMA, without encasement
  - Stage 4: cephalad regional disease, including retropancreatic/retroperitoneal nodal disease, and encasement of the SMA/SMV
- Resection of bulky mesenteric nodal disease may result in ischemia of more length of small bowel than required to clear the primary disease, determining the needed extent of small bowel resection.
  - Avoid extensive small bowel resection.
  - Favor mesenteric-sparing small bowel resection, with “peeling-off” of nodal mass from mesenteric vessels, to limit the length of small bowel resected.

  - If mesenteric nodal disease initially deemed unresectable (e.g., due to proximal localization on superior mesenteric artery), consider referral to specialized center.
- Stage 1–3, and selected stage 4 nodal disease can be resected [40]:
  - Stage 1 and 2: as part of segmental small bowel resection
  - Stage 3: segmental small bowel resection, and separate resection of the proximal nodes along the vessels (incision of the peritoneum and dissection off the vessels up to the root of the mesentery)
  - Stage 4: typically deemed unresectable, depending on localization can be resected in specialized centers.
- Consider sparing the ileocecal valve to reduce the functional impacts of diarrhea (due to post-enterectomy syndrome or carcinoid syndrome).
- Consider cholecystectomy at the time of surgery to avoid subsequent issues with gallstone disease from potential for long-term use of somatostatin analogs and/or ischemic cholecystitis from potential embolization for liver metastases.

Colonic NETs

Characteristics, workup, and management of colonic NETs are summarized in Table 18.8.

Appendiceal NETs

Characteristics, workup, and management of appendiceal NETs are summarized in Table 18.9.

Table 18.8 Characteristics and management of locoregional colonic NETs

Distant metastases [2]		60%
Workup	Labs	24 h u5HIAA
	Endoscopy	Colonoscopy
	Imaging	CT chest-abdo-pelvis Consider SSTR-PET if identification of additional disease will alter management
Management [45]	<2 cm Limited to mucosa or submucosa No lymphadenopathy on imaging	Endoscopic resection with tattoo of resection site [45]
	≥2 cm Or when endoscopic criteria not met	Segmental colectomy with LND – same oncological principles as for colonic adenocarcinoma
	Distant metastases	Limited role for resection of primary tumor and liver cytoreduction (exception: functional tumors, for palliation of endocrinopathy) See section below on metastatic disease

U5HIAA urinary 5-hydroxyindoleacetic, *LND* lymph node dissection

Table 18.9 Characteristics and management of locoregional appendiceal NETs [46]

Workup	Labs	24 h u5HIAA
	Endoscopy	Colonoscopy to rule out synchronous neoplasm
	Imaging	CT chest-abdo-pelvis Consider SSTR-PET if identification of additional disease will alter management
Management	<1 cm No lymphadenopathy on imaging	Appendectomy If incidental finding post-appendectomy: R0 resection: no additional surgery R1 resection: completion surgery, consider partial cecectomy to achieve negative margin
	1–2 cm No lymphadenopathy on imaging	Appendectomy If incidental finding post-appendectomy: No high-risk feature: no additional surgery High-risk feature (G2 or invasion mesoappendix >3 mm): completion right hemicolectomy
	1–2 cm Lymphadenopathy on imaging	Right hemicolectomy If incidental finding post-appendectomy: completion right hemicolectomy
	>2 cm	Right hemicolectomy If incidental finding post-appendectomy: completion right hemicolectomy
	Distant metastases	Same principles as for small bowel NETs

u5HIAA urinary 5-Hydroxyindoleacetic Acid

Special Notes

- Management of appendiceal well-differentiated NETs that are 1–2 cm is controversial.
  - Survival for appendiceal NET is excellent, regardless of whether patients undergo appendectomy or right hemicolectomy [46].
  - The role of right hemicolectomy is to achieve a larger LND, and there is a higher rate of microscopic nodal metastases with right hemicolectomy [46–49].
  - There is no established survival benefit from right hemicolectomy in this subset of patients [46–49].
  - Right hemicolectomy carries a risk of short- (anastomotic leak) and long-term morbidity (functional diarrhea).
  - The risk of nodal metastases is increased if: lymphadenopathy identified on imaging, tumor >1 cm, invasion of mesoappendix >3 mm, and tumor localization at the base of the appendix [46].
  - Therefore, decisions should be personalized for each patient, balancing risks associated with right hemicolectomy and LND against chance of residual disease/recurrence. It is recommended that management of these patients be discussed at multidisciplinary rounds.
- Appendiceal NENs with mixed histology should be treated according to their most aggressive histological component.

Rectal NETs

Characteristics, workup, and management of rectal NETs are summarized in Table 18.10.

Special Notes

- Complete endoscopic excision of incidental well-differentiated rectal NETs that are less than 1 cm may be adequate [21, 53, 54].
- In case of indeterminate margins following endoscopic resection, two options are possible for G1 tumors[48]:
  - Clinical monitoring with sigmoidoscopy and pelvis MRI q 1–2 years for prolonged period time due to long interval to recurrence with indolent biology
  - Completion transanal excision of the scar to clear any residual disease and achieve R0 resection.
  - Patients with complete excision (R0) of T1 rectal NETs do not require further surveillance and can be discharged

Table 18.10 Characteristics and management of locoregional rectal NETs [46, 50–52]

Nodal metastases	T1 (<2 cm invading submucosa)	1%
	T2 (>2 cm invading submucosa, or any size beyond muscularis propria)	26%
	T3/4 (any size invading beyond sub-serosa)	53%
Distant metastases	T1	< 1%
	T2	25%
	T3/4	67%
Workup	Labs	Hormonal testing if clinical manifestation suggestive of endocrinopathy (rare)
	Endoscopy	Colonoscopy with tattoo of site ERUS if need to confirm depth on invasion
	Imaging	CT chest-abdo-pelvis MRI pelvis if need to stage pelvis Consider SSTR-PET if identification of additional disease will alter management
Management	<1 cm No lymphadenopathy on imaging	
	T1	Endoscopic resection Or Transanal excision[a]
	≥T2 Locoregional lymphadenopathy	Total mesorectal excision – same oncological principles as for rectal adenocarcinoma

[a]See special note below

- In case of indeterminate margins following endoscopic resection for G2 tumors: consider transanal excision of the scar/residual disease to ensure complete excision [45].
- Transanal minimally invasive surgery (TAMIS) facilitates transanal excision for rectal NETs with low morbidity [52].
- Management of rectal NETs should be individualized, and discussion at MCC is recommended.

Pancreatic NETs (pNETs)

10% of all pNETs are functional [55].

- Functionality is primarily determined based on clinical symptoms due to excess hormones.
- Biochemical testing is not indicated routinely.
- Biochemical testing is indicated in the presence of symptoms suspicious of endocrinopathy. Screening and confirmatory testing are required to meet all criteria and establish an endocrine diagnosis (See above section Endocrinopathy).
- Note: Endocrinopathy is not defined by positive stains on IHC.

Characteristics, workup, and management of pancreatic NETs subtypes are summarized in Table 18.11.

Special Notes

- *Small nonfunctional PNETs* (<2 cm):
  - *Typical imaging characteristics*: Isodense on noncontrast phase, avidly hyperenhancing on arterial phase, and hyperenhancing on venous phase, homogeneous lesion with smooth contours that does not distort the pancreatic parenchyma. The differential diagnosis is: metastatic renal cell carcinoma or melanoma (associated with history of those malignancies), or solid serous cystadenoma and splenule (benign lesions) [59, 60].
  - *EUS-biopsy* is indicated if there is doubt about diagnosis on imaging. EUS biopsy is limited in accuracy to grade small PNETs due to small tumor size and intratumoral heterogeneity.
  - *Observation is recommended* in small nonfunctional PNETs with no evidence of nodal metastases on imaging. Retrospective analyses indicates growth 0.1 mm/year, favorable long-term survival, no progression to metastatic or unresectable disease, rare need for surgery during follow-up (majority due to patient preference) [61–63].
  - *Monitoring regimen:* [60, 64]
    Cross-sectional imaging at 6 months initially to demonstrate stability
    Thereafter: cross-sectional imaging every 1–2 years
    If the lesion is visible on ultrasound, this modality can also be used for monitoring

Table 18.11 Characteristics and management of locoregional pancreatic NETs [23, 55–58]

		Non-functional		Insulinoma	Gastrinoma	Glucagonoma Somatostatinoma	VIPoma
		<2 cm	>2 cm				
Nodal metastases		6%	30%				
Distant metastases		Rare	60%	10%	60%	80%	80%
Associated conditions – MEN-1		25%		5%	25%	15%	6%
Workup	Labs	As indicated by clinical signs and symptoms		See above section on endocrinopathy work-up			
	Endoscopy	EUS: Localization of small tumors Identification of relationship with pancreatic duct Biopsy (FNA or FNB) for histology diagnosis and grading Note: for small PNET <2 cm, biopsy is not required for observation, as small size limits accuracy of biopsy for histology and grading					
	Imaging	CT chest-abdo-pelvis MRI pancreas Consider SSTR-PET if identification of additional disease will alter management					
Management – surgical		Monitoring[a]: if no clinical lymphadenopathy (imaging)	Surgical resection with LND	Surgical resection: for symptoms, local resection favored[a] Intraoperative ultrasound Blind distal pancreatectomy is not indicated[a]	Hypergastrinemia: PPIs [17] Surgical resection with LND: for symptoms and curative intent to prevent distant metastases	Surgical resection with LND	Surgical resection with LND
Medical management of endocrinopathy		NA		Diet changes (snacks, frequent smaller meals with complex carbs, fat, and protein) Diazoxide Somatostatin analogs Verapamil Afinitor (for side effect of hyperglycemia) Last resort: steroids	Somatostatin analogs High dose PPIs H2 blockers	Somatostatin analogs (glucagonoma only) Management of diabetes Pancreatic enzymes (somatostatinoma)	Somatostatin analogs Volume and electrolyte replacement

LND lymph node dissection
[a]See special notes below

- *Pancreatic sparing resections* (enucleation, central pancreatectomy) can be considered in selected patients with small lesions
  - They have higher rate of postoperative pancreatic fistula but lower rates of long-term endocrine and exocrine insufficiency [65].
  - To consider for insulinoma and gastrinoma without evidence of nodal disease
  - When deciding between observation versus enucleation versus formal resection, location of tumor (head vs. tail), the associated surgical morbidity with surgical resection, patients' wishes, and their comorbidities all need to be taken into account.
  - Ideal candidates are tumors <2 cm in the head (enucleation) or neck (central pancreatectomy) of the pancreas.
- *LND* for PNETs is not associated with better progression-free or overall survival [66]
  - LND is performed for accurate nodal staging.
  - Nodal metastases identified on imaging should be resected, especially for functional tumors.
- *Insulinoma* [64, 67–69]
  - It is an indolent disease – only 5–15% are potentially malignant.
  - Surgery is undertaken mostly to control and prevent complications from the endocrinopathy.
  - 80–90% are isolated and < 2 cm.
  - Endocrine cure is 95–100% with resection, with 10-year recurrence of 6%.
  - If the primary PNET cannot be localized on imaging:
    There is no indication for blind resection of the tail of the pancreas, as the risk is the same throughout the gland.
    Laparoscopic intraoperative ultrasound can be considered in expert centers, as part of the imaging workup.
    The role of formal surgical exploration is limited, considering the low risk of malignancy, the need for extensive mobilization of the pancreas, 10% of lesions are nonvisible and nonpalpable, and the ability to manage symptoms medically.
  - Patients can be effectively managed medically with somatostatin analogs and diazoxide.
  - Benign insulinomas (no nodal or distant metastases) do not require long-term follow-up. Routine surveillance has not been shown to reduce the incidence of relapsing insulinomas [7].
- *Gastrinoma* [70–75]
  - It is an aggressive disease – 60% are malignant and metastases are frequent.
  - MEN-1 patients with gastrinoma have better overall survival than patients with sporadic gastrinoma.
  - Endocrine cure is 50% immediately after resection and 40% at 10 years.
  - If the PNET is localized:
    Surgery is indicated.
    LND is important to improve endocrine cure.

  - If the PNET is not localized on imaging:
    Surgical exploration with duodenotomy is extremely rarely needed in contemporary practice.
    Nonlocalized tumors are most often located in the duodenum, small, with lower gastrin levels, and associated with longer overall survival.
    Results of surgical exploration with duodenotomy rely on data from patients treated prior to the introduction of new imaging techniques (1980 to 2000).
    Long-term endocrine cure with exploration is 46% at 10 years.
    Medical therapy with PPI can effectively control hyperacidity and symptoms for up to 20 years.
- *Other rare functional PNETs*: While there are no large series reported, consensus statements and expert opinions are to resect locoregional tumors [64, 68, 76].
- *Local ablation* can be used for symptomatic patients with functional PNETs but not medically fit for surgery. Options include pancreatic radiofrequency ablation, alcohol ablation, or stereotactic ablative radiotherapy (SABR) [78, 79].
- *Aggressive locoregional resection for functional PNETs:* Debulking procedures for locally advanced functional PNETs can be used in selected patients, with the goal to control endocrine symptoms. This has to be discussed in multidisciplinary teams and balance patients' wishes, comorbidities, technical feasibility and risks of the surgical procedure, alternative options for therapy, and response to medical management of the endocrinopathy.

Special cases: PNETs as part of hereditary syndromes [23, 57, 58, 77, 80].

- *MEN-1:*
  - 80–100% will develop non-functioning pNETs.
    54% gastrinomas (>80% duodenal): majority are multifocal
    18% insulinoma
    <5% glucagonoma, somatostatinoma, VIPoma
  - Prognosis:
    0–13% of those pNETs will grow and cause symptoms [14].
    The majority have good prognosis without surgery [13].
  - Surgery:
    Usually not indicated due to low rate of symptoms and growth, good prognosis, and multifocality requiring extensive procedures that may not clear all the disease.
    Indication for surgery: Nonfunctioning PNET >2 cm.
  - If MEN-1 is suspected when working up a PNET: Measure serum calcium and parathormone, as 95% of MEN-1 will have hyperparathyroidism.
  - Associated conditions: Parathyroid adenoma, pituitary adenoma, adrenal tumors, thymic and bronchial NETs.
- *VHL:* [80]
  - Two-thirds will develop pNET.
  - 98% are nonfunctioning PNETs.

- 10–20% develop pheochromocytoma or rare extra-adrenal paragangliomas. Check serum or urine metanephrines, normetanephrines prior to any surgery.
- Prognosis: The natural history of those pNETs is variable, but they are less aggressive than sporadic PNETs.
- Surgery:
  Usually not indicated
  Indications for surgery: >3 cm and with either (1) mutation in exon 3 of the VHL gene or (2) doubling time > 500 days.

Metastatic

Workup and management recommendations for metastatic NETs are summarized in Table 18.12.

Special Notes

- Compared to other cancers, the indolent nature of NET liver metastases and the pattern of growth by pushing rather than infiltrating within the parenchyma makes surgical debulking possible [40].
- NET liver metastases can be divided in *three types:* [81]
  - Type 1: single metastasis
  - Type 2: isolated bulky metastases with smaller bilobar lesions
  - Type 3: disseminated bilobar metastases with no normal liver
- *Benefits of liver debulking:*
  - Reduce tumor burden for symptom control: Endocrine control achieved in 96%
  - Potentially improve efficacy of antiproliferative effects of long-acting somatostatin analogs, by reducing tumor burden.
  - Delay the need for other lines for medical therapy.
- *R0 resection is not achievable for metastatic NETs*
  - Recurrence is expected (>90%) [82, 83].
  - There is no survival benefit in attempting R0 resection.
  - Avoid anatomic or extensive resection with the goal of achieving R0 resection, to preserve function.
- *Goal of liver debulking:* Cytoreduction of 70% of liver metastases. It yields the same results as traditional goal of 90% [84, 85].
- *Contraindications for liver debulking* [40]:
  - Poor performance status
  - Significant liver replacement (>50–70%)
- *Indications and benefits of liver debulking are for small intestinal primary NETs.*
  - For other primaries, the benefits of liver debulking are controversial.
  - Liver debulking can be considered for other *functional* NETs, when benefits of symptom controls are a goal of therapy.
  - *For PNETs:* Liver resection and debulking and extrahepatic metastasectomy are controversial. PNETs have a worse prognosis than small intestinal NETs, are rarely functional, and have fewer long-term local complications. Retrospective series are limited to small samples from single institutions [86].

Table 18.12 Characteristics and management of metastatic GEP-NET

Workup	Labs	24 h-u5hIAA Other depending on primary tumor site and targeted by clinical signs and symptoms (see prior sections)
	Imaging	CT chest-abdo-pelvis MRI liver Consider SSTR-PET if identification of additional disease will alter management
	Endoscopy	Depending on primary tumor site (see prior sections)
	Other	Echocardiogram if elevated u5HIAA
Surgical management	Resectable (debulking possible)	*Liver*: Consider liver debulking to achieve >70% cytoreduction* Use parenchymal-preserving technique and avoid anatomic resections Consider concomitant intraoperative ablation to increase proportion of cytoreduction Combine with medical management *Extrahepatic*: Consider debulking for reduction of tumor burden, local or endocrine symptoms in selected patients with G1 NET, and good performance status[a]
	Unresectable (debulking not possible)	Liver embolization (TAE, TACE, RFA)* Liver ablation (RFA, SABR) Combine with medical management Liver transplantation in selected patients
Medical management (see below for more details)		Long-acting somatostatin analogs Targeted therapy (Afinitor, Sunitinib) Peptide receptor radionuclide therapy (PRRT) Cytotoxic chemotherapy: capecitabine-temozolomide
Resection of primary tumor site if unresectable metastases[a]	Small intestine	Consider
	Pancreas	In highly selected patients
	Colon	Not usually
	Rectum	Not usually

TAE transarterial embolization, *TACE* transarterial chemoembolization, *RFA* radiofrequency ablation, *SABR* stereotactic ablative radiotherapy
[a]See special notes

Resection of metastatic disease for PNETs should be individualized depending on tumor burden, grade, response to prior therapies, and patient age and comorbidities.
Functional PNETs: Consider resection if necessary for symptom control.
Nonfunctional PNETs: No routine resection of metastases – highly selected cases in specialized NETs centers.

- *Technical considerations:*
  - Consider cholecystectomy at the time of surgery for any patient-potential long-term use of somatostatin analogs or eventual need for liver embolization.
  - Liver resection: Parenchymal sparing procedures (PSP) are recommended, including enucleation, wedge resection, and intraoperative ablation [40].
    PSP preserves functional liver parenchyma which ensures patients remain candidates for future procedures upon progression or recurrence (such as repeat surgery, liver embolization, ablation).
    Avoid anatomic resection and/or portal vein embolization in preparation for extensive anatomic resection.
- Liver debulking can be *combined* with:
  - Postoperative ablative therapies (HAE/TACE).
  - Medical therapy with long-acting somatostatin analogs.
  - Limited evidence is currently available on the benefits of multimodal therapy with PRRT.
- *Extrahepatic NETs metastases* [87]:
  - They are not a contraindication to liver debulking, but the burden of extrahepatic disease and morbidity associated with resection should be carefully considered.
  - Cytoreduction of extrahepatic disease can be considered in selected patients with good performance status, G1 tumors, and small bowel NETs primaries.
    Goals of improving symptoms and endocrinopathy, improving local symptoms, reducing tumor burden, and delaying the need for additional lines of medical therapy
    Endocrine response in 70% after surgery
    Favorable long-term outcomes: 77% 5-year overall survival and 51% 5-year progression-free survival
- *Resection of primary tumor in case of unresectable metastases:*
  - Primary PNETs have a different risk profile than small intestinal NETs. Local complications are less common and can be managed nonoperatively (radiation therapy for bleeding and stents for obstruction). Resection of the primary carries higher morbidity and mortality (whipple or distal pancreatectomy).
  - Emerging retrospective studies have suggested a benefit for resection of primary PNETs in the setting of unresectable metastases. Overall survival of resected patients was superior than for patients who were offered resection but declined it [88].
  - Resection of primary PNET with unresectable metastases can be considered in carefully selected cases (lower Ki67, lower liver tumor burden <25%, located in body/tail of pancreas) [88, 89].

Medical Management in NETs

Systemic Therapy: Adjuvant Therapy

There is no evidence for adjuvant therapy following resection of locoregional G1-G2 GEP-NETs.

Systemic Therapy: Somatostatin Analogs

- Somatostatin analogs play two roles in medical management of NETs: (1) symptom control and (2) antiproliferative effect.
- Antiproliferative effect (prolonged progression-free survival) of long-acting forms has been demonstrated in randomized controlled trials for well-differentiated enteric and pancreatic NETs (PROMID trial, CLARINET trial).
- Long-acting agents are the backbone of systemic therapy for NETs and can be used alone or in combination with surgery in case of residual disease, for recurrent disease, or metastatic disease.

Systemic Therapy: Chemotherapy

- Well-differentiated NETs are traditionally resistant to chemotherapy agents, due to slow proliferation. In certain cases such as bulky/progressive disease that is not responding to other treatments, cytotoxic chemotherapy can be considered [60, 90]. However, advances in alternative treatment options such as peptide receptor radionuclide therapy (PRRT) continues to diminish the role of cytotoxic chemotherapy in well-differentiated NETs.
  - Capecitabine–temozolomide can be used for well-differentiated NETs:
    Benefit in overall and progression-free survival in advanced PNETs in ECOG-ACRIN E2211 randomized trial [91]
    Activity reported in small phase 2 trials for all NETs liver metastases [92].
  - FOLFOX can be used in selected cases of well-differentiated NETs; some activity has been demonstrated in small phase 2 trials [93].
- For advanced/metastatic high grade (G3) NETs or poorly-differentiated NECs, chemotherapy is the mainstay of treatment. Platinum-based chemotherapy (cisplatin–etoposide) is the regimen of choice [94].

Systemic Therapy: Biologic Agents

- Indicated for metastatic or progressing GI and pancreatic NETs.
- PNETs: Everolimus and Sutent have been associated with improved progression-free survival and overall survival [95–98].
- GI NETs: In a phase 3 randomized placebo-controlled trial (RADIANT-4), everolimus showed improved PFS and better disease control over placebo in advanced non-functional well-differentiated GINET, while maintaining the overall quality of life in these patients [98, 99].

Systemic Therapy: Peptide Receptor Radionuclide Therapy (PRRT)

- For patients with well-differentiated NETs, which are somatostatin receptor positive, PRRT can be utilized as a treatment option.

- Currently, the use is mostly limited to advanced progressive/metastatic well-differentiated NETs that do not respond to long-acting somatostatin analog.
- A phase 3 randomized controlled trial (NETTER-1) of PRRT showed improved PFS, with suggested improved OS at interim analysis when using ^{177}Lu-Dotatate compared to escalation of dose of Octreotide LAR in patients with inoperable somatostatin receptor positive well-differentiated GINET, whose disease was progressing on standard dose of Octreotide LAR [100]. In addition, time to deterioration of quality of life was significantly higher in the ^{177}Lu-Dotatate group [101]. PNETs were not included in this trial.
- The possible applications of PRRT in treatment of advanced somatostatin receptor positive NETs is evolving.

Perioperative Management

Elevated u5HIAA and/or Carcinoid Syndrome

- *Carcinoid heart disease*: Preoperative echocardiogram to rule out carcinoid heart disease prior to general anesthetic:
  - If carcinoid heart disease is identified: refer to cardiology for assessment regarding medical management and valve replacement.
  - If valve replacement is indicated, abdominal surgery should be delayed. In patients with very elevated u5HIAA who need better endocrine control prior to cardiac surgery, alternative nonoperative options can be used, including somatostatin analogs and liver embolization.
  - If valve replacement is not indicated, abdominal surgery can proceed when the patient is deemed optimized by cardiology.
- *Carcinoid crisis*: Physiological stress and tumor manipulation during surgery under general anesthetic can trigger acute release of serotonin leading to carcinoid crisis:
  - Plan for perioperative octreotide administration to control serotonin secretion in patients with elevated u5HIAA [102].
  - If an infusion of octreotide is initiated during surgery: continue for 24 hours and discontinue if patient is hemodynamically stable.
  - Intraoperative crisis occurs in up to one-third of the patients.
  - Other products have also been implicated in carcinoid crisis: bradykinin, kallikrein, and histamine, but are not targeted by perioperative octreotide preparation.

Table 18.13 provides an example of guidelines used for perioperative management of patients with carcinoid syndrome.

Table 18.13 Perioperative clinical preparation for NETs with elevated u5HIAA

Clinical scenario	Preparation
Patients well controlled on long-acting somatostatin analog (20 mg–30 mg IM)	Additional dose of long-acting somatostatin analog 2–3 weeks prior to procedure Supplementary dose of octreotide 250 μg–500 μg SC 1–2 h before procedure Carcinoid crisis with hypotension: Fluid resuscitation Intraoperative octreotide 500 μg–1000 μg IV q5 min, may require infusion 50 μg–200 μg/h Patients who have required supplemental doses intraoperatively should have 50 μg–200 μg/h infusion for 4–24 h postoperatively
Patients poorly controlled on long-acting somatostatin analog	Additional dose of octreotide LAR 60 mg 2–3 weeks prior to procedure Supplementary dose of octreotide IR 500 μg–1000 μg SC 1–2 h before procedure Infusion of 100 μg–250 μg/h starting 1 h before procedure, continue 12–24 h after surgery, wean as tolerated
Patients not on therapy or for emergency surgery	500 μg–1000 μg SC 1–2 h before procedure Consider postoperative infusion 100 μg–250 μg/h

Adapted from: Belo S, Department of Anesthesia. Protocol for Perioperative Management of Patients with Carcinoid Syndrome. Sunnybrook Heath Sciences Centre. University of Toronto. 2011

Functional PNETs [68, 103]

- Carcinoid syndrome is rare with PNET (<50 cases reported).
- *For functional PNETs: the endocrine syndrome should be optimized prior to surgery.*
- *Insulinoma:*
  - Diazoxide: control of hypoglycemia (50–60%)
  - Somatostatin analogs: control insulin hypersecretion (35–50%)
- *Gastrinoma*:
  - PPI: management of hyperacidity and ulcer disease
- Somatostatin analogs: control insulin hypersecretion*Glucagonoma*:
  - Somatostatin analogs: minimize the catabolic state
  - Doppler ultrasound: rule out DVT
  - Management of electrolytes disturbances
  - Management of hyperglycemia
- *VIPoma*:
  - Somatostatin analogs: control diarrhea
  - Management of electrolytes disturbances

Follow-Up

- There is no level-1 evidence regarding the benefits or ideal regimen for surveillance and follow-up of NETs.
- Recommendations for resected primary NETs have been released by the Commonwealth Neuroendocrine Tumors Society (CommNETS) following a

RAND-UCLA appropriateness methods study. These recommendations take into consideration the high rate but slow pace of recurrence in GEP-NETs [31].
  - Cumulative incidence of recurrence 48.5% at 10 years.
  - Median time to recurrence is 8.7 years for small intestine NET and 7.2 years for PNETs.
  - Low and decreasing risk of recurrence after 10 years post-resection.
  - Thoracic imaging is not recommended.
  - CT scan is the modality of choice. The role of ultrasound and MRI to detect recurrence is not well established, but they can be considered as alternative when it is desirable to avoid CT scan.
- Monitoring of patients with active disease must take into consideration the prolonged survival of GEP-NETs, presence of endocrinopathy, and ability to treat progression of disease (please see Table 18.14).

Table 18.14 Surveillance and monitoring in GEP-NETs

		Modality	Frequency	Consideration for more frequent follow-up[a]
Pancreas – resected		CT abdo-pelvis Nonfunctioning: no lab Functioning: measure of relevant hormonal assay	Q 1 year × 3 years Q 2 years thereafter until 10 years Discuss with patient after 10 years	Higher grade (Ki76 > 5%) Positive lymph nodes
Small intestine **Colon – resected**		CT abdo-pelvis No routine lab	Q 1y × 3 years Q 2 years thereafter until 10 years Discuss with patient after 10 years	Higher grade (Ki67 > 10%) Higher ratio of positive lymph nodes
Appendix – resected	**<1 cm** **Appendectomy**	Low clinical risk: minimal or no follow-up.		G2 >2 cm Positive lymph nodes
	G1 **1-2 cm** **Appendectomy or right hemicolectomy**	CT abdo-pelvis No routine lab	Q 1y × 3 years Q 2 years thereafter until 10 years Discuss with patient after 10 years	

Table 18.14 (continued)

		Modality	Frequency	Consideration for more frequent follow-up[a]
Rectum – resected	**T1 No nodal disease R0 resection**	No follow-up		T2 G2 Positive lymph nodes
	T1 No nodal disease R1 resection or margin unknown	Sigmoidoscopy	Q 1 year Duration undetermined	
	Others	CT abdo-pelvis No routine lab	Q 1y × 3 years Q 2 years thereafter until 10 years Discuss with patient after 10 years	
Metastatic or visible disease – monitoring (with or without resection)		CT abdo-pelvis CT chest if thoracic disease requiring monitoring Lab: relevant hormonal assay if elevated	Q 6 months Duration: while active disease under treatment	

Adapted from Singh S et al. JAMA Oncol. 2018;4(4):583–5 [31]
[a]Increasing frequency of follow-up may be considered in higher risk cases: q6–12 months x 3 years, and q 1 year thereafter until 10 years, discuss with patient after 10 years

Relevant Publications on the Management of GEP NETs

Study	Methods	Results
RADIANT-4 [98]	**Everolimus** vs. placebo Advanced nonfunctional lung and GINET Phase 3 $N = 302$ Primary end point: PFS	Median PFS 11 vs. 3.9 months. Disease control rate 81 vs. 64% OS not different at median f/u 33 months (HR 0.73, 95% CI 0.48–1.11)
NETTER-1 [100]	**Octreotide LAR** 60 mg vs. 117-Lu Dotatate Somatostatin receptor positive midgut GINET with inoperable disease progressing on octreotide LAR 30 mg) Phase 3 $N = 230$ Primary end point: PFS	Median PFS 8.4 months, but not reached at 30 months yet in 117-Lu Dotatate arm Interim analysis suggested improved OS for 117-Lu Dotatate (HR 0.4; $P = 0.0004$) Higher objective response rate with 117-Lu Dotatate (18% vs. 3%)

(continued)

Study	Methods	Results
PROMID [104]	**Octreotide LAR** 30 mg vs. placebo **N**ewly diagnosed, treatment-naïve patients with well-differentiated (G1) midgut NETs (both functional and nonfunctional) Phase 3 Primary end point: TTP	Median TTP 14.3 vs. 6 months ($p < 0.001$) Reduction of disease progression 66%
CLARINET [105]	**Lanreotide** vs. placebo Metastatic or unresectable, G1 or G2, midgut or hindgut NETs Phase 3 $N = 204$ Primary end point: PFS	Median PFS 18.0 vs. median not reached ($p < 0.001$) 24 months PFS 65.1% vs. 33.0% No difference in OS
RADIANT-3 [106]	**Everolimus** (m-TOR inhibitor) vs. placebo Metastatic or unresectable pancreatica NETs with radiologic progression Phase 3 $N = 410$ Primary end point: PFS	Median PFS 11 vs. 4.6 months ($p < 0.001$) Grade 3 or 4 drug-related adverse events 5%
Sutent Trial [95]	**Sunitinib** (tyrosine kinase inhibitor) vs. placebo Well-differentiated metastatic or unresectable pancreatica NETs and no candidates for surgery Phase 3 $N = 171$ Primary end point: PFS	Median PFS 11.4 vs. 5.5 months ($p < 0.001$) Improved OS (HR 0.42; $p = 0.02$) ORR 9.3% ($p = 0.007$)
CAPTEM [107]	**Capecitabine–Temozolomide** as first line in metastatic well to moderately differentiated pancreatica NET Retrospective $N = 30$ Primary end point: ORR	ORR: 70% Median PFS: 18 months

[a]RADIANT-3, Sutent, and CAPTEM results are applicable only for PNETs; *PFS* progression-free survival, *TTP* time to tumor progression, *ORR* objective response rate, *OS* overall survival

Referring to Medical Oncology

1. All NETs, particularly functional, should ideally be managed in conjunction with medical oncology and/or endocrinology as per individual institution [108].
2. Metastatic disease
3. Unresectable pNETs
4. Any poorly differentiated or high grade (G3) NETs
5. Patients with elevated 5-HIAA or carcinoid syndrome preoperatively
6. Patients with carcinoid syndrome requiring somatostatin analogs for symptom control
7. Candidates for clinical trials

Referring to Radiation Oncology/Interventional Radiology

1. Unresectable and metastatic tumors should be referred for discussion of new radioablative and ablative therapies.

Referring to Multidisciplinary Cancer Conference (MCC)

1. All NETs would benefit from discussion and collaboration with MCC, and ideally, due to their unique needs, would be best managed in a conjoint multidisciplinary clinic [108].

Toronto Pearls

- *Pathology*:
  - Pathology interpretation is crucial to the proper identification of neuroendocrine tumors. Review of pathology by a specialized pathologist can alter the grading and therefore management of patients.
  - IHC can help identify suspected primary NET site in case of metastatic presentations.
  - NETs profile can change over the course of disease, or from one site to another. Repeat biopsies can be considered to better tailor treatment [109].
- *Multidisciplinary clinics* can facilitate access to care and multimodal therapy for NETs. Such team include: surgical oncology, medical oncology, radiation oncology, endocrinology, with supportive services from interventional radiology, radiology, cardiology, psychiatric oncology, clinical nutrition, and nursing [108].
- *Surgery*:
  - Surgery has a role in the management of locoregional and metastatic NETs, even with large burden of metastatic disease, but 60% never see a surgeon [110]. All patients with NETs should be assessed by a surgeon with expertise in management of those patients.
  - Treatment of primary neuroendocrine tumors does require some experience in order to ensure that maximum but not over-aggressive LND is done, particularly to intestinal NETs. Mesentery-sparing resections are favored over resection of large extent of intestine, in order to minimize functional impact while ensuring resection of the disease.
  - Surgical therapy of neuroendocrine liver metastases is very different from the strategies used for other cancers, and parenchymal preservation is a very important principle of treatment. Anatomical liver resections should be avoided [111].
  - Cytoreductive surgery for metastatic NETs plays an important therapy-sparing role in the sequencing of therapies. By reducing tumor burden and symptoms, cytoreduction can delay the need to escalate medical therapy,

thereby maintaining treatment options for a longer period of time. This is crucial when managing a chronic malignancy.

- *Multimodal therapy* is key in NETs. Surgical, medical, and ablative therapies can be combined and sequenced for maximal effect for patients.
  - Sequencing of therapies will take place over several years [108].
  - When discussing treatment options and sequencing, it is important to consider tumor grade, primary tumor site, endocrine symptoms, and tumor burden, as well as sparing therapies for the future and not compromising eligibility for future therapies.
  - Treatment options should be re-evaluated at each visit.
- *Patient support*: Serotonin secretion in NETs can be associated with neuropsychological symptoms, including subclinical cognitive and depressive disorders, even when 24 h-u5HIAA is below detectable levels. Patient support should include screening for those symptomatic involvement of psychology or psychiatric oncology services [112, 113].
- *Protocol for liver embolization:*
  - Give 100 μg octreotide iv bolus prior to procedure in angiography holding area (100 μg in 50 ml NS over 10 min).
  - Start continuous infusion of octreotide at 50 μg/h (500 μg in 100 ml NS, i.e., 10 ml/h) for duration of procedure.
  - After 6 h from the start of octreotide infusion, decrease rate to 5 ml/h.
  - Stop infusion after the bag is finished unless patient is clinically symptomatic (e.g., flushing, palpitations, alteration of mental status, diarrhea, wheezing) or vital signs are abnormal.
- *Radiation therapy:*
  - Delivery of *PRRT* requires the use of up-to-date agents, an experienced team, and careful dosimetry.
  - *Radiation* therapy remains an important component of management of GEP-NETs, including all metastatic neuroendocrine tumors. In patients with good performance status, consider ablative approaches to maximize local control, even in the context of metastatic disease.

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