

## ONCOLOGY KNOWLEDGE HUB · FOR HEALTH PROFESSIONALS

# Pancreatic Neuroendocrine Tumours

## A mini review for clinicians

For postgraduate residents (medical, surgical and radiation oncology, endocrinology, gastroenterology, nuclear medicine, hepatobiliary–pancreatic surgery, radiology, pathology, medicine), practising clinicians and medical students

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Updated 16 October 2026. Educational summary written in our own words from current guidelines and primary trials; no drug doses; not advice for an individual patient. Verify current guidelines and Indian regulatory approvals before treatment decisions. Patients and families: please see the patient guides at drharitha.co.in.

# Pancreatic Neuroendocrine Tumours

Upper GI & Pancreas, part 2 · Well-differentiated NETs G1–G3 · Functioning syndromes · MEN1 and VHL · Surveillance or surgery · SSA, PRRT, CAPTEM and targeted drugs · Neuroendocrine carcinoma · Key points for clinicians · Last updated 16 October 2026

## 01 At a glance

- Pancreatic neuroendocrine tumours (PanNETs) arise from islet cells. They are rare (about **1.3 per 100,000 people a year**, 1–2% of pancreatic tumours) but rising, mostly because scans done for other reasons now find small ones. Most present in the fourth to sixth decades.
- **Two questions decide almost everything:** is the tumour well differentiated (NET G1, G2 or G3) or poorly differentiated (NEC), and what is its grade by Ki-67 ([WHO 2022](#)<sup>[1]</sup>)? A NET and an NEC of the pancreas are different diseases with different staging, treatment and outlook.
- **50–85% are non-functioning** and present as an incidental mass or with symptoms of size. The rest cause a hormone syndrome (insulinoma, gastrinoma, glucagonoma, VIPoma, somatostatinoma) that must be controlled before and during tumour treatment.
- **Outlook is usually measured in years:** even with distant spread, median survival for G1–G2 pancreatic NETs was about 50 months in US registry data ([Dasari 2017](#)<sup>[2]</sup>), against about 11 months for metastatic NEC ([NORDIC NEC](#)<sup>[3]</sup>).
- **Not every tumour needs an operation:** most sporadic, asymptomatic non-functioning tumours of 2 cm or less can be watched ([ASPEN](#)<sup>[4]</sup>); larger, functioning or higher-grade tumours are resected.
- **Think inherited:** MEN1, VHL, NF1 and tuberous sclerosis account for a minority of cases but change thresholds for surgery and require family testing.
- **India:** Ga-68 DOTA PET and Lu-177 PRRT are available in larger Indian centres; India has produced Lu-177 and given PRRT since about 2008, which keeps this treatment more affordable than in many countries ([IJMPO 2019](#)<sup>[5]</sup>; [AJNMMI 2020](#)<sup>[6]</sup>).

### One family, four behaviours: grade and differentiation decide almost everything

| NET G1<br>Ki-67 <3%                                                                                                                                                                                                                    | NET G2<br>Ki-67 3–20%                                                                                                                                                                                                                                   | NET G3<br>Ki-67 >20% (usually 20–55%)                                                                                                                                                                                                                        | NEC<br>poorly differentiated |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------|
| Slow, often SSTR-positive; years of life even with liver spread                                                                                                                                                                        |                                                                                                                                                                                                                                                         | Fast, SSTR-poor, FDG-avid; behaves like small cell cancer                                                                                                                                                                                                    |                              |
| <b>What they are</b> <ul style="list-style-type: none"> <li>• Islet-cell tumours: 1–2% of pancreatic tumours</li> <li>• About 1.3 per 100,000 a year, rising as scans find small ones</li> <li>• 50–85% are non-functioning</li> </ul> | <b>How they present</b> <ul style="list-style-type: none"> <li>• Incidental mass on a scan done for something else</li> <li>• A hormone syndrome: low sugar, ulcers, rash, watery diarrhoea</li> <li>• Liver metastases with a small primary</li> </ul> | <b>What changed</b> <ul style="list-style-type: none"> <li>• SSTR PET (Ga-68 DOTATATE) for staging and therapy choice</li> <li>• Watch most sporadic non-functioning tumours ≤2 cm</li> <li>• PRRT moved earlier: first line for G2–G3 (NETTER-2)</li> </ul> |                              |

Figure 1. Pancreatic neuroendocrine neoplasms at a glance. Well-differentiated tumours (NET G1–G3) and poorly differentiated carcinomas (NEC) share a name but not a biology, a staging system or a treatment (WHO 2022; incidence from US registry data).

## 02 Clinical presentation, common traps & causes

### How pancreatic NETs come to attention

| Type                           | How often (new cases per million a year)                                                  | Typical story                                                                                                                                                  | Spread at diagnosis                                     |
|--------------------------------|-------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------|
| Non-functioning                | Most PanNETs (50–85%)                                                                     | Incidental on CT, MRI or endoscopic ultrasound; or pain, weight loss, jaundice, a palpable mass, or liver metastases with an unknown primary                   | Depends on size and grade; many small ones never spread |
| Insulinoma                     | 1–3 (about 4 per million in the Mayo series, <a href="#">Service 1991<sup>[7]</sup></a> ) | Fasting hypoglycaemia: confusion, odd behaviour, visual change, sweating, palpitations, seizure-like episodes; often weight gain from eating to avoid symptoms | About 1 in 10                                           |
| Gastrinoma (Zollinger–Ellison) | 0.5–2                                                                                     | Severe, recurrent or post-bulbar ulcers; reflux; diarrhoea that settles on a PPI; complications such as bleeding, stricture or perforation                     | Often nodes; liver spread in a minority at diagnosis    |
| VIPoma                         | 0.05–0.2 (about 1 per million)                                                            | Large-volume watery, tea-coloured, odourless diarrhoea that continues when fasting; low potassium, dehydration, flushing in 20%                                | 60–80%                                                  |
| Glucagonoma                    | 0.01–0.1                                                                                  | Necrolytic migratory erythema, weight loss, diabetes, anaemia, cheilitis and glossitis, venous clots, neuropsychiatric change                                  | 50–80%                                                  |
| Somatostatinoma                | About 1 in 40 million                                                                     | Usually a mass (pain, weight loss, jaundice); the syndrome of diabetes, gallstones and steatorrhea is rare (under 10%)                                         | Most                                                    |

**Functioning syndromes: the clue, the test, where the tumour sits, how often it has spread**

|                                                                                                                                                                                                                                                                                                                                                  |                                                                                                                                                                                                                                                                                                                                                                                                   |                                                                                                                                                                                                                                                                                                       |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Insulinoma</b> <ul style="list-style-type: none"> <li>• Clue: confusion, odd behaviour or "fits" when fasting; better with food</li> <li>• Test: supervised 72-hour fast (glucose, insulin, C-peptide, proinsulin)</li> <li>• Site: anywhere in the pancreas; usually solitary, small</li> <li>• Spread: about 1 in 10</li> </ul>             | <b>Gastrinoma (Zollinger–Ellison)</b> <ul style="list-style-type: none"> <li>• Clue: refractory or post-bulbar ulcers, reflux, diarrhoea that settles on PPI</li> <li>• Test: fasting gastrin <math>&gt;10\times</math> ULN with gastric pH <math>&lt;2</math>, off PPI under supervision</li> <li>• Site: duodenum 70–90%, pancreas 20–25%</li> <li>• 20–30% have MEN1: test them all</li> </ul> | <b>Glucagonoma</b> <ul style="list-style-type: none"> <li>• Clue: necrolytic migratory erythema, weight loss, diabetes, clots, glossitis</li> <li>• Test: fasting glucagon <math>&gt;500</math> pg/mL</li> <li>• Site: body and tail; usually large</li> <li>• Spread: 50–80% at diagnosis</li> </ul> |
| <b>VIPoma</b> <ul style="list-style-type: none"> <li>• Clue: watery diarrhoea <math>&gt;0.7</math> L a day that continues when fasting; low potassium</li> <li>• Test: raised VIP, repeated; stool osmotic gap <math>&lt;50</math></li> <li>• Site: tail in 75%; usually <math>&gt;3</math> cm</li> <li>• Spread: 60–80% at diagnosis</li> </ul> | <b>Somatostatinoma</b> <ul style="list-style-type: none"> <li>• Clue: diabetes, gallstones, steatorrhea (syndrome is rare)</li> <li>• Test: somatostatin <math>&gt;3\times</math> ULN only if the syndrome is present</li> <li>• Site: pancreatic head or ampulla (ampullary in NF1)</li> <li>• Spread: most at diagnosis</li> </ul>                                                              | <b>Non-functioning (most)</b> <ul style="list-style-type: none"> <li>• Clue: incidental, or pain, jaundice, weight loss from size</li> <li>• Test: no hormone panel unless symptoms; tissue + SSTR PET</li> <li>• Site: anywhere</li> <li>• Behaviour: set by size, grade and stage</li> </ul>        |

Figure 2. Functioning syndromes. Suspect them from the symptoms, prove them with the hormone in the right conditions, then find the tumour. Do not order hormone panels in patients without symptoms (UpToDate topic reviews; ENETS 2023 functioning-tumour guidance).

**Inherited syndromes**

| Syndrome            | Lifetime PanNET risk | Clues                                                                                                                       | Practical point                                                                                                                           |
|---------------------|----------------------|-----------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------|
| MEN1                | 80–100%              | Hypercalcaemia (often the first sign), pituitary tumour, multiple pancreatic or duodenal tumours, gastrinoma at a young age | Every gastrinoma patient is screened for MEN1 ( <a href="#">Niederle 2021<sup>[8]</sup></a> ; <a href="#">Brandi 2021<sup>[9]</sup></a> ) |
| Von Hippel–Lindau   | Up to 20%            | Retinal or cerebellar haemangioblastoma, kidney cancer, pheochromocytoma, many pancreatic cysts                             | Missense or exon 3 variants carry more metastatic risk                                                                                    |
| Neurofibromatosis 1 | About 10%            | Café-au-lait spots, neurofibromas; ampullary or duodenal somatostatin-rich tumours                                          | Seldom a hormone syndrome; less likely to metastasise than sporadic somatostatinoma                                                       |
| Tuberous sclerosis  | About 1%             | Skin, brain and kidney lesions                                                                                              | Treat the PanNET by the usual rules                                                                                                       |

**Inherited syndromes behind pancreatic NETs: risk, pattern and when to operate****MEN1 (MEN1 gene, 11q13)**

- PanNETs in 80–100% over life; often many
- Also parathyroid (first sign), pituitary, thymic NETs
- Duodenal gastrinomas: PPI, not routine surgery
- Operate: non-functioning  $\geq 2$  cm or growing; every insulinoma

**VHL (VHL gene, 3p25)**

- PanNETs in up to 20%; cysts very common
- Also kidney cancer, haemangioblastoma, phaeo
- Operate: head  $> 2$  cm, body/tail  $> 3$  cm
- Belzutifan if fast-growing or unresectable

**NF1 (17q11)**

- PanNET in about 10%
- Classic: ampullary/duodenal somatostatinoma
- Café-au-lait spots, neurofibromas
- Rarely a hormone syndrome

**Tuberous sclerosis**

- PanNET in about 1%
- Skin, brain, kidney (angiomyolipoma)
- Often already on everolimus
- Treat the PanNET by usual rules

Germline testing: everyone with a suggestive family history, every gastrinoma and multiple tumours; consider it for all under 50. A negative family history does not exclude MEN1: about 1 in 10 variants are new (de novo).

Figure 3. Inherited syndromes. Hereditary PanNETs are usually multiple and more indolent, so surgery is reserved for larger or growing tumours and pancreas-sparing operations are preferred (MEN1 and VHL UpToDate reviews; international MEN1 consensus).

**Common traps**

- **Hypoglycaemia mislabelled** as epilepsy, a psychiatric illness or "giddiness": check a glucose during an episode; insist on Whipple's triad (symptoms, low glucose, relief with glucose).
- **Zollinger–Ellison hidden by PPIs**: suspect it with ulcers beyond the bulb, multiple or refractory ulcers, ulcers without H. pylori or NSAIDs, thick gastric folds, or chronic diarrhoea. Do not stop a PPI casually to test: complications can follow.
- **Necrolytic migratory erythema treated as eczema or fungal infection** for months; it is not specific (zinc deficiency, liver disease and other cancers mimic it), so measure glucagon.
- **VIPoma treated as infective diarrhoea**: secretory diarrhoea (stool osmotic gap under 50) that persists on fasting points away from infection and laxatives.
- **Chromogranin A used for diagnosis**: PPIs, kidney failure, atrophic gastritis, heart failure and inflammatory disease raise it. Histology makes the diagnosis.
- **A positive hormone stain is not a syndrome**: tumours staining for somatostatin, gastrin or insulin are called functioning only when the patient has the clinical syndrome.
- **Not every hypervascular pancreatic mass is a NET**: think of renal cell carcinoma metastasis (especially in VHL), solid pseudopapillary neoplasm, adenocarcinoma, lymphoma, focal or autoimmune pancreatitis. Physiological SSTR uptake in the uncinate process can mimic a tumour.
- **Liver metastases from an "unknown primary"** with neuroendocrine histology: SSTR PET, multiphasic imaging and EUS usually find a small pancreatic or intestinal primary.

**SHARE WITH PATIENTS: WHAT MAKES THESE TUMOURS DIFFERENT**

Plain-language myth pages written for patients and families. Send them from the clinic to reinforce what you discussed.

[All pancreatic cancers are the same disease?](#)

[Pancreatic cancer is always hereditary?](#)

## 03 Screening, workup & staging essentials

### Diagnostic approach

- **Tissue confirms the diagnosis**, from the primary (EUS-guided fine-needle biopsy) or the safest, most aggressive-looking metastasis. Ask the pathologist for differentiation, Ki-67 and mitotic count on the sample.
- **Stage with multiphasic imaging**: triple-phase CT (non-contrast, arterial, portal venous) or multiphasic MRI with diffusion. Arterial images show the hypervascular primary and liver metastases; MRI is more sensitive for small liver deposits.
- **Add SSSTR PET** (Ga-68 DOTATATE or DOTANOC, or Cu-64 DOTATATE) at baseline in most well-differentiated tumours: whole-body staging, occult primaries and eligibility for SSA and PRRT ([Sadowski 2016<sup>\[10\]</sup>](#), [Hope 2018<sup>\[11\]</sup>](#)). It may be omitted for a very small (under 1–1.5 cm) G1 tumour at low risk of spread.
- **FDG PET** for NET G3 and NEC, before surgery for NEC, and when a low-grade tumour behaves aggressively.
- **Functioning tumours not seen on CT, MRI or SSSTR PET**: EUS (detects 2–3 mm lesions), GLP-1 receptor (exendin) PET for insulinoma, and rarely selective arterial calcium stimulation with hepatic venous sampling. Modern imaging finds nearly all of them.

#### Which test, for which tumour

|                                       | Non-functioning G1–G2 | Insulinoma | Gastrinoma | NET G3 | NEC | Liver metastases |
|---------------------------------------|-----------------------|------------|------------|--------|-----|------------------|
| Multiphasic CT (arterial + venous)    | ●                     | ●          | ●          | ●      | ●   | ●                |
| MRI with diffusion                    | ○                     | ○          | ○          | ○      | ○   | ●                |
| SSSTR PET–CT (Ga-68 / Cu-64)          | ●                     | ○          | ●          | ●      | ●   | ●                |
| FDG PET–CT                            | ●                     | ●          | ●          | ●      | ●   | ○                |
| EUS ± fine-needle biopsy              | ●                     | ●          | ●          | ○      | ○   | ●                |
| GLP-1 receptor (exendin) PET          | ●                     | ○          | ●          | ●      | ●   | ●                |
| Calcium stimulation / venous sampling | ●                     | ○          | ○          | ●      | ●   | ●                |

● usual first choice      ○ helpful when the first test fails      ● rarely needed

SSSTR PET is less sensitive for insulinomas and high-grade tumours; a very small G1 tumour at low risk of spread may not need it.

Figure 4. Matching the test to the tumour. Multiphasic CT or MRI stages almost every patient; SSSTR PET adds whole-body staging and decides SSA and PRRT eligibility; FDG PET marks aggressive disease (UpToDate diagnosis, insulinoma, gastrinoma and G3 reviews).

### Proving a hormone syndrome (only when symptoms suggest one)

| Syndrome   | Test                                                                                                                     | Diagnostic finding                                                                                                         | Cautions                                                                              |
|------------|--------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------|
| Insulinoma | Supervised 72-hour fast (mixed-meal test if symptoms are after meals)                                                    | Glucose under 55 mg/dL with inappropriately high insulin, C-peptide and proinsulin, and a glucose rise after glucagon      | Screen for sulfonyleureas; exogenous insulin suppresses C-peptide                     |
| Gastrinoma | Fasting gastrin after holding the PPI for 7–14 days (H2-blocker cover, specialist supervision) + gastric pH at endoscopy | Gastrin above 10 times the upper limit (≈1000 pg/mL) with gastric pH under 2 ( <a href="#">Berna 2006<sup>[12]</sup></a> ) | Atrophic gastritis, H. pylori and PPIs raise gastrin; secretin test only if equivocal |

| Syndrome        | Test                    | Diagnostic finding                                      | Cautions                                                   |
|-----------------|-------------------------|---------------------------------------------------------|------------------------------------------------------------|
| Glucagonoma     | Fasting plasma glucagon | Above 500 pg/mL                                         | A normal level does not exclude it in the classic syndrome |
| VIPoma          | Serum VIP, repeated     | Raised VIP with secretory diarrhoea over 0.7 L a day    | Follow the laboratory's collection rules                   |
| Somatostatinoma | Plasma somatostatin     | Over 3 times the upper limit with the clinical syndrome | Somatostatin staining alone is not a diagnosis             |

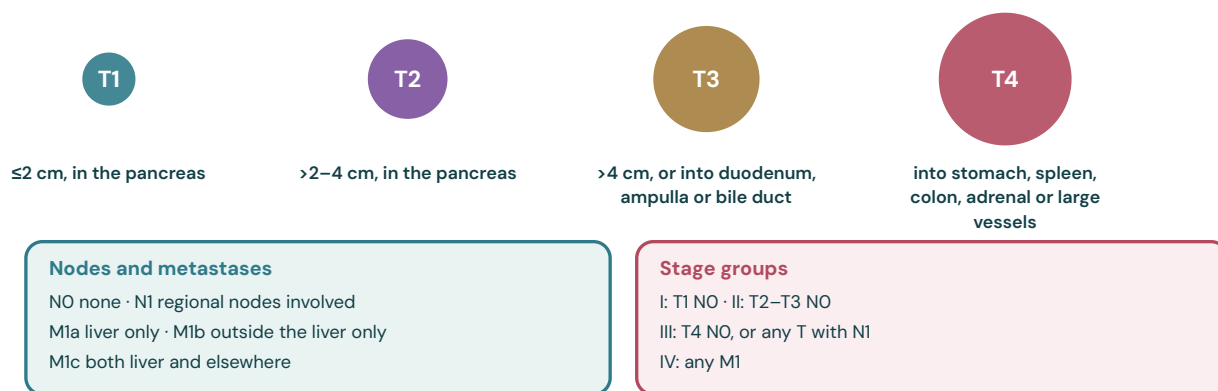
### Who needs germline testing

- Everyone with a family history suggesting MEN1, VHL, NF1 or tuberous sclerosis; every patient with gastrinoma; multiple pancreatic NETs; associated tumours (hyperparathyroidism, pituitary tumour, haemangioblastoma, kidney cancer, pheochromocytoma).
- Consider it for apparently sporadic tumours in people under 50, regardless of family history. About 1 in 10 MEN1 variants arise new, so a clean family history does not exclude it.
- MEN1 surveillance (international consensus): yearly clinical review with calcium, PTH and prolactin; pancreatic imaging (MRI or EUS, avoiding radiation) every 2–3 years; urgent work-up of new symptoms.

### Staging

- Well-differentiated pancreatic NETs use their own AJCC system (version 9), separate from pancreatic cancer; T categories follow size ( $\leq 2$ ,  $>2-4$ ,  $>4$  cm) and invasion. Poorly differentiated NECs are staged like pancreatic adenocarcinoma.
- Gastrinomas of the duodenum use the duodenal/ampullary NET system.

#### Staging well-differentiated pancreatic NETs: AJCC version 9 (separate from pancreatic cancer)



Multiple tumours: stage by the largest and add (m). Spread into peripancreatic fat does not change T. NEC is staged like pancreatic cancer.

Figure 5. TNM for pancreatic NETs (AJCC version 9, 2023), redrawn in our own words. Size thresholds also drive surgical decisions (section O5).

#### SHARE WITH PATIENTS: BIOPSY AND TESTS

Plain-language myth pages written for patients and families. Send them from the clinic to reinforce what you discussed.

#### A pancreatic biopsy makes cancer spread?

## 04 Biomarkers that change treatment

### WHO 2022 grading by Ki-67 index (the higher of Ki-67 and mitotic count decides)



Mitoses per 2 mm<sup>2</sup>: G1 <2 · G2 2–20 · G3 >20. Most NET G3 reach grade 3 on Ki-67 alone; a mitotic count >20 favours NEC.

#### Grey zone 20–55%

Morphology decides. Ask for p53, Rb (lost in NEC) and DAXX/ATRX (lost in NET); re-review NET G3 with Ki-67 >55% and NEC with Ki-67 <55%.

#### Why it matters

G1–G2: SSA, PRRT, targeted drugs, CAPTEM. NET G3: CAPTEM, FOLFOX or PRRT. NEC: platinum + etoposide; NGS for rare targets.

#### Sampling error

Ki-67 varies within a tumour and rises over time: grade on the hottest area; re-biopsy if a tumour starts behaving differently.

Figure 6. Grading. Ki-67 bands follow the WHO 2022 classification; the 55% re-review rule and the immunostains for the grey zone follow the UpToDate pathology review.

| Marker                                                   | What it tells you                                                                                                      | What it changes                                                                                                                                                                  |
|----------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Differentiation (morphology ± p53, Rb, DAXX/ATRX)        | NET versus NEC. DAXX or ATRX loss in about half of pancreatic NETs (including G3); Rb loss or abnormal p53 favours NEC | NET treatments versus platinum–etoposide; prognosis                                                                                                                              |
| Ki-67 index and mitotic count                            | Grade G1 (under 3%), G2 (3–20%), G3 (over 20%)                                                                         | Surveillance versus surgery for small tumours; SSA alone (low Ki-67) versus PRRT (Ki-67 10–55%, <b>NETTER-2</b> <sup>[13]</sup> ) or chemotherapy; above 55%: NEC-type treatment |
| SSTR expression (PET uptake)                             | Target for somatostatin analogues and PRRT                                                                             | SSA and PRRT need uptake in every significant lesion; SSTR-negative disease goes to CAPTEM or targeted drugs                                                                     |
| FDG avidity                                              | Glycolytic, more aggressive clones                                                                                     | Shorter intervals, earlier chemotherapy; re-biopsy if discordant with grade                                                                                                      |
| Hormones (insulin, gastrin, glucagon, VIP, somatostatin) | Functional status; marker of activity if raised at baseline                                                            | Hormone control; checked with imaging every 6–12 months after resection                                                                                                          |
| Chromogranin A                                           | Weak: rises with PPIs, kidney failure, atrophic gastritis; falls with SSAs regardless of tumour size                   | Not for diagnosis or routine follow-up after surgery; a ≥50% rise predicted progression with sensitivity only 34% in a prospective study                                         |
| NETest (blood RNA signature)                             | High accuracy in pooled studies                                                                                        | Investigational: not yet a basis for changing treatment without imaging                                                                                                          |
| Germline MEN1, VHL, NF1, TSC                             | Inherited syndrome                                                                                                     | Surgical thresholds, pancreas-sparing surgery, belzutifan (VHL), family testing                                                                                                  |
| Tumour NGS (NEC, NET G3 in later lines)                  | MSI-H/dMMR, TMB-high, BRAF V600E, NTRK and RET fusions                                                                 | Immune checkpoint inhibitors, dabrafenib + trametinib, TRK or RET inhibitors after chemotherapy                                                                                  |

## 05 Local therapy: surgery, liver-directed therapy & radiotherapy

### Surgery for localised disease

#### Localised sporadic tumours: who needs an operation?

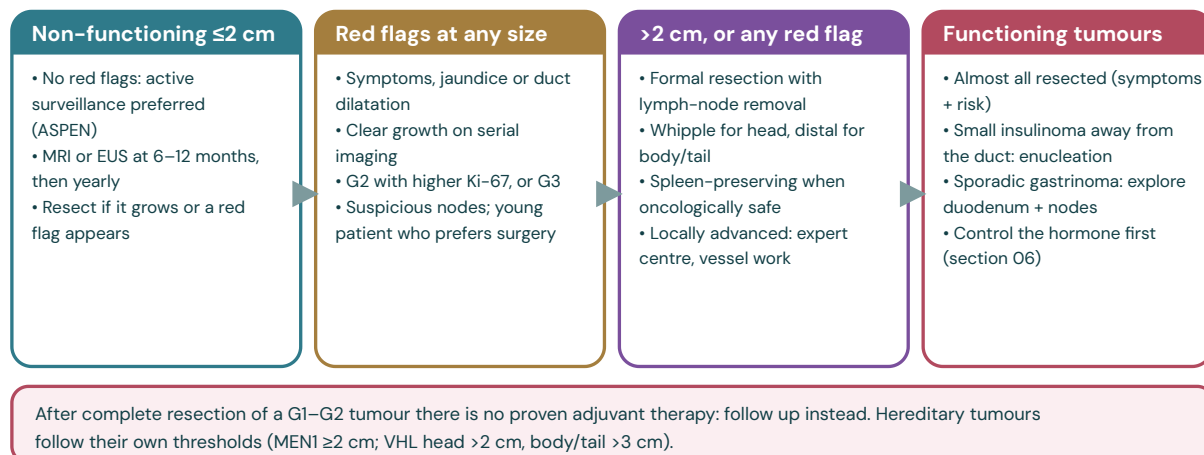


Figure 7. Who needs an operation. The UpToDate topic on surgery for sporadic PanNETs was not in the source set: the  $\leq 2$  cm surveillance rule is from the prospective ASPEN cohort and ENETS/NCCN guidance (web-verified, October 2026); red flags summarise guideline criteria. Please check against local surgical practice.

- **Small, sporadic, non-functioning tumours (2 cm or less):** active surveillance is now preferred for most asymptomatic patients. The prospective international ASPEN cohort concluded this at its interim analysis ([Partelli 2022](#)<sup>[4]</sup>), and its final report (ESMO 2025, more than 860 patients under surveillance) found survival similar to surgery, with relevant growth infrequent and distant spread rare. ENETS and NCCN accept observation up to 2 cm; NANETS individualises tumours of 1–2 cm.
- **Red flags that favour surgery** at any size: symptoms, jaundice or main-duct dilatation, clear growth on serial imaging, higher grade, suspicious nodes, and patient preference after counselling (younger patients face decades of surveillance).
- **Larger tumours (over 2 cm):** formal resection (pancreaticoduodenectomy for the head, distal pancreatectomy for the body and tail, central pancreatectomy in selected cases) with removal of regional lymph nodes. Total pancreatectomy is rarely needed.
- **Enucleation** suits small, benign-appearing tumours, especially insulinomas, away from the main pancreatic duct. In one series of head lesions it caused more clinically relevant fistulas than a Whipple (40% vs 14%) but spares pancreatic function. It is not used for tumours over 2 cm or when malignancy is possible, because no nodes are removed.
- **Functioning tumours:** complete resection to negative margins is the standard. Insulinoma surgery cures more than 90%; persistent hypoglycaemia after surgery means repeat localisation and reoperation. Sporadic gastrinoma: PPI, then exploration with duodenotomy and lymph-node dissection; small duodenal tumours may be resected endoscopically by experts. Failure to control symptoms after resection predicts earlier relapse ([Zaidi 2019](#)<sup>[14]</sup>).
- **Hereditary tumours:** MEN1 non-functioning tumours are resected at 2 cm or more or if growing or higher grade; MEN1 gastrinoma is controlled with a PPI and surgery is debated; MEN1 insulinoma is resected (often

local excision of head tumours plus distal subtotal pancreatectomy). VHL: resect head tumours over 2 cm and body or tail tumours over 3 cm; pancreas-sparing operations because more tumours may follow.

- **After complete resection** of a G1–G2 tumour, no adjuvant therapy has been shown to help; NET G3 is also followed after surgery. Localised NEC needs perioperative platinum–etoposide (section 06).

## Metastatic disease: surgery and liver-directed therapy

### Liver metastases from well-differentiated NETs: matching the tool to the burden

#### Resectable (all or ≥90%)

- Resect liver + primary when safe
- 5-year survival 61–77% in series
- Relapse is common: plan follow-up
- Ablation for spots <3 cm

#### Liver-predominant, unresectable

- Bland embolization, chemo-embolization
- or Y-90 radioembolization
- Response >50% (hormones or size)
- Y-90 before PRRT: long-term liver safety unclear

#### Diffuse or extrahepatic

- Systemic therapy leads
- Liver-directed therapy for symptoms
- Debulking only in selected cases
- Liver transplant: investigational

Before any liver procedure in a functioning tumour, control the hormone (SSA, fluids, glucose); hormone crises can follow embolization or surgery. Imaging underestimates liver disease: many tiny deposits are found only in the resected specimen.

Figure 8. Liver-directed therapy. Survival figures come from observational surgical series (no randomised trials); embolization choices are made by an experienced interventional team (UpToDate local-options review).

- **Resect when everything can be removed:** when both the primary and liver-predominant metastases are resectable, surgery is preferred to systemic therapy. Five-year survival after liver resection is 61–77% in series and symptoms improve in most, though relapse is the rule (84% at 5 years in the Mayo series, [Sarmiento 2003<sup>\[15\]</sup>](#)).
- **Debulking:** a 90% cytoreduction threshold gave longer progression-free survival than 70% in observational studies, with similar overall survival; selection bias is large and there are no randomised trials.
- **Unresectable liver-predominant disease:** bland embolization, chemo-embolization or Y-90 radioembolization control symptoms and tumour growth (responses over 50%). Drug-eluting beads cause more biliary injury; late liver fibrosis has been reported after Y-90, and its safety before later PRRT is not established. Ablation suits lesions under about 3 cm.
- **Liver transplantation** is investigational for neuroendocrine liver metastases and is considered only in highly selected patients in expert programmes.
- **Before any procedure in a functioning tumour:** control the hormone (SSA, fluids, potassium, glucose) because tumour breakdown can release a surge.

## Radiotherapy

- External-beam radiotherapy has a limited role in well-differentiated pancreatic NETs: palliation of painful bone metastases or a bleeding or obstructing mass. Most "radiation" for these tumours is delivered internally, as PRRT (section 06).
- NEC: for unresectable locoregional disease, chemotherapy plus radiotherapy is suggested over either alone; prophylactic cranial irradiation is not used.

## 06 Systemic therapy: indications & options

### First, control the hormone

Controlling the hormone comes first: it keeps patients safe while the tumour is treated

|                                                                                                                                                                                                                                                              |                                                                                                                                                                                                                                              |                                                                                                                                                                                                                                                                              |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Insulinoma</b> <ul style="list-style-type: none"> <li>• Frequent meals; glucose on hand</li> <li>• Diazoxide first (predictable)</li> <li>• SSA only if diazoxide fails: it can worsen lows</li> <li>• Refractory: everolimus, PRRT, debulking</li> </ul> | <b>Gastrinoma</b> <ul style="list-style-type: none"> <li>• High-dose PPI, lifelong if not cured</li> <li>• Never stop PPI abruptly</li> <li>• Off-PPI gastrin test only under supervision</li> <li>• SSA if acid symptoms persist</li> </ul> | <b>VIPoma</b> <ul style="list-style-type: none"> <li>• IV fluids and potassium first (often litres a day)</li> <li>• SSA quickly controls diarrhoea</li> <li>• Steroids or antidiarrhoeals if refractory</li> <li>• Correct fluids before surgery or embolization</li> </ul> |
| <b>Glucagonoma</b> <ul style="list-style-type: none"> <li>• SSA for rash and catabolism</li> <li>• Nutrition, amino acids, zinc</li> <li>• Treat diabetes</li> <li>• Watch for venous clots</li> </ul>                                                       | <b>Somatostatinoma</b> <ul style="list-style-type: none"> <li>• SSA reduces secretion</li> <li>• Treat diabetes and steatorrhoea (enzymes)</li> <li>• Gallstones are common</li> <li>• Usually a mass problem</li> </ul>                     | <b>After SSA starts</b> <ul style="list-style-type: none"> <li>• Gallstones, loose fatty stools, B12</li> <li>• Mild glucose rise</li> <li>• Continue SSA after progression only</li> <li>• in functioning tumours</li> </ul>                                                |

Figure 9. Hormone control by syndrome. No doses are given: use local protocols. Based on the UpToDate insulinoma, gastrinoma, VIPoma, glucagonoma, somatostatinoma and systemic-therapy reviews.

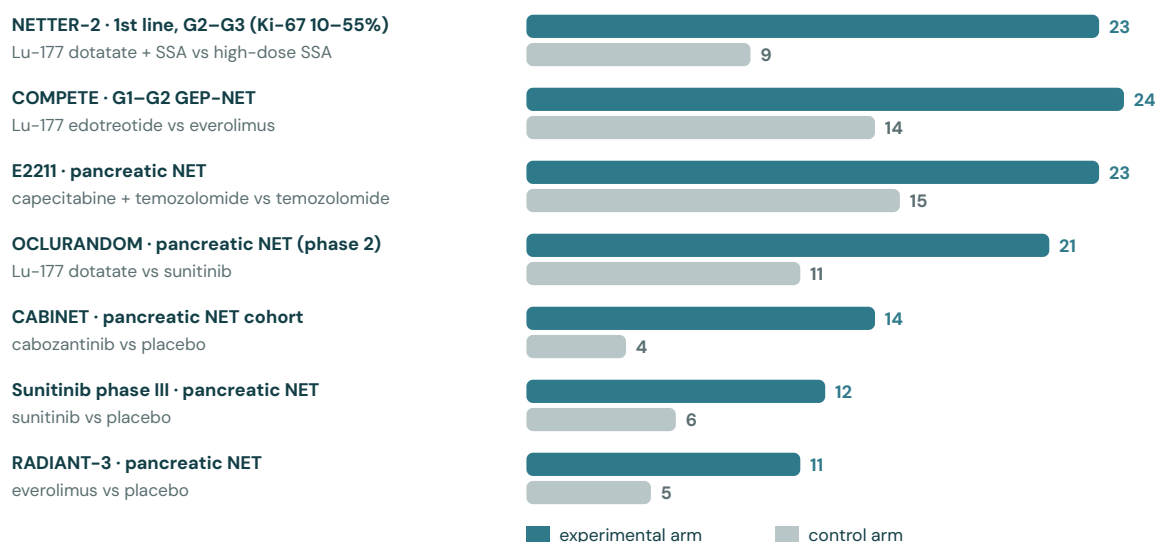
- **Insulinoma:** diazoxide is more predictable than SSAs; SSAs can worsen hypoglycaemia by suppressing glucagon, so start them only with monitoring. Everolimus can control refractory hypoglycaemia.
- **Gastrinoma:** high-dose PPI for every patient, usually reducible later; potassium-competitive acid blockers are an alternative; SSA if refractory.
- **VIPoma:** replace fluid and potassium first (some patients need several litres a day), then an SSA; steroids or antidiarrhoeals for refractory diarrhoea.
- **Glucagonoma and somatostatinoma:** SSA, nutrition, diabetes control; watch for clots in glucagonoma.
- **Continue the SSA after progression** in functioning tumours (hormone control); in non-functioning tumours it can be stopped when a second-line therapy starts.

### Well-differentiated G1–G2 tumours: controlling growth

- **Watch** asymptomatic, low-volume, slowly growing disease: there is no proof that early treatment prolongs life ([NANETS<sup>\[16\]</sup>](#)).
- **Somatostatin analogues** are first line for SSTR-positive, low-volume disease: in [CLARINET<sup>\[17\]</sup>](#), lanreotide prolonged progression-free survival (median not reached vs 18 months; 2-year 65% vs 33%) in G1–G2 non-functioning GEP-NETs, including pancreatic primaries, without an overall survival difference; octreotide showed the same principle in midgut NETs ([PROMID<sup>\[18\]</sup>](#)).
- **PRRT with Lu-177 dotatate** is the usual next step after SSA progression in SSTR-positive disease. In [OCLURANDOM<sup>\[19\]</sup>](#) (pancreatic NETs, phase 2) it gave a median progression-free survival of 21 vs 11 months over sunitinib with less severe toxicity (44% vs 72%); in a large Dutch cohort, pancreatic NETs had a 55% response and median survival of 71 months ([Brabander 2017<sup>\[20\]</sup>](#)). [NETTER-1<sup>\[21\]</sup>](#) (midgut only) established PRRT plus SSA over high-dose SSA. In [COMPETE<sup>\[22\]</sup>](#), Lu-177 edotreotide beat everolimus (24 vs 14 months; HR 0.67) in G1–G2 GEP-NETs; edotreotide remains investigational for pancreatic NETs.

- **First-line PRRT for higher G2 and G3:** in [NETTER-2<sup>\[13\]</sup>](#) (Ki-67 10–55%, 54% pancreatic), Lu-177 dotatate plus SSA gave 23 vs 9 months over high-dose octreotide (HR 0.28; response 43% vs 9%); the pancreatic subgroup benefited (HR 0.34).
- **Capecitabine plus temozolomide (CAPTEM)** is preferred for bulky, symptomatic or rapidly progressive disease because responses are frequent: in [E2211<sup>\[23\]</sup>](#), progression-free survival 23 vs 15 months over temozolomide alone, response 40%, at the cost of more grade 3–4 toxicity (44% vs 22%). Streptozocin-based regimens are an alternative where available ([Moertel 1992<sup>\[24\]</sup>](#)).
- **Targeted drugs** for progressive disease: everolimus ([RADIANT-3<sup>\[25\]</sup>](#): 11 vs 5 months; overall survival 44 vs 38 months, not significant, [Yao 2016<sup>\[26\]</sup>](#)), sunitinib ([Raymond 2011<sup>\[27\]</sup>](#): 12 vs 6 months) and cabozantinib after prior therapy ([CABINET<sup>\[28\]</sup>](#) pancreatic cohort: 14 vs 4 months; response 19%).
- **Sequencing** (Algorithm 3): SSTR-positive, low volume → SSA; high volume → SSA + PRRT (Ki-67 10–20%), SSA + liver-directed therapy, or CAPTEM; rapid progression → CAPTEM. SSTR-negative → CAPTEM if rapid, otherwise cabozantinib, everolimus or sunitinib. After SSA → PRRT; after SSA and PRRT → CAPTEM (bulky or fast) or a targeted drug; repeat PRRT in selected patients, ideally in a trial.

#### Median progression-free survival in the trials that shape treatment (months)



Cross-trial comparison is not valid: populations, lines and grades differ. None of these trials showed a significant overall survival gain.

Figure 10. Progression-free survival in the trials behind today's choices (rounded medians as reported in the UpToDate reviews; NETTER-2 and COMPETE included pancreatic and intestinal primaries).

## High-grade disease: NET G3 and NEC

**NET G3 or NEC? Two different diseases above a Ki-67 of 20%**

|                             | NET G3 (well differentiated)          | NEC (poorly differentiated)           |
|-----------------------------|---------------------------------------|---------------------------------------|
| <b>Microscope</b>           | Organoid, uniform cells               | Sheets, necrosis; small or large cell |
| <b>Ki-67</b>                | Usually 20–55%                        | Usually >55% (often >70%)             |
| <b>Genes</b>                | MEN1, DAXX/ATRX; p53 and Rb kept      | TP53 and RB1 lost; KRAS in some       |
| <b>SSTR PET / FDG PET</b>   | Often SSTR-positive; FDG variable     | SSTR-poor; FDG-avid                   |
| <b>First treatment</b>      | CAPTEM or FOLFOX; PRRT + SSA if SSTR+ | Platinum + etoposide                  |
| <b>Outlook (metastatic)</b> | Years for many (CAPTEM series: 32 mo) | About 1 year (NORDIC NEC: 11 mo)      |

Ki-67 >55% or rapid progression in a "NET G3": treat like NEC. A NET that loses SSTR uptake and speeds up may have transformed: re-biopsy.

Figure 11. NET G3 versus NEC. Distinguishing them changes the first treatment; survival figures are from observational cohorts quoted in the UpToDate G3 and NEC reviews.

- **NET G3 (Ki-67 20–55%),** SSTR-positive: SSA alone only for minimal, asymptomatic disease; moderate burden → PRRT + SSA or chemotherapy (CAPTEM or FOLFOX); major burden or symptoms → chemotherapy first (faster onset, easier to start). SSTR-negative → CAPTEM or FOLFOX. In a retrospective series of NET G3 treated with CAPTEM, response was 41% and median survival 32 months. Ki-67 over 55% or rapid progression: treat as NEC.
- **Localised NEC:** surgery with platinum-etoposide (neoadjuvant preferred for locoregionally advanced tumours); chemoradiation for unresectable locoregional disease.
- **Metastatic NEC:** platinum (cisplatin or carboplatin) plus etoposide first ([NORDIC NEC<sup>\[3\]</sup>](#): response 31%, progression-free 4 and overall 11 months); platinum plus irinotecan is equivalent ([TOPIC-NEC<sup>\[29\]</sup>](#)). Send tumour NGS at diagnosis.
- **After first-line NEC therapy:** relapse 6 months or more after stopping → re-treat with platinum; earlier → irinotecan- or oxaliplatin-based regimens or temozolomide ± capecitabine (nal-IRI + 5-FU and docetaxel were tested in [NET-O2<sup>\[30\]</sup>](#)). MSI-H/dMMR → checkpoint inhibitor ([KEYNOTE-158<sup>\[31\]</sup>](#)); BRAF V600E → dabrafenib + trametinib ([NCI-MATCH<sup>\[32\]</sup>](#)); NTRK or RET fusion → matched inhibitor.

**India now (October 2026)**

- PRRT: Lu-177 has been produced in India (BARC, BRIT) and used for PRRT since about 2008, so PRRT is offered at larger nuclear medicine centres at lower cost than imported products; one centre reports more than 4,000 treatments ([AJNMMI 2020<sup>\[6\]</sup>](#)).
- Ga-68 DOTA PET is available in metropolitan centres; tracer logistics limit it elsewhere, so plan scans with the nuclear medicine team.
- Available in India (October 2026): octreotide LAR, lanreotide, everolimus, sunitinib, cabozantinib, streptozocin and belzutifan; capecitabine and temozolomide (CAPTEM) are oral and widely used. Discuss cost and scheme or insurance cover before planning a long sequence.
- Lu-177 edotreotide is investigational here as elsewhere.

**Quick reference** (also as a printable PDF on the Printable Teaching Resources page)

**Table A. Diagnosis and staging tests and what they change**

| Test                                                                         | When                                                                                                  | What it changes                                                                                                         | Pitfalls                                                                                                                                                    |
|------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Multiphasic CT (non-contrast, arterial, portal venous) or MRI with diffusion | Every patient at diagnosis; follow-up                                                                 | Finds the hypervascular primary and liver metastases; resectability; MRI is more sensitive for small liver deposits     | Small insulinomas and duodenal gastrinomas can be missed                                                                                                    |
| SSTR PET-CT (Ga-68 DOTATATE, DOTANOC or Cu-64 DOTATATE)                      | Most well-differentiated tumours at baseline; occult primary; before SSA or PRRT                      | Whole-body staging; changes management more often than CT, MRI or older scintigraphy; uptake = SSA and PRRT eligibility | Less sensitive for insulinoma and high grade; physiological uptake in the uncinate process; meningiomas, healing fractures and inflammation also take it up |
| FDG PET-CT                                                                   | NET G3, NEC, or a tumour behaving faster than its grade                                               | FDG-avid disease predicts aggressive behaviour; staging before surgery for NEC                                          | Low-grade NETs are often FDG-negative                                                                                                                       |
| EUS with fine-needle biopsy                                                  | Tissue diagnosis; small or occult functioning tumours; distance from the main duct before enucleation | Detects lesions of 2–3 mm; gives Ki-67 grade on a core                                                                  | Small samples can under-grade a heterogeneous tumour; less useful for duodenal gastrinoma                                                                   |
| Hormone tests (only with symptoms)                                           | Suspected syndrome                                                                                    | Insulin/C-peptide/proinsulin during hypoglycaemia; gastrin off PPI with gastric pH; glucagon; VIP; somatostatin         | PPIs, atrophic gastritis and H. pylori raise gastrin; random insulin levels mislead                                                                         |
| Chromogranin A                                                               | Not for diagnosis or routine post-surgery follow-up                                                   | At most a trend marker in metastatic disease with a high baseline, same assay each time                                 | PPIs, renal failure, atrophic gastritis, heart failure and SSAs alter it                                                                                    |
| Germline testing                                                             | Family history; all gastrinomas; multiple tumours; consider under 50                                  | MEN1, VHL, NF1, TSC: changes surgical thresholds, surveillance and family testing                                       | A negative family history does not exclude MEN1 (about 10% de novo)                                                                                         |
| Tumour NGS                                                                   | NEC and NET G3 needing later lines                                                                    | MSI-H/dMMR, TMB-high, BRAF V600E, NTRK and RET fusions open targeted or immune therapy                                  | Rare in well-differentiated NETs                                                                                                                            |

**Table B. Treatment by setting**

| Setting                                      | Usual plan                                                                              | Alternatives and notes                                                                                                                     |
|----------------------------------------------|-----------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------|
| Sporadic non-functioning ≤2 cm, no red flags | Active surveillance: MRI or EUS at 6–12 months, then yearly                             | Resect if growth, duct dilatation, jaundice, higher grade or patient preference after counselling ( <a href="#">ASPEN</a> <sup>[4]</sup> ) |
| Non-functioning >2 cm or with red flags      | Formal resection with lymph-node removal                                                | Enucleation only for small, low-grade tumours away from the main duct; no proven adjuvant therapy for G1–G2                                |
| Insulinoma                                   | Enucleation or limited resection; cure in more than 90%                                 | Diazoxide or SSA while waiting or if unfit; ablation in selected high-risk patients                                                        |
| Sporadic gastrinoma                          | High-dose PPI, then duodenal exploration + lymph-node dissection ± pancreatic resection | Small duodenal tumours: endoscopic resection in experienced hands                                                                          |
|                                              |                                                                                         |                                                                                                                                            |

| Setting                            | Usual plan                                                                                 | Alternatives and notes                                                                                         |
|------------------------------------|--------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------|
| MEN1                               | PPI for gastrinoma; surgery for insulinoma and non-functioning $\geq 2$ cm or growing      | Pancreas-sparing operations; parathyroid surgery first when hypercalcaemic                                     |
| VHL                                | Surveillance if head $\leq 2$ cm or body/tail $\leq 3$ cm; resect above these              | Belzutifan for fast growth (doubling time under 500 days), to delay surgery, or if unresectable                |
| Metastatic, liver-only, resectable | Resect primary and liver ( $\pm$ ablation)                                                 | Debulking $\geq 70$ –90% only in selected patients; transplant investigational                                 |
| Metastatic G1–G2, unresectable     | By SSTR status, burden and pace (Algorithm 3)                                              | Watch, SSA, PRRT, CAPTEM, everolimus, sunitinib, cabozantinib, liver-directed therapy                          |
| NET G3                             | CAPTEM or FOLFOX; PRRT + SSA if SSTR-positive ( <a href="#">NETTER-2</a> <sup>[13]</sup> ) | Ki-67 $>55\%$ or rapid progression: treat as NEC                                                               |
| NEC, localised                     | Surgery with perioperative platinum-etoposide, or chemoradiation                           | No prophylactic cranial irradiation                                                                            |
| NEC, metastatic                    | Platinum + etoposide (or irinotecan)                                                       | Second line FOLFIRI, FOLFOX, CAPTEM or nal-IRI + 5-FU; immunotherapy for MSI-H/TMB-high; BRAF, NTRK, RET drugs |

**Table C. Systemic options for well-differentiated pancreatic NETs: evidence and best fit**

| Option                                             | Key evidence                                                                                                                                                                                                                                       | Best fit                                                                  | Watch for                                                                                         |
|----------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------|
| Somatostatin analogue (octreotide LAR, lanreotide) | <a href="#">CLARINET</a> <sup>[17]</sup> : PFS not reached vs 18 months (HR 0.47); <a href="#">PROMID</a> <sup>[18]</sup> in midgut NETs                                                                                                           | SSTR-positive, low volume, slow; any functioning tumour for symptoms      | Gallstones, steatorrhea, B12 deficiency, mild hyperglycaemia; may worsen insulinoma hypoglycaemia |
| PRRT (Lu-177 dotatate) + SSA                       | <a href="#">OCLURANDOM</a> <sup>[19]</sup> (21 vs 11 months vs sunitinib); <a href="#">NETTER-2</a> <sup>[13]</sup> first line G2–G3 (23 vs 9 months); <a href="#">COMPETE</a> <sup>[22]</sup> (Lu-177 edotreotide vs everolimus, 24 vs 14 months) | SSTR-positive in every lesion, after SSA, or first line for Ki-67 10–55%  | Nausea, cytopenias, renal function; rare therapy-related MDS/AML; radiation precautions at home   |
| Capecitabine + temozolomide (CAPTEM)               | <a href="#">E221</a> <sup>[23]</sup> : PFS 23 vs 15 months vs temozolomide; response 40%                                                                                                                                                           | Bulky, symptomatic or rapidly progressing; SSTR-negative; NET G3          | Cytopenias (check counts), nausea, vomiting, diarrhoea, fatigue                                   |
| Everolimus                                         | <a href="#">RADIANT-3</a> <sup>[25]</sup> : PFS 11 vs 5 months                                                                                                                                                                                     | Progressive disease, any SSTR status; refractory insulinoma hypoglycaemia | Stomatitis, hyperglycaemia, infection, pneumonitis                                                |
| Sunitinib                                          | <a href="#">Phase III</a> <sup>[27]</sup> : PFS 12 vs 6 months                                                                                                                                                                                     | Progressive pancreatic NET (not intestinal)                               | Hypertension, hand-foot reaction, diarrhoea, hypothyroidism                                       |
| Cabozantinib                                       | <a href="#">CABINET</a> <sup>[28]</sup> : pancreatic cohort PFS 14 vs 4 months                                                                                                                                                                     | After everolimus, sunitinib or PRRT                                       | Hypertension, fatigue, clots, diarrhoea, palmar-plantar reaction                                  |
| Streptozocin-based chemotherapy                    | <a href="#">Moertel 1992</a> <sup>[24]</sup> , <a href="#">Kouvaraki 2004</a> <sup>[33]</sup>                                                                                                                                                      | Where available (mainly Europe); bulky disease                            | Kidney toxicity, nausea                                                                           |

**Table D. Managing common problems during treatment**

| Problem                                          | Likely cause                                                                                         | First steps                                                            | When to act fast                                                           |
|--------------------------------------------------|------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------|----------------------------------------------------------------------------|
| Confusion, sweating or a fit before breakfast    | Hypoglycaemia (insulinoma, or SSA unmasking it)                                                      | Glucose now; frequent meals; diazoxide; review SSA                     | Any loss of consciousness: emergency care                                  |
| Watery diarrhoea, cramps, weakness               | VIPoma crisis, SSA failure, enzyme deficiency or bile-acid loss after surgery                        | Fluids and potassium; check stool volume; SSA; enzymes if fatty stools | Dizziness, low urine output, potassium below normal                        |
| Ulcer pain, black stools, vomiting               | Acid hypersecretion (gastrinoma), PPI stopped or under-dosed                                         | Restart high-dose PPI; endoscopy                                       | Bleeding or perforation signs                                              |
| Fever, cough or breathlessness on everolimus     | Infection or pneumonitis                                                                             | Hold drug; chest imaging; treat infection                              | Low oxygen saturation                                                      |
| Falling counts after PRRT or CAPTEM              | Marrow toxicity                                                                                      | Counts before each cycle; adjust or delay                              | Fever with neutropenia; persistent cytopenia months after PRRT (think MDS) |
| High blood pressure on sunitinib or cabozantinib | VEGF-pathway inhibition                                                                              | Home BP log; antihypertensives                                         | Headache, chest pain, BP $\geq 180/110$                                    |
| Pain, fever or nausea after embolization         | Inflammatory reaction to the treated tumour; biliary injury is more frequent with drug-eluting beads | Analgesia, fluids; imaging if symptoms persist                         | Rigors, rising bilirubin                                                   |
| New hormone symptoms after a procedure           | Hormone release from tumour breakdown                                                                | SSA cover; correct glucose, fluids, potassium                          | Haemodynamic instability                                                   |

## 07 Management algorithms

These decision paths pull together sections 02–06. Colours: teal for favourable paths, purple for intermediate, rose for advanced or high-risk paths.

### ALGORITHM 1

### Suspected pancreatic NET: from first suspicion to a staged, graded diagnosis

**Hypervascular pancreatic mass, a hormone syndrome, or neuroendocrine liver metastases** → multiphasic CT or MRI → NET multidisciplinary team

#### HORMONE SYMPTOMS

**Prove the syndrome first:** 72-hour fast, gastrin off PPI with gastric pH, glucagon, VIP or somatostatin

**Control the hormone**  
(diazoxide, PPI, fluids, SSA)

Localise: CT/MRI → SSTR PET  
(GLP-1R PET for insulinoma) → EUS

*Every gastrinoma: test for MEN1*

#### INCIDENTAL OR MASS SYMPTOMS

**EUS-guided biopsy:**  
differentiation, Ki-67, mitoses

**NET G1–G2** → SSTR PET (may skip if <1–1.5 cm, G1)

**NET G3 / NEC** → FDG PET ± SSTR PET

AJCC version 9 stage

*No hormone panel without symptoms;  
no chromogranin A for diagnosis*

#### LIVER METASTASES FIRST

**Biopsy the safest metastasis**  
(grade on the hottest area)

SSTR PET, multiphasic imaging and EUS to find the primary

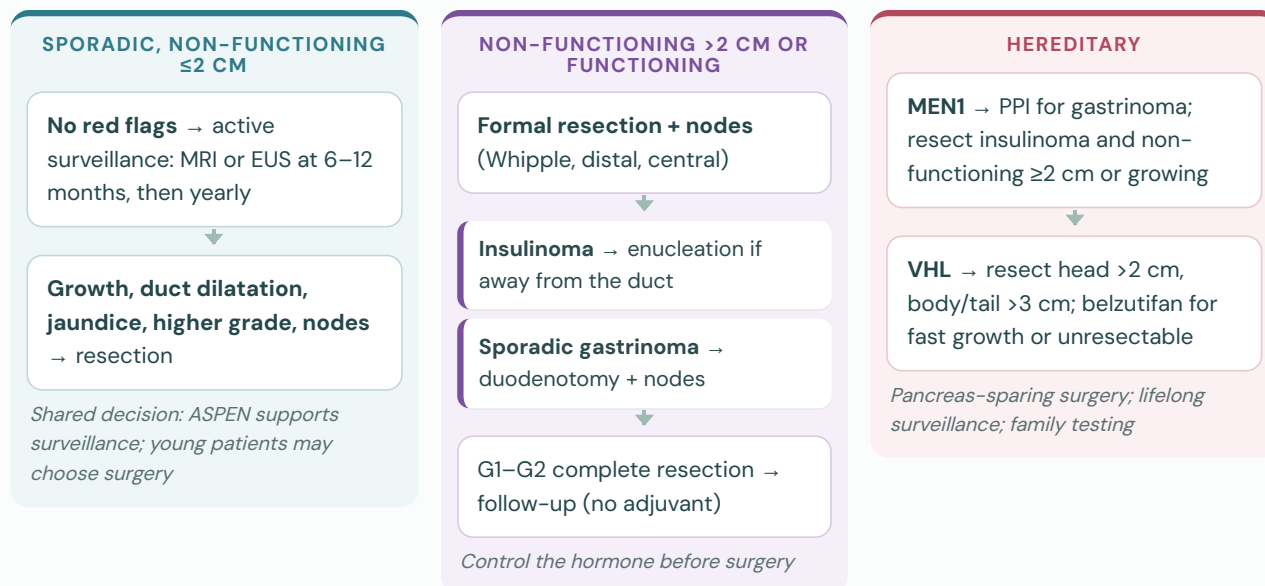
*Go to Algorithm 3 (G1–G2) or 4 (G3, NEC)*

All patients: family history and germline testing when indicated (all gastrinomas, multiple tumours, consider under 50) · photograph and record the hormone symptoms · discuss in a NET multidisciplinary team.

## ALGORITHM 2

## Localised disease: who needs an operation?

**No distant metastases** → function, size, grade, duct and nodes, hereditary status → fitness and patient preference

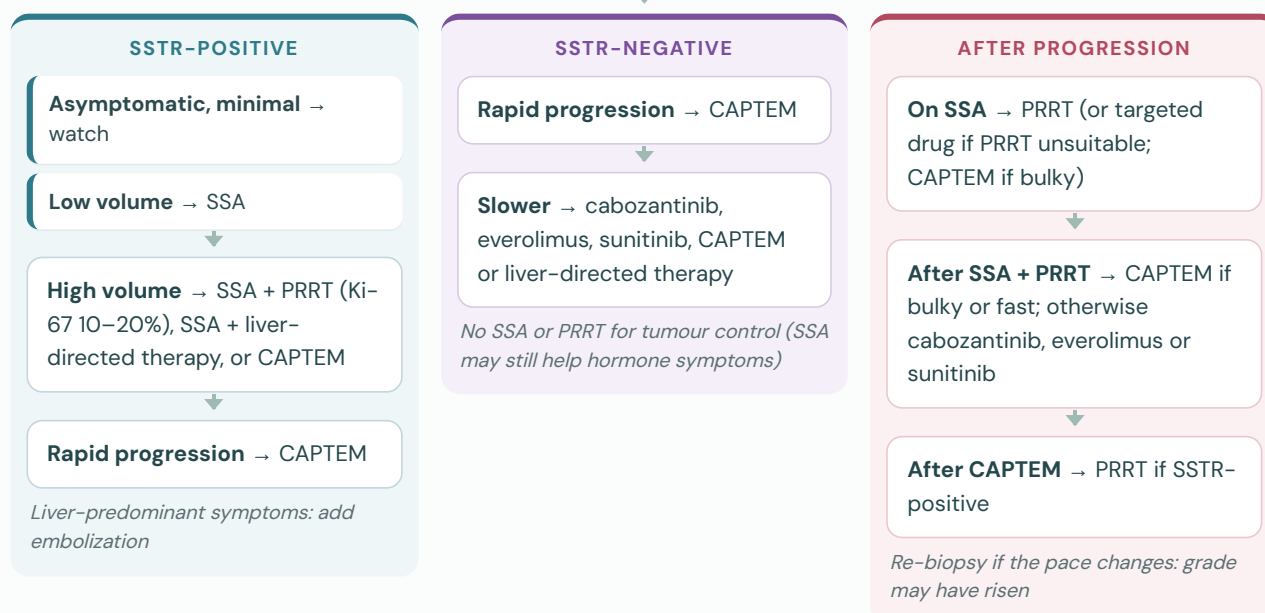


All patients: high-volume pancreatic surgeon · vaccines and fever plan if splenectomy · diabetes and digestion check after resection · follow-up for 10 years.

## ALGORITHM 3

## Metastatic well-differentiated G1–G2 disease: what first, what next

**Unresectable or metastatic NET G1–G2** → resectable? (surgery preferred) → SSTR PET, burden, pace, symptoms, liver predominance

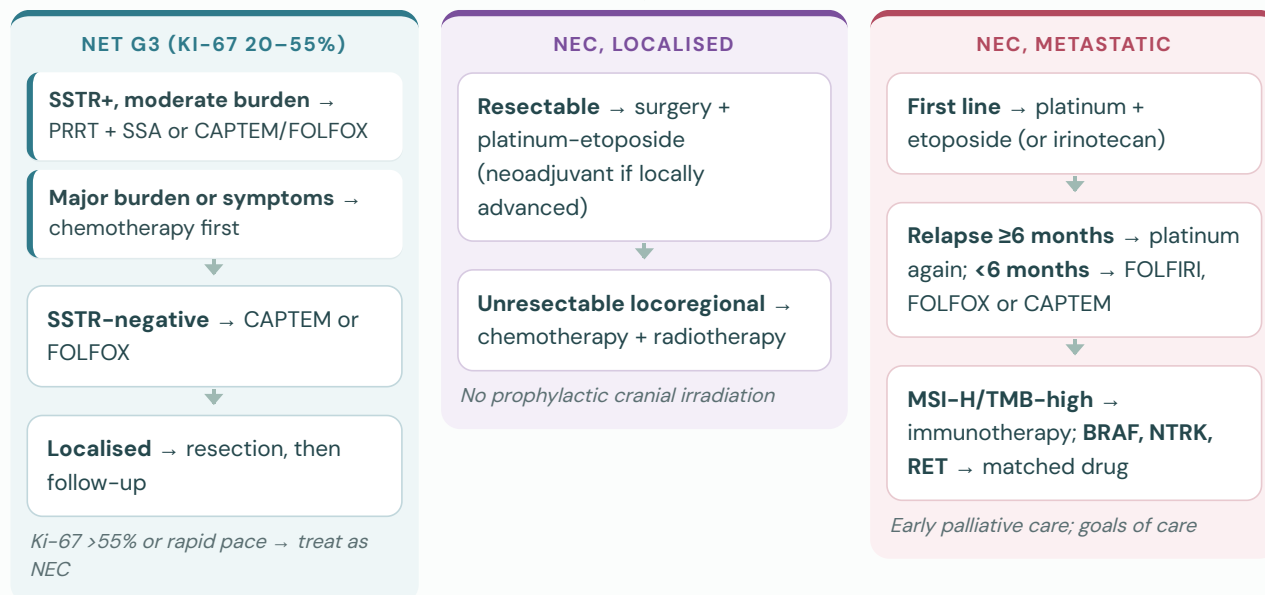


All patients: hormone control first · keep SSA after progression only in functioning tumours · CT/MRI every 3–6 months on treatment · trial at every line · bone and quality-of-life care.

## ALGORITHM 4

## High-grade disease: NET G3 versus NEC

**Ki-67 over 20%** → pathology review (morphology, p53, Rb, DAXX/ATRX) → SSTR and FDG PET → NGS



All patients: FDG PET before surgery for NEC · NGS on tissue (or ctDNA) · scans every 2–3 months on treatment · trial where available.

## o8 Survivorship, follow-up & reducing recurrence

### A simple follow-up rhythm after resection of a pancreatic NET

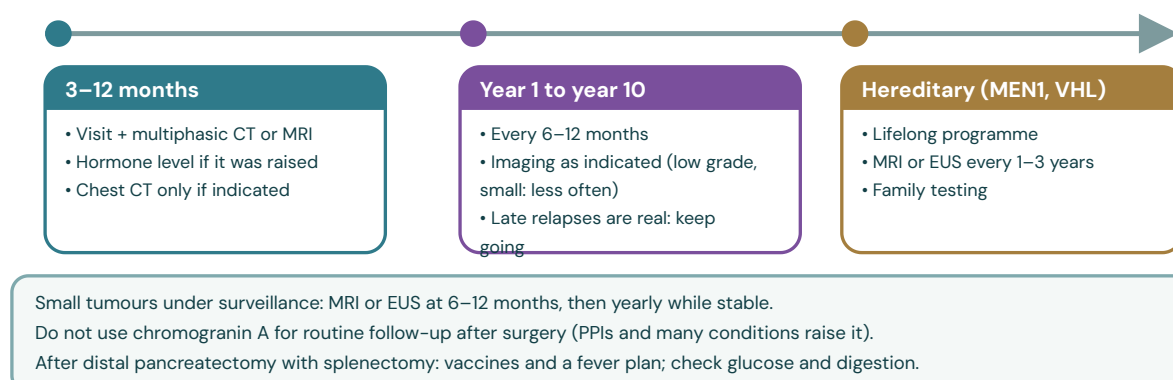


Figure 12. A simple follow-up rhythm, adapted from NCCN as quoted in the UpToDate functioning-tumour reviews: history, examination, marker if initially raised, and multiphasic imaging from 3–12 months, then every 6–12 months up to 10 years.

### Follow-up after resection (NCCN, as quoted in the UpToDate reviews; adapt to grade and resources)

| Situation                                               | What and how often                                                                                                                | Notes                                                                                      |
|---------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------|
| After resection, any functioning or non-functioning NET | History, examination, hormone level if it was raised, multiphasic CT or MRI at 3–12 months; then every 6–12 months up to 10 years | Low-grade, small, node-negative tumours can be imaged less often; NEC needs closer imaging |
| Small tumour under active surveillance                  | MRI or EUS at 6–12 months, then yearly while stable                                                                               | Resect if it grows, the duct dilates or the grade rises                                    |
| Metastatic disease on treatment or watch-and-wait       | Imaging every 3–6 months (2–3 months for NEC); 6–12-monthly once stable for years                                                 | Same imaging technique each time; SSTR PET when the plan may change                        |
| MEN1 or VHL                                             | Lifelong programme (MRI or EUS every 1–3 years plus syndrome-specific tests)                                                      | Family testing; pancreas-sparing decisions                                                 |

### When relapses happen: slow disease, many options

Relapse can come 5–10 years after surgery, most often in the liver. Grade at relapse may be higher than at diagnosis.

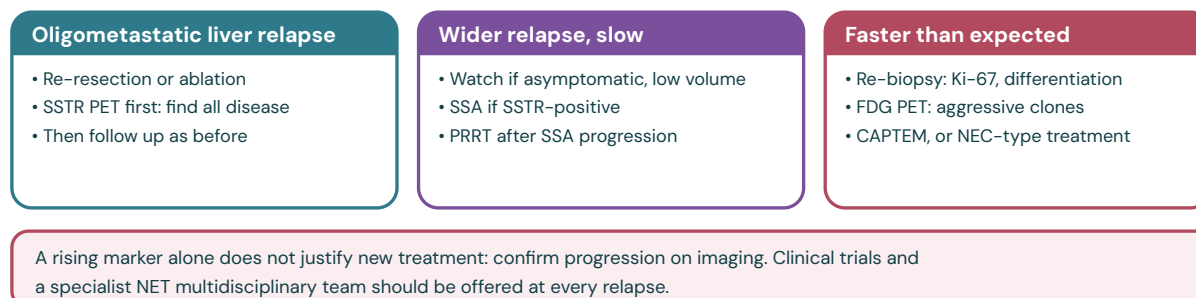


Figure 13. When relapses happen. Options follow the systemic-therapy and liver-directed algorithms; grade migration at relapse is described in the G3 and pathology reviews.

- **Digestion and diabetes:** exocrine insufficiency after Whipple or total pancreatectomy and with long-term SSAs (fatty stools: enzymes); diabetes after distal or total pancreatectomy. Check glucose, B12, vitamin D

and iron.

- **Somatostatin analogues long term:** gallstones, steatorrhoea, B12 deficiency and mild hyperglycaemia; ask about biliary pain.
- **After PRRT:** blood counts for years (therapy-related myeloid neoplasms are the most serious late effect) and kidney function.
- **Targeted drugs:** everolimus (glucose, lipids, mouth ulcers, pneumonitis); sunitinib and cabozantinib (blood pressure, thyroid, proteinuria, wound healing).
- **After splenectomy:** pneumococcal, meningococcal and Hib vaccines; standby antibiotics and urgent care for fever.
- **Family:** share germline results; offer testing to first-degree relatives in MEN1 and VHL families.
- **Living with a slow cancer:** many patients live for years with metastatic disease; plan work, finances and mental health support as for a chronic illness.

#### SHARE WITH PATIENTS: FOLLOW-UP

Plain-language myth pages written for patients and families. Send them from the clinic to reinforce what you discussed.

**If pancreatic cancer is treated successfully, follow-up isn't needed?**

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## 09 Landmark trials

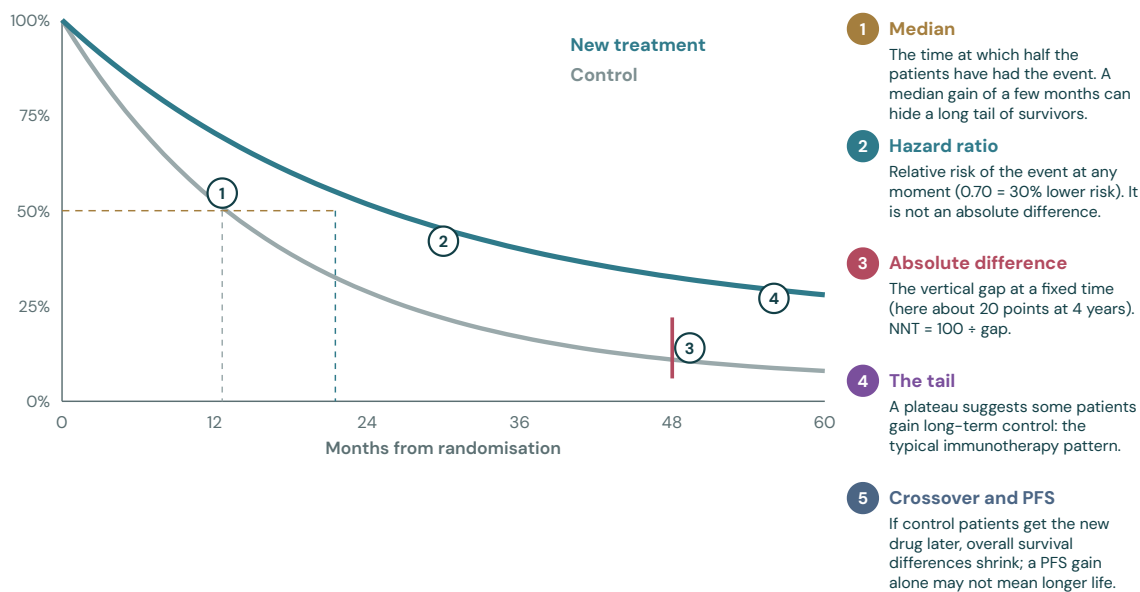


Figure 14. How to read a survival curve (illustrative). Use the absolute gap at a fixed time and overall survival, not the median or PFS alone, when weighing benefit against toxicity and cost.

- **CLARINET**<sup>[17]</sup>: lanreotide vs placebo in G1–G2 non-functioning GEP-NETs → progression-free survival prolonged (HR 0.47) → SSA as first-line tumour control.
- **RADIANT-3**<sup>[25]</sup>: everolimus vs placebo in progressive pancreatic NETs → 11 vs 5 months → mTOR inhibition approved.
- **Sunitinib phase III**<sup>[27]</sup>: sunitinib vs placebo in progressive pancreatic NETs → 12 vs 6 months (stopped early) → first antiangiogenic standard.
- **E2211**<sup>[23]</sup>: capecitabine + temozolomide vs temozolomide → 23 vs 15 months; response 40% → CAPTEM as the preferred chemotherapy when shrinkage matters.
- **NETTER-1**<sup>[21]</sup>: Lu-177 dotatate + SSA vs high-dose SSA in midgut NETs → large progression-free benefit; final overall survival difference not significant (**Strosberg 2021**<sup>[34]</sup>) → PRRT established.
- **OCLURANDOM**<sup>[19]</sup>: Lu-177 dotatate vs sunitinib in progressive pancreatic NETs (randomised phase 2) → 1-year progression-free 81% vs 42% → PRRT ahead of sunitinib.
- **NETTER-2**<sup>[13]</sup>: first-line Lu-177 dotatate + SSA vs high-dose SSA for Ki-67 10–55% → 23 vs 9 months → PRRT moved to first line for higher-grade tumours.
- **COMPETE**<sup>[22]</sup>: Lu-177 edotreotide vs everolimus in G1–G2 GEP-NETs → 24 vs 14 months, less toxicity → second PRRT agent (investigational for pancreatic NETs).
- **CABINET**<sup>[28]</sup>: cabozantinib vs placebo after prior therapy → pancreatic cohort 14 vs 4 months → a third targeted option.
- **TOPIC-NEC**<sup>[29]</sup>: etoposide-cisplatin vs irinotecan-cisplatin in digestive NEC → similar survival → either platinum doublet first line.
- **ASPEN (interim analysis)**<sup>[4]</sup>: prospective cohort of sporadic non-functioning tumours ≤2 cm → surveillance safe for most → fewer unnecessary pancreatectomies.

## 10 Practice pearls & pitfalls

- Ask two questions of every pathology report: well or poorly differentiated, and what is the Ki-67? Then decide.
- Grade on the hottest area: a small EUS core can under-grade a heterogeneous tumour.
- A NET G3 with Ki-67 above 55%, or an NEC with Ki-67 below 55%, deserves a second pathology opinion.
- Episodes of confusion or "fits" before breakfast are hypoglycaemia until proved otherwise; check glucose during the episode.
- Never stop a PPI casually to measure gastrin in suspected Zollinger–Ellison syndrome: arrange it with a gastroenterologist and H2-blocker cover.
- Screen every gastrinoma patient for MEN1, starting with calcium and PTH.
- Do not order chromogranin A to diagnose or to follow a resected tumour.
- Most sporadic, asymptomatic, non-functioning tumours of 2 cm or less can be watched; explain the plan in writing so the patient does not feel abandoned.
- Control the hormone before biopsy, surgery, embolization or PRRT: fluids and potassium in VIPoma, glucose in insulinoma, PPI in gastrinoma.
- SSAs can worsen hypoglycaemia in insulinoma: diazoxide first.
- PRRT needs uptake in every significant lesion; an FDG-avid, SSTR-negative lesion will escape it.
- Choose CAPTEM when you need shrinkage (symptoms, bulk, borderline resectability); choose SSA or watch when you need time.
- Keep the SSA after progression only if the tumour is functioning.
- A tumour that suddenly speeds up needs a new biopsy: grade can rise over time.
- In India, Lu-177 for PRRT is made in-country and larger centres offer it; plan the sequence with the nuclear medicine team early.

## 11 Case vignettes: lines of management

### CASE 1 Incidental · ≤2 cm · surveillance

#### A small spot on a kidney-stone CT

58 years, man

1.4 cm body lesion

No symptoms

A 58-year-old engineer has a CT for renal colic. It shows a 1.4 cm arterially enhancing lesion in the pancreatic body. He is well; no family history of endocrine disease.

*Before you open the answer: what is the likely diagnosis, what must be done before treatment, and what is the plan?*

#### 1 CHARACTERISE

Multiphasic MRI: 1.4 cm, well defined, no duct dilatation, no nodes, liver clear. EUS: solid lesion 5 mm from the main duct; fine-needle biopsy shows a well-differentiated NET, Ki-67 2% (G1).

#### 2 HORMONES?

No symptoms: no hormone panel and no chromogranin A. SSTR PET optional for a small G1 tumour at low risk; done here because of uncertainty about nodes: uptake only in the primary.

#### 3 DECIDE TOGETHER

Sporadic, asymptomatic, non-functioning, ≤2 cm, G1, no red flags: active surveillance, as supported by ASPEN, explained in writing with the reasons for surgery if things change.

#### 4 FOLLOW-UP

MRI at 6 months, then yearly. At 3 years the lesion is 1.5 cm and unchanged in character: continue.

#### TEACHING POINTS

- Small sporadic non-functioning tumours are usually indolent; a pancreatectomy carries real risk.
- Red flags (growth, duct dilatation, jaundice, higher grade, nodes) change the plan.
- Surveillance is a plan, not neglect: give dates and reasons.

**See:** Sections O3 and O5, Figure 7 (surgery), Algorithm 2.

### CASE 2 Functioning · insulinoma · cure

#### Morning "fits" in a schoolteacher

32 years, woman

Glucose 38 mg/dL

Weight gain

A 32-year-old teacher has had three episodes of confusion and jerking before breakfast, treated as epilepsy. She has gained 6 kg and carries biscuits. Family members found her glucose 38 mg/dL during an episode; she recovered with sugar.

*Before you open the answer: what is the likely diagnosis, what must be done before treatment, and what is the plan?*

#### 1 PROVE IT

Supervised 72-hour fast: symptomatic hypoglycaemia at 14 hours with inappropriately high insulin, C-peptide and proinsulin; sulfonylurea screen negative; glucose rose after glucagon. Whipple's triad confirmed.

#### 2 KEEP HER SAFE

Frequent meals; glucose at hand; diazoxide while waiting. No SSA (it can deepen hypoglycaemia).

#### 3 FIND IT

Multiphasic CT: 1.2 cm hypervascular lesion in the pancreatic head, away from the duct on EUS. Calcium, PTH and prolactin normal (MEN1 unlikely).

4

**OPERATE**

Enucleation at a high-volume centre: well-differentiated NET G1, margins clear. Glucose normal the next morning; antiepileptic stopped with the neurologist.

5

**FOLLOW-UP**

Clinical review and glucose; imaging only if symptoms return. Recurrence after remission is under 10%.

**TEACHING POINTS**

- Hypoglycaemia is often misdiagnosed as epilepsy or a psychiatric disorder.
- Biochemistry first, imaging second.
- Most insulinomas are small, solitary and curable by enucleation.

**See:** Sections 02, 03 and 05, Figure 2, Table A.

**CASE 3 Gastrinoma · MEN1****Ulcers that never heal and a kidney stone**

36 years, man

Post-bulbar ulcers

Calcium 11.6 mg/dL

A 36-year-old has had duodenal ulcers for 4 years despite PPIs and H. pylori eradication, chronic diarrhoea, and a kidney stone last year. His mother had "parathyroid surgery".

*Before you open the answer: what is the likely diagnosis, what must be done before treatment, and what is the plan?*

1

**SUSPECT**

Post-bulbar and multiple ulcers, diarrhoea and a stone: Zollinger–Ellison with MEN1 until proved otherwise.

2

**TEST SAFELY**

Endoscopy: thick folds, gastric pH 1.5. Gastrin off PPI for 10 days with H2-blocker cover, arranged by the gastroenterologist: 14 times the upper limit. Calcium high, PTH raised; prolactin normal.

3

**GENETICS AND IMAGING**

Germline MEN1 pathogenic variant. SSTR PET: two small duodenal lesions and a 1.1 cm pancreatic tail lesion; liver clear.

4

**TREAT**

High-dose PPI long term (symptoms controlled). Subtotal parathyroidectomy with thymectomy for hyperparathyroidism. Duodeno-pancreatic surgery discussed: not routine for MEN1 gastrinoma; he chooses surveillance.

5

**FAMILY AND FOLLOW-UP**

Cascade testing offered to siblings and children; yearly calcium, PTH, prolactin; pancreatic MRI every 2–3 years; resect the tail lesion if it reaches 2 cm or grows.

**TEACHING POINTS**

- Every gastrinoma patient is screened for MEN1.
- Stopping a PPI for testing must be supervised.
- In MEN1, gastrinoma is controlled with a PPI; surgery for non-functioning tumours starts at 2 cm.

**See:** Sections 02, 03 and 05, Figure 3, Algorithm 2.

**CASE 4 Metastatic G2 · SSA → PRRT****Liver spots on a check-up scan**

55 years, woman

Ki-67 8% (G2)

SSTR-positive

A 55-year-old woman has multiple liver lesions on an ultrasound for dyspepsia. She feels well. Liver biopsy: well-differentiated NET, Ki-67 8%. CT: 3 cm pancreatic tail primary, about 15 liver metastases in both lobes.

*Before you open the answer: what is the likely diagnosis, what must be done before treatment, and what is the plan?*

#### 1 STAGE

Ga-68 DOTATATE PET: intense uptake in the primary and all liver lesions; no other sites. Not resectable (bilobar, many lesions).

#### 2 START

Asymptomatic, moderate burden, SSTR-positive: lanreotide (CLARINET); CT or MRI every 3–6 months.

#### 3 PROGRESSION AT 26 MONTHS

Liver lesions grow; still SSTR-positive in every lesion; Ki-67 on re-biopsy 12%. Lu-177 dotatate PRRT (OCLURANDOM, NETTER-1 principle) at the regional nuclear medicine centre; SSA stopped (non-functioning).

#### 4 RESPONSE

Partial response; counts and kidney function monitored; well 3 years later.

#### TEACHING POINTS

- Unresectable low-burden SSTR-positive disease: SSA first.
- PRRT is the usual second step after SSA progression.
- Non-functioning tumours do not need the SSA continued once PRRT starts.

**See:** Section 06, Figure 10, Algorithm 3.

#### CASE 5 NET G3 · first-line PRRT or CAPTEM

### Bulky disease with a Ki-67 of 30%

49 years, man

Ki-67 30%

SSTR + and FDG +

A 49-year-old man has upper abdominal pain and 5 kg weight loss. CT: 6 cm pancreatic head mass with liver metastases (about 30% of the liver). Biopsy: well-differentiated NET, Ki-67 30%, p53 and Rb normal.

*Before you open the answer: what is the likely diagnosis, what must be done before treatment, and what is the plan?*

#### 1 CLASSIFY

Well differentiated with Ki-67 20–55% and normal p53/Rb: NET G3, not NEC. SSTR PET positive in all lesions; FDG PET also positive.

#### 2 CHOOSE FIRST LINE

Symptomatic, moderate-to-major burden: chemotherapy (CAPTEM) chosen for rapid response; PRRT + SSA (NETTER-2) discussed as an equal alternative for moderate burden.

#### 3 NEXT

Partial response after 6 months of CAPTEM; at progression a year later, PRRT + SSA.

#### 4 IF THINGS CHANGE

If a new biopsy showed Ki-67 above 55% or NEC morphology, switch to platinum-etoposide.

**TEACHING POINTS**

- NET G3 and NEC are different diseases; differentiation and immunostains decide.
- NETTER-2 makes PRRT a first-line option for Ki-67 10–55%.
- Bulky or symptomatic disease: chemotherapy first.

**See:** Sections O4 and O6, Figure 11, Algorithm 4.

**CASE 6** NEC · platinum-etoposide · NGS**Rapid jaundice and a Ki-67 of 80%**

63 years, man

Large-cell NEC

Liver and bone

A 63-year-old man has jaundice, 8 kg weight loss in 6 weeks, and bone pain. CT: 4 cm pancreatic head mass, many liver lesions, lytic spine lesions. Biopsy: poorly differentiated large-cell neuroendocrine carcinoma, Ki-67 80%, Rb lost.

*Before you open the answer: what is the likely diagnosis, what must be done before treatment, and what is the plan?*

1

**RELIEVE AND STAGE**

Biliary metal stent; FDG PET: widespread avid disease. Staged like pancreatic adenocarcinoma: stage IV.

2

**TREAT**

Carboplatin + etoposide (NORDIC NEC; TOPIC-NEC shows irinotecan-cisplatin is equivalent); palliative radiotherapy to the painful spine; early palliative care.

3

**TEST THE TUMOUR**

NGS: MSI-stable, no BRAF, NTRK or RET alteration.

4

**RELAPSE AT 5 MONTHS**

Within 6 months of stopping: second-line FOLFIRI rather than repeat platinum; goals-of-care discussion with the family.

**TEACHING POINTS**

- NEC behaves like small cell cancer; median survival about a year.
- Send NGS at diagnosis: MSI-H, BRAF, NTRK and RET change later lines.
- Relapse timing guides re-use of platinum.

**See:** Sections O4 and O6, Algorithm 4.

**CASE 7** VHL · surveillance and belzutifan**A 2.5 cm tail lesion in a young woman with VHL**

27 years, woman

VHL (exon 3)

2.5 cm tail NET

A 27-year-old with known VHL (previous cerebellar haemangioblastoma) has a 2.5 cm solid, arterially enhancing lesion in the pancreatic tail on her surveillance MRI, plus several cysts. A year ago it was 1.6 cm.

*Before you open the answer: what is the likely diagnosis, what must be done before treatment, and what is the plan?*

1

**INTERPRET**

Hereditary NET in the body/tail below the 3 cm VHL threshold, but growing fast (doubling time well under 500 days) and with an exon 3 variant (higher metastatic risk).

2

**OPTIONS**

Resection now (pancreas-sparing) or belzutifan to shrink it and delay surgery; surveillance alone is less suitable given the growth.

3

**PLAN**

Belzutifan started in a VHL clinic (also helps kidney lesions); MRI in 3 months; resect if it continues to grow or reaches 3 cm.

4

**FAMILY**

Siblings offered testing; lifelong VHL surveillance.

**TEACHING POINTS**

- VHL thresholds: head over 2 cm, body or tail over 3 cm.
- Growth rate and genotype matter as much as size.
- Belzutifan can delay or avoid surgery in selected VHL patients.

**See:** Sections O2 and O5, Figure 3, Algorithm 2.

## 12 References & guidelines

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- Cross-checked in October 2026 against 22 UpToDate topic reviews: pancreatic NEN presentation, diagnosis and staging; pathology and classification of GEP–NENs; systemic therapy for G1–G2 pancreatic and gastrointestinal NETs; well-differentiated G3 GEP–NETs; poorly differentiated GEP–NEC; metastatic GEP–NET imaging, biomarkers and prognosis; local options for liver metastases; tumour biomarkers; insulinoma; gastrinoma (diagnosis and management); glucagonoma; VIPoma; somatostatinoma; MEN1 (manifestations, management, gene test interpretation); von Hippel–Lindau disease (diagnosis, surveillance and management); resection of lesions of the head of the pancreas; total pancreatectomy.
- The UpToDate topic on surgery for sporadic pancreatic NENs was not available: surgical selection for small non-functioning tumours rests on the ASPEN study (interim report and ESMO 2025 final results, web-verified 16 October 2026) and guideline positions quoted there. India PRRT facts web-verified on 16 October 2026.
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Educational summary for health professionals, written in our own words from current guidelines and primary trials. No drug doses are given. Exocrine pancreatic cancer (ductal adenocarcinoma) has its own module in the Upper GI & Pancreas series; oesophageal and gastric cancers will follow. Verify current guidelines, Indian regulatory approvals and individual patient factors before treatment decisions.