NET (Neuroendocrine Tumours) Essentials

Diagnosis and Disease Management Overview

Learning Objectives

- Understand the challenges to diagnosis of neuroendocrine tumours (NETs)
- Discuss disease management of NETs
- Disseminate the new pancreatic NET (pNET) consensus recommendations and discuss their impact on patient care

Introduction to NETs

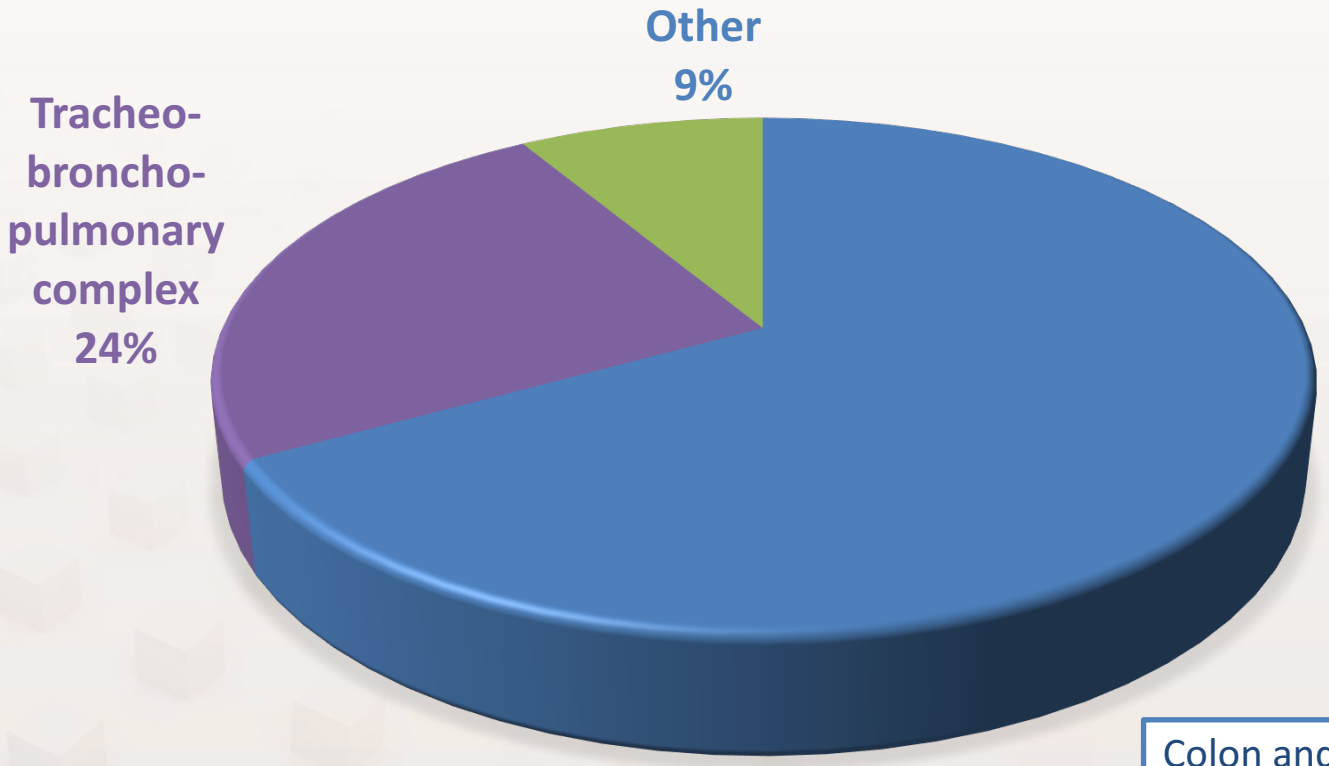
- Heterogeneous group of rare tumours
  - Can be slow growing or grow more rapidly (non-functioning)
  - Can be symptomatic or occur without symptoms (functioning)
  - Can cause hormone hypersecretion (functioning) or occur without causing hormone hypersecretion (non-functioning)
- Originate from the diffuse neuroendocrine system throughout the body
  - Include endocrine tumours of the thymus, lung, pancreas, and gastrointestinal tract

Use of the term "carcinoid tumour" should be discouraged—these are now known as well-differentiated NETs or small bowel NETs, rectal NETs, etc.

Oberg and Castellano. *Cancer Metastasis Rev.* 2011;30 Suppl 1:3-7

Common Sites of Origin

NETs are a heterogeneous group of tumours most often found in the bronchial or gastrointestinal systems



Kocha et al. *Curr Oncol*. 2010;17(3):49-64.
Modlin et al. *Cancer*. 2003;97:934-959.
Oberg and Castellano. *Cancer Metastasis Rev.* 2011;30 Suppl 1:3-7

Non-functioning Tumours

- Not associated with a distinct hormonal syndrome
- Patients may present with abdominal pain, bleeding, and weight loss
- In many cases, non-functioning tumours are asymptomatic
- Often found incidentally during surgery, and their neuroendocrine origin recognized only after histological examination

Kocha et al. *Curr Oncol*. 2010;17(3):49-64.
Oberg. *Ann Oncol*. 2010;21(Suppl.7):vii72-vii80.

Functioning Tumours

- Associated with hypersecretion of functional hormones that can cause distinct clinical syndromes

- Functioning tumours represent approximately two thirds of NETs and in the case of small bowel NETs, carcinoid syndrome is the primary clinical manifestation
  - Occurs in 8%–35% of patients and frequently associated with midgut NETs
  - Caused by release of serotonin, corticotrophin, histamine, dopamine, substance P, neurotensin, prostaglandin, kallikrein, and tachykinin
  - Usually associated with metastasis with systemic venous outflow (eg, liver)

Kocha et al. *Curr Oncol*. 2010;17(3):49-64.
NET Alliance. Could it be a neuroendocrine tumor (NET)? Novartis Pharma. 2013;1-28.
Oberg and Castellano. *Cancer Metastasis Rev.* 2011;30 Suppl 1:3-7

Carcinoid Heart Disease

- Carcinoid syndrome can lead to endocardial damage, mostly involving the tricuspid and pulmonary valves, and the endocardium
- Association between elevated 5-HIAA and the development of carcinoid heart disease
- Heart failure is a serious manifestation of carcinoid syndrome, and occurs in 57%–77% of patients
  - Nearly half of the patients that die of carcinoid syndrome succumb to right ventricular heart failure

Kaltsas et al. *Endocr Rev*. 2004;25(3):458-511.
Kocha et al. *Curr Oncol*. 2010;17(3):49-64.

Preventing and Controlling Carcinoid Crisis

- Short-acting somatostatin analogues (SSA) are used for prevention and symptom control
- All patients with functioning NETs should receive SSAs preoperatively and intraoperatively

Administration	Dose
Preoperative Patients with functioning NETs and symptoms well controlled with a long-acting SSA	• Supplemental dose of short-acting octreotide 1–2 hours before surgery • 500–1000 µg intraoperative bolus IV infusion repeated every 5 min until symptom control, if necessary
Intraoperative Treatment of carcinoid crisis	• IV octreotide infusions titrated to blood pressure control
Emergency surgery	• Octreotide 500–1000 µg IV bolus or 500 µg SC given 1–2 hours before surgery, followed by IV infusion of 50–200 µg/hour, if necessary

Kocha et al. *Curr Oncol*. 2010;17(3):49-64.

WHO Grading System

Led to the differentiation of 3 broad histologic categories

WHO Grade (2010)	Mitotic Count (per hpf)	Ki-67 Index (%)
NET G1	<2	≤2
NET G2	2–20	3–20
NEC G3	>20	>20

HPF, high-power fields; NEC, neuroendocrine carcinoma;
WHO, World Health Organization

National Comprehensive Cancer Network (NCCN). Clinical Practice Guidelines in Oncology: Neuroendocrine Tumors. 2015:1-108.
Singh et al. *Ann Surg Oncol*. 2014;1-15.

Laboratory Work-up

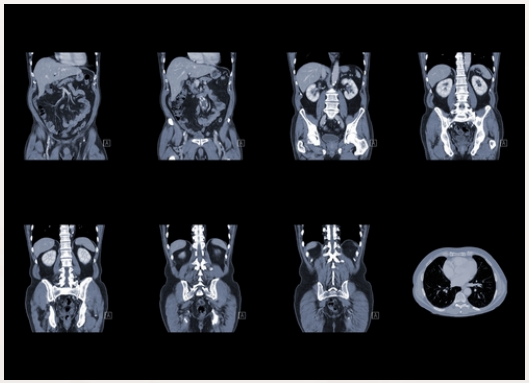
Laboratory test	Tumour type	Diagnostic accuracy
5-HIAA (24-hr urine sample)	• Well-differentiated functional gastroenterohepatic NETs • Foregut[†] and midgut[‡] NETs associated with carcinoid syndrome	• 73% sensitivity and 100% specificity for well-differentiated functional gastroenterohepatic NETs
Chromogranin A (CgA)*	• All tumour types	• 62.9% sensitivity and 98.4% specificity for NETs
Neuron-specific enolase*	• Intestinal NETs • Non-functioning pNETs	• Lower specificity than CgA
Pancreatic polypeptide	• All tumour types • Particularly, NETs originating in the gut mucosa and pancreas	• Intermediate specificity • 57% sensitivity in non-functioning pNETs (95% sensitivity in combination with CgA) • 63% sensitivity in functioning pNETs

*Nonspecific serum tumor markers
[†]Tumours of the lung, thymus, stomach and duodenum
[‡]Tumours of the jejunum, ileum, appendix and caecum

Jensen et al. *Neuroendocrinol*. 2012;95:98-119.
Kocha et al. *Curr Oncol*. 2010;17(3):49-64.
Oberg and Castellano. *Cancer Metastasis Rev.* 2011;30 Suppl 1:S3-S7.
Singh et al. *Ann Surg Oncol*. 2014;1-15
Vinik et al. *Pancreas*. 2010;39:713-734.

Diagnostic Imaging

Purpose	Imaging modality
Determine anatomic location	CT, MRI, US
Determine extent of tumours	CT, MRI, US
Monitor response to treatment	CT, MRI, US
Reveal the functional activity of tumours	PET, SRS



CT, computed tomography; MRI, magnetic resonance imaging; PET, positron emission tomography; SRS, somatostatin receptor scintigraphy; US, ultrasonography

Kocha et al. *Curr Oncol*. 2010;17(3):49-64.
Singh et al. *Ann Surg Oncol*. 2014;1-15

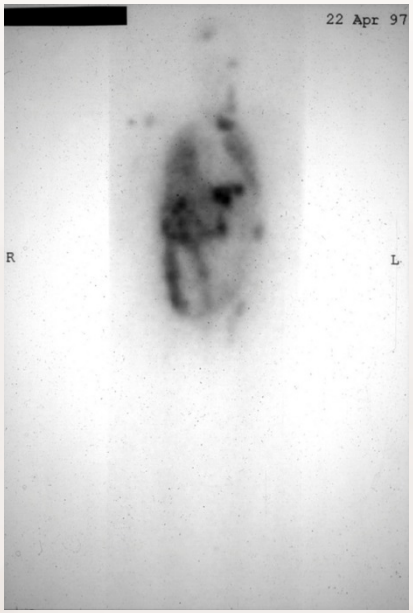
Somatostatin Receptor Scintigraphy (OctreoScan)

- Measures binding of radiolabelled somatostatin analogues to somatostatin receptors on the surface of NETs
- 111In-octreotide is considerably more sensitive and specific for detecting NETs
  - Detects 90% of NETs
  - Most sensitive modality (81%–96%) for identifying liver metastases
- Recommended at the initial diagnosis for all patients with suspected NETs
- Effective in monitoring the efficacy of therapy and assessing disease progression (in combination with single-photon emission CT)
- Mandatory before considering peptide receptor radionuclide therapy
- Not recommended in poorly differentiated high-grade carcinoma

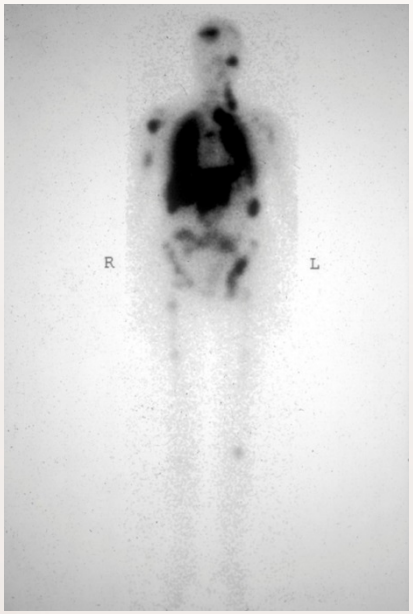
Modlin et al. *MJA*. 2010;193:46-52.
Nilsson et al. *Neuroendocrinol*. 2006;84:212-215
Oberg and Castellano. *Cancer Metastasis Rev.* 2011;30 Suppl 1:S3-S7
Singh et al. *Ann Surg Oncol*. 2014;1-15.

OctreoScan

Whole body imaging process that allows visualization of NET location and extrahepatic manifestation



Anterior



Posterior

Oberg. *Clin Oncol*. 2012;24:282-293.
Reubi. *Neuroendocrinology*. 2004;80(Suppl 1):51–56.

Surgical Management of NETs

- Treatment of choice and the only approach that can achieve a cure in patients with NETs
- In metastatic disease, surgery can:
  - Be performed with curative intent if R0 resection can be achieved
  - Improve hormone-mediated symptoms
  - Improve quality of life
  - Reduce tumour bulk
  - Prevent further local and system effects
  - Improve survival

http://image.sciencesource.com/preview/SP4362-Pancreatic-cancer-Whipple-surgery.jpg

Boudreaux et al. *Pancreas*. 2010;39:753-766
Kaltsas et al. *Endocr Rev*. 2004;25(3):458-511.

Overview of Medical Management

Therapy	Use
Sandostatin / Lanreotide	• Functioning tumours: manage symptoms, reduce 5-HIAA levels, and stabilize tumour growth • Non-functioning tumours: tumour stabilization in newly diagnosed treatment-naïve patients with well-differentiated midgut NETs
Cytotoxic treatments	• High-proliferating NETs (low-proliferating gastroenterohepatic NETs are often resistant to chemotherapy) – Most commonly reported regimen: streptozocin in combination with 5-fluorouracil or doxorubicin
Targeted therapy	• Pancreatic NETs: SUTENT® (sunitinib) and AFINITOR® (everolimus) • Worldwide regulatory filings planned for everolimus in 2015 for the treatment of advanced non-functional (NET) of gastrointestinal or lung origin based on phase 3 clinical trial findings (significant extension of progression-free survival)

Note: this information will be reviewed in more detail during the patient cases

AFINITOR® (everolimus tablets) Product Monograph. Kirkland, Quebec: Pfizer Canada Incorporated; December 2014.
Kocha et al. *Curr Oncol*. 2010;17(3):49-64.
Novartis. Novartis drug Afinitor® extended progression-free survival in phase III trial in advanced gastrointestinal or lung neuroendocrine tumors. https://www.novartis.com/news/media-releases/novartis-drug-afinitor%C2%AE-extended-progression-free-survival-phase-iii-trial. Accessed July 2, 2015.
SUTENT® (sunitinib capsules) Product Monograph. Dorval, Quebec: Novartis Pharmaceuticals Canada Incorporated; November 2014.

Peptide Receptor Radionuclide Therapy (PRRT)

- PRRT is an investigational approach using a radioactive isotope linked to a somatostatin analogue
  - Specifically targets NET cells with their high density of somatostatin receptors
  - Permanent effects on the kidneys and bone marrow are generally mild
- PRRT with ^{90}Y- or ^{177}Lu-labeled octreotide derivatives is a treatment for inoperable or metastatic, well or moderately differentiated NETs
- Since PRRT lacks marketing authorization, it is only available within the context of clinical trials
- Prerequisites to therapy:*
  - Demonstrate sufficient tumour targeting using “tracer” administration of the proposed therapeutic agent
  - Perform ^{111}In-DTPA^{0}-octreotide scintigraphy to assess the degree of uptake

Bodei et al. *J Nucl Med*. 2014;55:1753-1756.
Boudreaux et al. *Pancreas*. 2010;39:753-766.
Kocha et al. *Curr Oncol*. 2010;17(3):49-64.
Modlin et al. *MJA*. 2010;193:46-52.

*Note that the treatment algorithm is not fully understood

^{131}I-MIBG, ^{131}I-metaiodobenzylguanidine;
^{90}Y-DOTATOC, ^{90}YDOTA-Phe^{1}-Tyr^{3}-octreotide;
^{177}Lu-DOTATATE, ^{177}Lu-DOTA-Tyr^{3}-octreotate.

Symptomatic Management—Somatostatin Analogues

- Developed as somatostatin receptor agonists to block hormone release from NETs
- Indicated in the management of functioning GEP-NETs:
  - Reduce hormone production
  - Provide symptom control
  - Reduce risk of carcinoid crises
- Octreotide and lanreotide* can be used to control clinical symptoms in NETs that predominantly express somatostatin receptor subtypes 2 (sstr2) or 5 (sstr5)

*Not approved for this indication in Canada

NCT00690430. Efficacy and Safety of Pasireotide Long Acting Release vs. Octreotide Long Acting Release in Patients With Metastatic Carcinoid Disease. 2015 ClinicalTrials.gov. Available at: https://clinicaltrials.gov/ct2/show/NCT00690430. Accessed March 17, 2015.
Oberg. *Clin Oncol*. 2012;24:282-293.
SOMATULINE® AUTOGEL® (lanreotide injection) Product Monograph. Wrexham, England: Ipsem Biopharm Limited; January 2015.
Webber. *Curr Opin Endocrinol Diabetes Obes*. 2013;20:27-31.

Symptomatic Management—Octreotide and Lanreotide

- Octreotide (Sandostatin LAR®)
  - Effectively controlled stool frequency and flushing episodes in a controlled study of 93 patients with NETs and carcinoid syndrome
  - Patients had a 50% reduction in urinary 5-HIAA
  - 66% of patients on octreotide LAR 10–30 mg/month had complete or partial treatment success
- Lanreotide (Somatuline® Autogel®)
  - Efficacy assessed in 71 patients over 6 months
  - 65% and 18% of patients had at least a 50% reduction in flushing and diarrhea episodes, respectively
  - 18% of patients had ≥50% reduction in diarrhea
  - Biochemical response rate comparable with that of octreotide
  - Not approved in Canada for this indication

LAR, long-acting repeatable

Oberg. *Clin Oncol*. 2012;24:282-293.
SOMATULINE® AUTOGEL® (lanreotide injection) Product Monograph. Wrexham, England: Ipsem Biopharm Limited; January 2015.

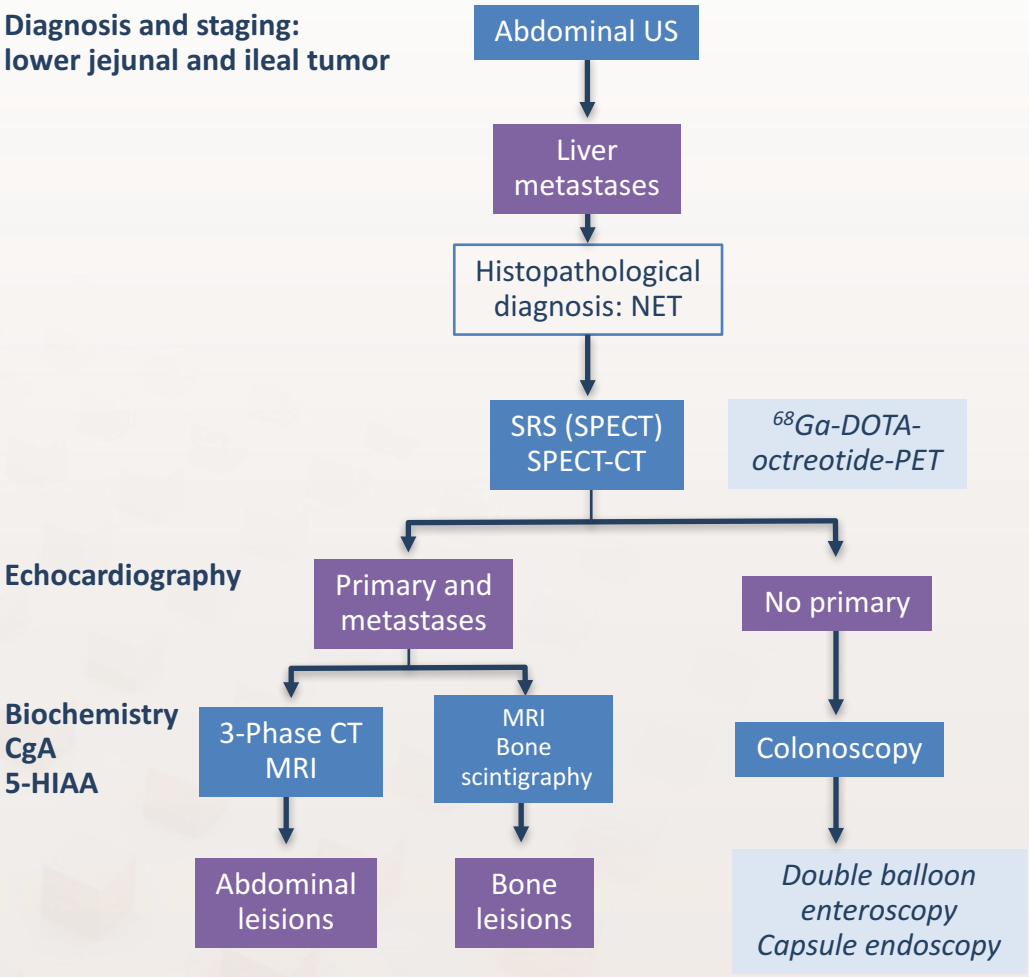
Clinical Presentation of Non-Functioning Midgut NETs

- Unlike functioning GEP-NETs, non-functioning GI tumours are not associated with a distinct hormone syndrome
  - More difficult to detect and may go undetected

- Non-functioning GEP-NETs often cause nonspecific symptoms related to increased tumour mass and/or metastases:
  - Abdominal pain
  - Bleeding
  - Weight loss

National Comprehensive Cancer Network (NCCN). Clinical Practice Guidelines in Oncology: Neuroendocrine Tumors. 2015:1-108.
Oberg. *Ann Oncol*. 2010;21(Suppl.7):vii72-vii80.

Diagnostic Algorithm



Eriksson et al. *Neuroendocrinol*. 2008;87:8-19

Obstruction

- Patients with small bowel primary tumours may experience symptoms of intermittent abdominal pain from episodic bowel obstruction
  - It is often difficult to distinguish from the GI symptoms of carcinoid syndrome
- Palliative small bowel resection is recommended
  - Patients should be evaluated by an experienced multidisciplinary team
  - Every effort to preserve bowel length should be taken

Boudreaux et al. *Pancreas*. 2010;39:753-766.
National Comprehensive Cancer Network (NCCN). Clinical Practice Guidelines in Oncology: Neuroendocrine Tumors. 2015:1-108.

Clinical Presentation of pNETs

Commonly discovered incidentally:

- Abdominal pain*
- Back pain*
- Anorexia-cachexia
- Obstructive jaundice*
- Weight loss*
- Peptide-specific functional syndromes

* Patients with non-functioning pNETs present with symptoms due to the tumour

Singh et al. *Ann Surg Oncol*. 2014;1-15.
Vinik et al. *Pancreas*. 2010;39:713-734.

Characteristics of pNET Subtypes

pNET	Hormone secreted	Symptoms
Gastrinoma	Gastrin	• Abdominal pain due to peptic ulcer disease, diarrhea, and reflux esophagitis
Glucagonoma	Glucagon	• Diabetes accompanied by necrolytic migratory erythema, depression deep vein thrombosis, and diarrhea
Insulinoma	Insulin	• Hypoglycemia and symptoms of neuroglycopenia (eg, confusion and altered consciousness) • Sympathetic overdrive eg, weakness and sweating
PPoma	Pancreatic polypeptide	• Silent • Liver metastasis
Serotonin-secreting	Serotonin	• Wheezing
Somatostatinoma	Somatostatin	• Diabetes, diarrhea or stearorrhea, gallbladder disease, hypochlorhydria, and weight loss
VIPoma (Verner-Morrison syndrome)	Vasoactive intestinal peptide (VIP)	• Profound, large-volume diarrhea • Hypokalemia • Achlorhydria

Vinik et al. *Pancreas*. 2010;39:713-734.

Key Messages

- Presentation of NETs is highly variable and patients may be asymptomatic until later stages of the disease
- Many NETs are identified incidentally during unrelated screening, diagnostic, or surgical procedures
- Imaging and laboratory studies provide important information about NETs
- Surgical excision and systemic therapy, such as SSAs are potential treatments for NETs
- Because of its anti-proliferative effect, SSAs are recommended for tumour stabilization in patients with GEP-NETs

Key Messages

- Biochemical evaluation of pNETs is guided by the presence of symptoms indicative of excess hormone
- Specific hormonal assays are necessary to establish the diagnosis of each functioning pNET
- Patients with functioning pNETs present with clinical symptoms caused by the overproduction of hormones
- Patients with non-functioning pNETs typically present with symptoms due to the tumour itself, including abdominal pain, weight loss, and/or jaundice