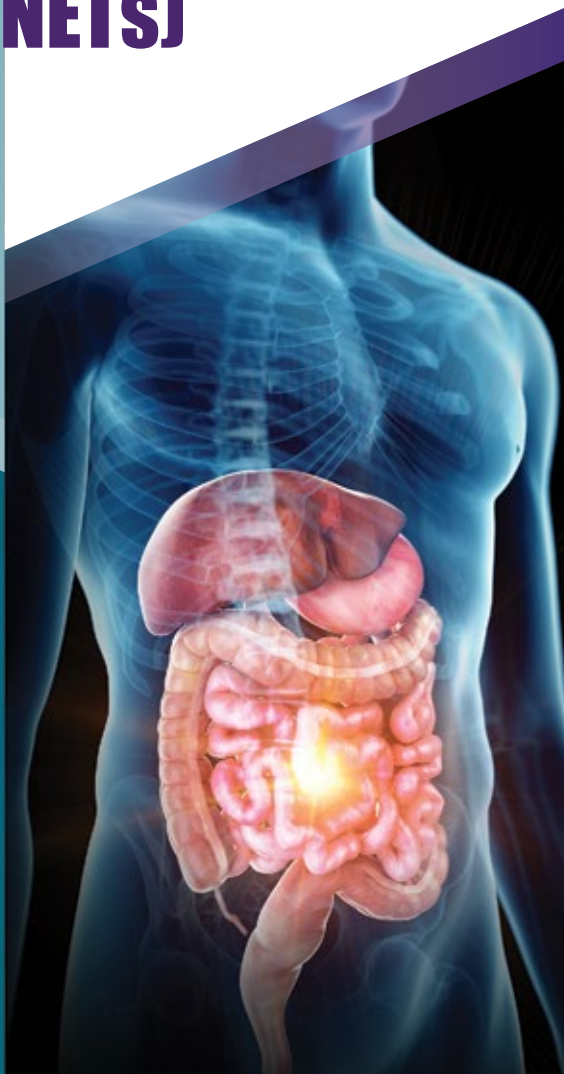
APNETS
Asia Pacific NeuroEndocrine Tumour Society
Malaysian chapter

# RECOMMENDATIONS FOR THE MANAGEMENT OF GASTROENTEROPANCREATIC NEUROENDOCRINE TUMOURS (GEP-NETs)



# RECOMMENDATIONS FOR THE MANAGEMENT OF GASTROENTEROPANCREATIC NEUROENDOCRINE TUMOURS (GEP-NETS)


## PUBLISHED BY

Asia-Pacific Neuroendocrine Tumours Society (Malaysian Chapter)


## TERMS OF REFERENCE

### Target audience

These recommendations are meant for the educational needs of the healthcare professionals involved in the management of patients with Gastroenteropancreatic Neuroendocrine Tumours (GEP-NETs).

### Statement of intent

These recommendations are not rigid rules or standards but are broad principles on the appropriate approaches to managing patients with GEP-NETs based on the available resources and facilities in Malaysia. The ultimate decision on the management of GEP-NETs should be made by a multidisciplinary neuroendocrine tumour board and individualised to the needs of each patient.

### Format

These recommendations are based on the available scientific information on management of GEP-NETs in the medical literature that was available to the writing committee.

### Period of validity

These recommendations were developed in 2019 and will be reviewed within 5 years (2024).

### Disclosure

The members of the writing committee had no conflicts of interest to declare.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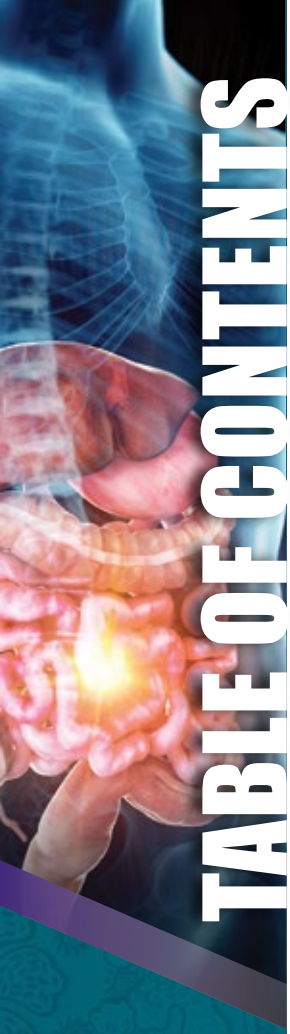
*Disclaimer: These recommendations do not guarantee the best treatment outcomes in every patient. The management of each individual patient with GEP-NETs is the responsibility of the healthcare provider.*



**This document on Recommendation for the Management of Gastroenteropancreatic Neuroendocrine Tumours (GEP-NETs) is available for download at, http://apnets.org/**



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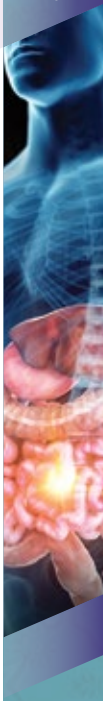
# CHAPTER 1:
# INTRODUCTION



Gastroenteropancreatic Neuroendocrine Tumours (GEP-NETs) are a heterogeneous group of tumours originating from neuroendocrine cells in the diffuse endocrine systems. The incidence and prevalence of GEP-NETs have increased over the last three decades.[1] However, epidemiological data for GEP-NETs for Malaysia and many Asia Pacific countries are lacking.

The heterogeneity of GEP-NETs, their diverse clinical presentations and limitations in available healthcare resources make their management challenging. Hence these recommendations were developed to serve as a guide for clinicians managing GEP-NETs in Malaysia. They are based on current scientific evidence available at the time of writing. These are not rigid rules or standards but broad principles on the best approaches to manage GEP-NETs tailored to the needs of the country based on available resources and facilities. The ultimate decision on the management of GEP-NETs should be made by a multidisciplinary neuroendocrine tumour (NET) board and individualised to the needs of each patient.

# CHAPTER 2:
# EPIDEMIOLOGY

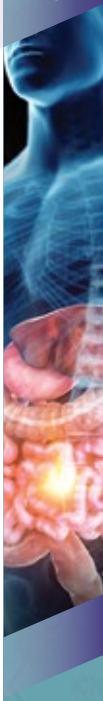
Neuroendocrine tumours (NETs) are rare, but their reported incidence is increasing. There are recent reports from institutional studies and NETs registries from some Asian countries such as Japan[2], Korea[3] and Taiwan[4], but data from South East Asia is lacking.

A multicentre study[5] involving six Malaysian tertiary centres with experience in managing GEP-NETs was conducted from January 2000 to April 2010 to study the epidemiology of GEP-NETs in the country (Table 1).

| | Patient number | • Epidemiology |
|---|---|---|
| Malaysia | 64 (multicentre) | • GEP-NETs<br>• Types<br>› carcinoids – 40.6%<br>› insulinoma – 39.1%<br>• Site<br>› pancreas – 67.2%<br>› stomach – 9.4%<br>› rectum – 9.4%<br>• Distant metastases at diagnosis – 48.4%<br>• Surgical treatment – 91%<br>› liver resection, arterial chemoembolisation and radiofrequency ablation were done following surgery in cases with liver metastases (< 8.0% of metastatic cases)<br>• Systemic therapy – 34.0% |

*Table 1: Epidemiology of GEP-NETs in Malaysia. Adapted from Gunavathy et al. 2014.*
*GEP-NETs: gastroenteropancreatic neuroendocrine tumours.*

# CHAPTER 3:
# DIAGNOSIS



Diagnosis of GEP-NETs requires a high index of suspicion in patients who present with persistent abdominal or gastrointestinal (GI) symptoms. In patients suspected to have GEP-NETs the following **blood and urine tests** may be done:

- serum Chromogranin A (CgA)
- urinary 5- hydroxyl-indole-acetic acid (5-HIAA)
- serum serotonin (5- hydroxytryptamine; 5-HT)
- pancreatic hormones such as insulin, gastrin, glucagon, vasoactive intestinal peptide (VIP) and somatostatin

**Endoscopy and/or cross-sectional imaging** may be necessary to localise the site of the primary tumour and determine the extent of local and distant spread, whilst **histopathological examination** (HPE) is essential to confirm the diagnosis of GEP-NETs.

## 3.1 CLINICAL PRESENTATION

The diagnosis of GEP-NETs may be delayed for several years as patients often present with non-specific symptoms.

Most patients with non-functioning GEP-NETs are asymptomatic and these neoplasms are often detected incidentally during imaging, endoscopy or surgery.

- Non-functioning tumours present late and often with metastases at diagnosis.
- These tumours may present with mass effects due to the primary tumour or metastases.

Functioning tumours typically present with features of carcinoid syndrome or pancreatic NETs (pNETs) syndromes related to hormone excess (Table 2).[6]

| Tumour | % | Secreted hormone | Malignant (%) | Clinical features | Biochemical (blood) evaluation |
|---|---|---|---|---|---|
| Insulinoma | 40-60 | Insulin | < 10 | Hypoglycaemia | Insulin, pro-insulin, C-peptide, 72-hours fasting insulin/ glucose ratio |
| Gastrinoma | 20-50 | Gastrin | 60-90 | Peptic ulcer disease, gastro-oesophageal reflux disorder, diarrhoea | Fasting gastrin (off proton pump inhibitors), secretin stimulation test |
| Glucagonoma | Rare | Glucagon | 50-80 | Necrolytic migratory erythema, diabetes, venous thrombosis, depression | Glucagon |
| Somatostatinoma | Rare | Somatostatin | > 70 | Diabetes, hypochlorhydria, cholelithiasis, diarrhoea | Somatostatin (not widely available) |
| VIPoma | Rare | Vasoactive intestinal peptide | 40-70 | Watery diarrhoea, hypokalaemia, achlorhydria | VIP |

*Table 2: Clinical features of functional pNETs. Cloyd. 2015 under Creative Commons Attribution-Non-commercial License.*

## 3.2 Endoscopy

**Endoscopy** is useful in the diagnosis, staging, treatment and follow-up of NETs.[7] Depending on the location, **upper GI endoscopy (OGDS), colonoscopy, capsule endoscopy or enteroscopy (single/double balloon)** may be required.[8]

Gastric and duodenal NETs may be single or multiple. Rectal NETs often present as a single raised hard nodule while small bowel NETs may present as mass lesions or strictures.[7]

**Endoscopic ultrasound (EUS)** is recommended for further evaluation of lesions in the GI tract and pancreas.

- It is able to provide an accurate assessment of the tumour, pancreas and its ductal system.
- It is able to assist in staging and obtaining tissue (EUS guided fine needle aspiration [FNA]) for histopathological confirmation (HPE/Ki-67 index) and grading.

pNETs characteristically appear as hypervascular lesions on contrast enhanced EUS. Doppler often highlights a rib of hypervascularisation in the peripheral zone. In comparison, adenocarcinomas are generally hypovascular.[7]

Endoscopy also serves as a primary screening modality for certain groups of patients at high risk of NETs such as those with Multiple Endocrine Neoplasia type 1 (MEN-1) syndrome[7,8] and von Hippel–Lindau (VHL) disease.

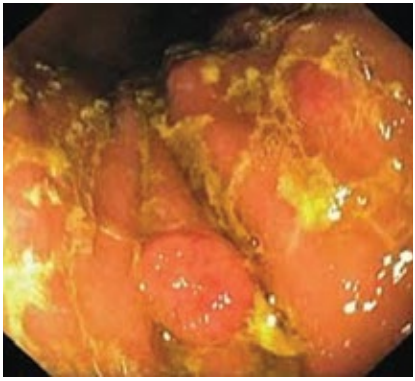


*Figure 1: Gastric NETs on endoscopy*

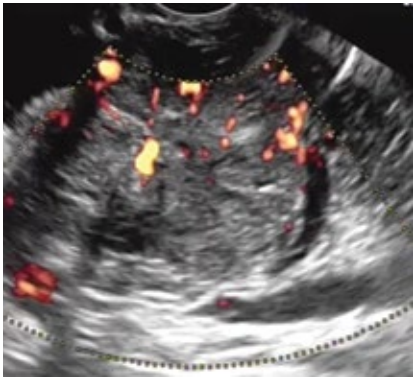


*Figure 2: A hypervascular lesion on EUS.*

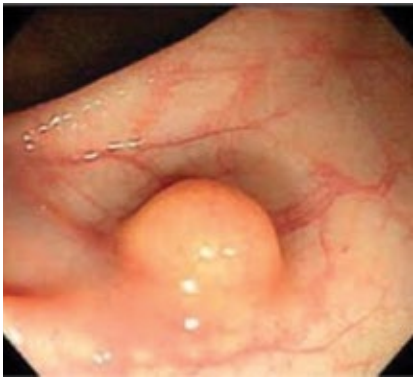


*Figure 3: Rectal NETs on endoscopy*

## 3.3 Imaging

The minimum requirement for morphological imaging of GEP-NETs is a contrast enhanced multiphase **computed tomography** (CT) scan or a contrast enhanced **magnetic resonance imaging** (MRI).

Functional imaging such as gallium 68–tetraazacyclododecane tetraacetic acid–octreotate ($^{68}$Ga-DOTA-peptide) positron emission tomography (PET)/CT scan or 18F-fluorodeoxyglucose ($^{18}$F-FDG) PET/CT scan or both should be considered in the following scenarios:

- pre-operative staging when there is suspicion of occult metastasis which is not demonstrated on CT scan or MRI
- post-operative restaging when accurate metastatic mapping is important prior to commencing systemic treatment
- evaluation of somatostatin receptor expression prior to **peptide receptor radionuclide therapy** (PRRT)
- evaluation of unknown primary

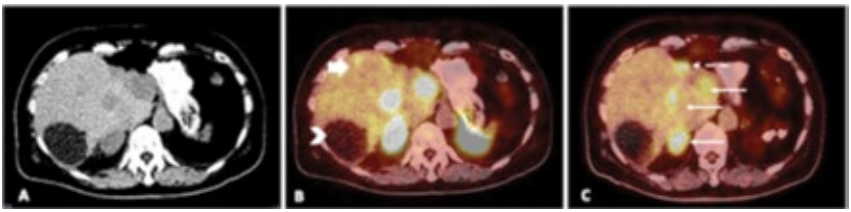
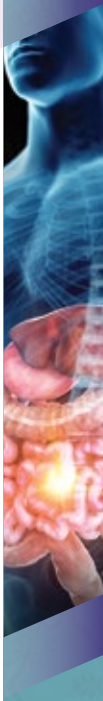



*Figure 4:* ***Dual tracer ($^{68}$Gallium-DOTATATE [GaTate] & $^{18}$F-FDG) PET-CT scan protocol.*** *62-year-old lady was referred for peptide receptor radionuclide therapy. She had Grade 2 pancreatic neuroendocrine tumour. Distal pancreatectomy and radiofrequency ablation to liver were performed. She developed progression during octreotide therapy. Fused GaTate images (B) and FDG images (C) showed previous RFA (arrow head), discordant GaTate lesion (broad arrow), concordant GaTate and FDG lesions (thin arrow) and discordant FDG lesion (dotted arrow). These features demonstrate presence of both intra-tumoural and inter-tumoural heterogeneity.*



## 3.4 Histopathology

The pathological diagnosis of GEP-NETs is based on the histomorphology of the tumour cells and their expression of neuroendocrine markers.

- The tumour is typically composed of uniform, polygonal cells arranged in nests or ribbons with close relationship to fine blood vessels (endocrine appearance).
- Immunohistochemical expression of CgA and/or synaptophysin is the most widely practised and cost-effective way to demonstrate their neuroendocrine nature.
- In rare situations where expressions of these markers are negative or equivocal, expression of additional neural markers may be sought, such as neural cell adhesion molecule (CD56) and Neuron Specific Enolase (NSE). While some of these tumours may also express specific peptides such as insulin, gastrin and somatostatin, it is not necessary to demonstrate their expressions to make a diagnosis of NET.

Historically, due to the histomorphological and peptide secretion variations of these tumours, confusing terminology such as carcinoid tumour, APUDoma (arising from cells with amine precursor uptake and decarboxylation properties), insulinoma and small cell carcinoma and uncertain criteria for malignancy have confounded the classification of GEP-NETs.

- The World Health Organization (WHO) 2010 classification[9] reflects a convergence of agreement to use the term "neuroendocrine tumour" for GEP-NETs. This classification emphasises use of proliferative activity (mitotic count and Ki-67 activity by immunohistochemistry [IHC]) to grade the tumours (Table 3).
  - Grade (G)1 and G2 NETs are also well-differentiated although differing in proliferative activity.
  - G3 tumours designated as neuroendocrine carcinoma (NEC), tend to be poorly differentiated and may be of small cell or large cell morphology.
  - However, it is understood that all grades of the tumour are capable of spreading and metastasising.

## CHAPTER 3: DIAGNOSIS

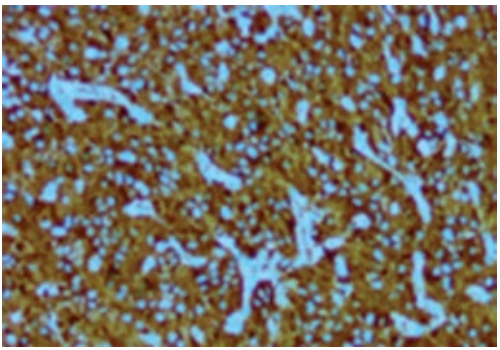


*Figure 5: A neuroendocrine tumour with strong cytoplasmic chromogranin-A expression (immunohistochemistry)*

Evidence soon emerged that pNETS differed from gastrointestinal neuroendocrine tumours (GI-NETs) in that even well-differentiated tumours may express G3 activity. There are also considerable molecular differences between GI-NETs and pNETs. Hence, a separate classification was adopted for pNETS in 2017.

### WHO Classification of GI-NETs (2010)

| Grade | Tumour differentiation | Mitotic index | Ki-67 index |
|---|---|---|---|
| NET G1 | Well-differentiated, low-grade | < 2/10 HPF | ⩽ 2% |
| NET G2 | Well-differentiated, intermediate-grade | 2-20/10 HPF | 3-20% |
| NEC G3 (small and large cell type) | Poorly-differentiated, high-grade | > 20/10 HPF | > 20% |

*Table 3: The 2010 WHO classification of GI-NETs based on three parameters.*
*NET: neuroendocrine tumour; G: grade; HPF: high-power field; NEC: neuroendocrine carcinoma.*
*Adapted from College of Pathologists, Academy of Medicine Malaysia, 2018.*

### WHO Classification of pNETs (2017)

| Grade | Tumour differentiation | Mitotic index | Ki-67 index |
|---|---|---|---|
| NET G1 | Well-differentiated, low-grade | < 2/10 HPF | < 3% |
| NET G2 | Well-differentiated, intermediate-grade | 2-20/10 HPF | 3-20% |
| NET G3 | Well-differentiated, high-grade | > 20/10 HPF | > 20% |
| NEC G3 (small and large cell type) | Poorly-differentiated, high-grade | > 20/10 HPF | > 20% |

*Table 4: The 2017 WHO classification of pNETs based on three parameters.*
*NET: neuroendocrine tumour; G: grade; HPF: high-power field; NEC: neuroendocrine carcinoma.*
*Adapted from College of Pathologists, Academy of Medicine Malaysia, 2018.*

The minimum standard for reporting of GEP-NETs should:

- be site specific (GI or pancreatic)
- use the latest WHO classifications which encompass tumour differentiation, mitotic index and Ki-67 activity
- include IHC for CgA and/or synaptophysin for confirmation of neuroendocrine nature

## 3.5 Blood biomarkers

### Recommendations

- CgA may aid the diagnosis of NETs. It should be done if symptoms strongly suggest a NET or if imaging modalities suggest the likelihood of a NET in an otherwise asymptomatic patient.
- Baseline CgA levels should be performed in all patients with confirmed NET.
- CgA may be used to assess tumour progression.
- CgA may be used to monitor response to therapy.

### Performing CgA

- Should be performed in an accredited laboratory with a standardised reference range.
- Borderline or doubtful results should be repeated with additional biomarkers such as NSE or 5-HIAA.
- Results must correlate with clinical symptoms and histological confirmation.

### False positives are seen in those with:

- long-term proton-pump inhibitor use
- chronic atrophic gastritis (especially with enterochromaffin-like cell hyperplasia)
- renal and liver insufficiency
- inflammatory bowel disease
- post-menopausal and trauma induced physical stress

**False negatives** are seen in poorly differentiated tumours.

### Other markers that can be performed in tertiary care centres:

- 5-Hydroxytrytophan (5-HTP)
- Adrenocorticotropic hormone (ACTH)
- Growth hormone (GH)
- Pentagastrin Provocative Test

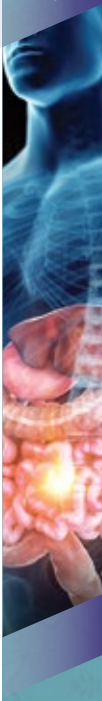
## 3.5.1 Site-specific hormonal assays

Site-specific hormonal assays may reflect origin of the primary tumour especially in functioning pNETs which can produce different hormones depending on the cell type involved (Table 5).[10]

| Syndrome | Test | Result |
|---|---|---|
| **Carcinoid** | | |
| Foregut | 24-h urinary 5-HIAA | Sometimes raised |
| Midgut | 24-h urinary 5-HIAA | Usually raised (70% of patients) |
| | Tachykinins (neurokinin A, B) | Raised |
| Hindgut | 24-h urinary 5-HIAA | Not raised (general markers used instead) |
| **Other NETs** | | |
| Gastrinoma | Fasting gastrin, gastric secretion studies | Raised basal serum gastrin, high gastric acid secretion |
| Insulinoma | Fasting insulin, glucose, C peptide (negative sulphonylurea screen) | Raised fasting insulin/glucose ratio, proinsulin, or C peptide |
| Glucagonoma | Fasting gut hormones, skin biopsy | Raised serum pancreatic glucagons and enteroglucagon |
| VIPoma | Fasting gut hormones | Raised fasting vaso-intestinal peptide |
| PPoma | Fasting gut hormones | Raised fasting pancreatic polypeptide |
| Somatostatinoma | Fasting gut hormones | Raised fasting somatostatin |
| **All NETs** | Serum chromogranin | Raised chromogranin A in most cases |
| **Ectopic hormones Syndrome** | GHRH, ACTH, HCG-α and –β Test | Raised but incidence very low |

*Table 5: Specific biochemical tests used in the diagnosis of GEP-NETs. 5-HIAA, 5-hydroxy indole acetic acid; GHRH, gonadotrophin releasing hormone; ACTH, adrenocorticotrophic hormone; β-HCG, β-human chorionic gonadotrophin. Adapted from Ramage JK, et al. 2005.*

However, it is usual to suspect the NET site and hormone secreted based on the clinical syndrome during presentation (Table 6).[11-14]



| Tumour type | Site | Symptoms/syndromes | Hormones |
|---|---|---|---|
| Carcinoid | Gastric, mid- and fore-gut, adrenal medulla | Flushing, diarrhoea | Serotonin<br>Substance P<br>Na+-K+-ATPase (NKA)<br>Thyrocalcitonin (TCT)<br>Pancreatic polypeptide (PP)<br>Calcitonin gene-related peptide (CGRP)<br>Vasoactive intestinal peptide (VIP) |
| | Gut, pancreas, lung | Wheezing | Serotonin<br>Substance P<br>Chromogranin A |
| | Midgut | Dermatitis (pellagra) | Serotonin |
| Gastrinoma | Pancreas, duodenum | Zollinger-Ellison (ZE), dyspepsia, peptic ulcer disease, low pH on endoscopy | Gastrin |
| Glucagonoma | Pancreas | Dermatitis, dementia, diabetes | Glucagon |
| Insulinoma | Pancreas | Whipple's triad | Insulin |
| Medullary carcinoma | Thyroid, pancreas | Metastatic carcinoid tumour (MCT), diarrhoea | Calcitonin |
| NETs | Pancreas | Acromegaly; Cushing's; anorexia, nausea and vomiting (hypercalcaemia); pigmentation | Growth hormone-releasing hormone (GH-RH); Adrenocorticotropic hormone (ACTH) and/or Corticotropin releasing factor (CRF); Parathyroid hormone-related protein (PTHRP); VIP |
| PPoma | Pancreas | Diarrhoea, silent liver metastases | PP |
| Sarcomas | Retroperitoneum | Hypoglycaemia | Insulin-like growth factor (IGF)/binding protein |
| Somastostatinoma | Pancreas, duodenum | Diarrhoea and/or steatorrhoea, diabetes, deep vein thrombosis, cholelithiasis, neurofibromatosis | Somatostatin |
| VIPoma | Pancreas | WDHHA (watery diarrhoea, hypokalaemia and achlorhydria), constipation, abdominal pain | VIP |

*Table 6: The type of tumours based on the various sites and their associated presenting symptoms/ syndromes based on the hormones they secrete.*
*Adapted from Oberg K, et al. 2012; Oladejo AO, 2009; Oronsky B, et al. 2017; Diez M, et al. 2013.*

# CHAPTER 4:
# STAGING

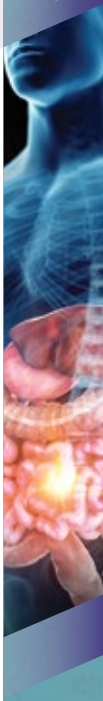
GEP-NETs are a morphologically and biologically heterogeneous group of neoplasms. This makes it difficult to devise a staging system that is capable of classifying all the different tumours into specific groups reflective of their prognosis.[15]

Staging of GEP-NETs is essentially based on multimodal imaging including, but not limited to:

- conventional imaging
  - contrast enhanced CT scan or MRI (should be the primary modalities for imaging)
- functional imaging
  - consider somatostatin receptor imaging, preferably $^{68}$Ga-DOTA PET/CT scan in grade G1 and G2 tumours
  - metabolic imaging such as $^{18}$F-FDG PET/CT scan in G3 tumours
  - use of both to evaluate tumoural heterogeneity when tumoural Ki-67 is > 10%

There are currently two staging systems for GEP-NETs namely the American Joint Committee on Cancer (AJCC) TNM (8$^{th}$ edition) and the ENETS systems. They are both useful for predicting survival and are identical for tumours of the stomach, small intestine, colon and rectum but differ for the pancreas[16] and appendix.[17,18] However, both these staging systems do not address staging for primary NETs of the liver and biliary system.[19,20] The AJCC 8$^{th}$ edition improves on prior editions but it has shortfalls in areas such as different T sizes for the various GEP-NETs.

# CHAPTER 5:
# TREATMENT



GEP-NETs are a heterogeneous group of rare neoplasms with a variable biological behaviour. Treatment of GEP-NETs needs to be planned by a multidisciplinary team and individualised to the needs of each patient based on the clinical presentation, cellular morphology, grade and stage of the disease.

Treatment options for GEP-NETs include endoscopic therapies, surgery, systemic therapies, loco-regional interventional radiology therapies, PRRT and supportive care (Figure 6).

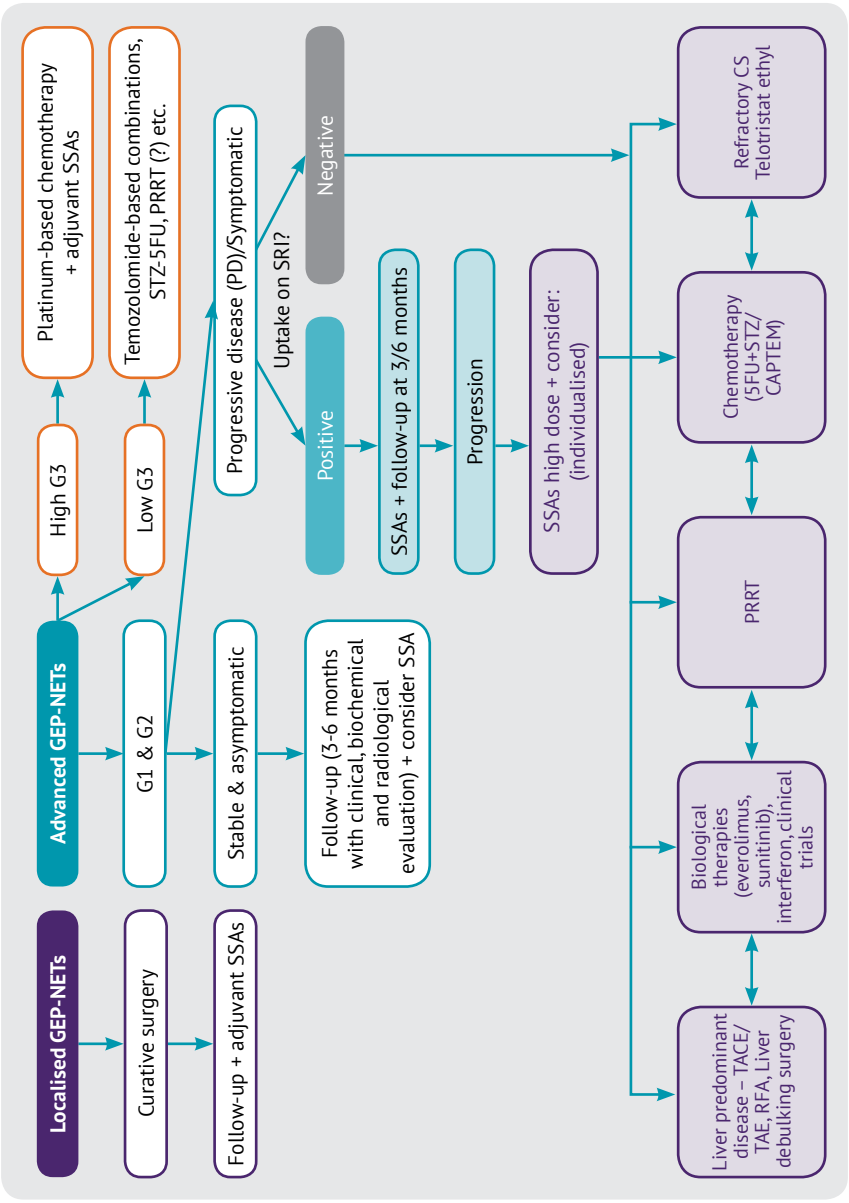
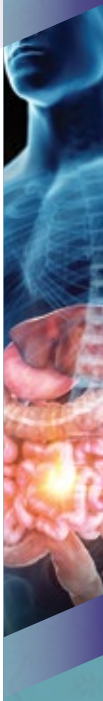



*Figure 6: Possible treatment algorithm in GEP-NETs.[21] SSA: somatostatin analogues; G1-G2: grades 1, 2, 3; SRI: somatostatin receptor imaging; STZ: streptozocin; 5-FU: 5-fluorouracil; PRRT: peptide receptor radionuclide therapy; TACE: transarterial chemoembolisation; TAE: transarterial embolisation; CAPTEM: capecitabine and temozolomide. Adapted from Uri I et al. 2018. Creative Commons Attribution 4.0 International License.*



## 5.1 Endoscopy

Removal of small neoplastic lesions from the intestinal lumen is possible with therapeutic endoscopic methods such as **endoscopic mucosal resection** (EMR) and **endoscopic submucosal dissection** (ESD).[7] This should be performed when,

- the lesion is confined to the mucosa or submucosa
- there is no evidence of lymph node involvement.

EUS should be performed prior to EMR and/or ESD to assess resectability. Endoscopic resection is indicated:[7]

- in cases of gastric type I and II carcinoids, with diameter < 1 cm, if the lesions are no more than 5 in number
- for duodenal lesions < 1 cm
- in ampullary lesions confined to the submucosa (endoscopic ampullectomy)
- for rectal lesions < 1 cm or between 1 and 2 cm

The specimen should be assessed for completeness of resection. Those with positive margins should be referred for surgery.

**Radio frequency ablation** (RFA) or ethanol injection may be performed in a select group of pNETs patients by an experienced and skilled endoscopist.

## 5.2 Surgery

Surgery is the mainstay of treatment in GEP-NETs as it offers the best chance of cure for localised disease and long-term survival in those with limited metastatic disease. The principal goal of surgery is to achieve an R0 resection with negative surgical margins. The type of surgery undertaken is based on tumour site, stage and type (Table 7).22-33

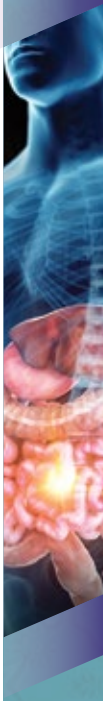
Recommendation: All patients with GEP-NETs should be considered for surgery following staging and multidisciplinary neuroendocrine tumour board meeting.

# CHAPTER 5: TREATMENT

| GEP-NET (Gastric) | Criteria | Surgery options |
|---|---|---|
| Gastric NET Type I (Hypergastrinemia) [22,24,25,27,28] | < 1 cm | Endoscopic resection or observation |
| | > 1 cm | Surgical resection (antrectomy or local excision) |
| Gastric NET Type II (Zollinger-Ellison Syndrome) [22,24,25,27-29] | < 2 cm | Endoscopic resection or observation |
| | > 2 cm | Surgical resection |
| Gastric NET Type III (Normal gastrinemia) [22,24,25,27,28] | | Radical partial or total gastric resection + regional lymphadenectomy |
| **GEP-NET (Small intestine)** | | |
| Duodenal NET [23,25,29] | < 1 cm, solitary, confined to the submucosal layer, without lymph node or distant metastasis | Endoscopic resection |
| | 1-2 cm | Endoscopic or surgical resection |
| | > 2 cm with or without lymph node metastases | Transduodenal excision or pancreatoduodenectomy |
| | Periampulary tumours | Pancreatoduodenectomy |
| | Gastrinoma | Pancreatoduodenectomy |
| Jejunal or Ileal NET [22,25,27] | | Segmental bowel resection with regional lymphadenectomy + examination of the entire length of bowel is essential |
| Ampullary NET | 1-2 cm, confined within the mucosal / submucosal layer, no infiltration of the muscularis mucosa and no evidence of metastasis | Endoscopic ampullectomy or transduodenal ampullectomy |
| | Any size tumour that has infiltrated beyond the muscularis with or without regional lymph node metastasis | Pancreatoduodenectomy |
| Appendiceal NET [25,29] | ⩽ 2 cm confined to the appendix | Appendicectomy |
| | ⩽ 2 cm involving base of appendix, lymphovascular invasion or invasion of mesoappendix | Right hemicolectomy + regional lymphadenectomy |
| | > 2 cm or incomplete resection with or without lymphovascular invasion | Re-exploration with a right hemicolectomy + regional lymphadenectomy |
| **GEP-NET (Large intestine)** | | |
| Colonic NET [6] | | Regional colectomy + lymphadenectomy |

| | | |
|---|---|---|
| Rectal NET[24,25,27,29] | < 1cm, confined to mucosa and submucosa | Endoscopic resection |
| | 1-2 cm, confined to mucosa and submucosa | Endoscopic resection or transanal excision |
| | > 2 cm, tumours invading beyond muscularis propria with or without lymphadenopathy | Surgical resection (low anterior resection or abdominoperineal resection) |
| **GEP-NET (Pancreatic)** | | |
| Non-functioning[22,24,25] | ⩽ 2 cm, well-differentiated, (G1); asymptomatic | Observe |
| | ⩽ 2 cm, well-differentiated (G1 or G2); symptomatic | Enucleation or parenchymal preserving segmental resection |
| | > 2 cm with or without lymph node metastasis | Proximal, central or distal pancreatectomy + regional lymphadenectomy ± splenectomy |
| Functioning - insulinoma, gastrinoma[22,24,29] | Exophytic or non-invasive tumours away from main pancreatic duct | Enucleation or parenchymal preserving segmental resection |
| | Deep or invasive tumours or in proximity to the main pancreatic duct | Proximal, central or distal pancreatectomy ± regional lymphadenectomy ± splenectomy |
| **GEP-NET (with hepatic metastasis)** | | |
| Primary hepatic NET | Localised to liver with no extrahepatic disease | Hepatic resection *(Type of hepatic resection will depend on the location of the tumour, the ability to provide an adequate future liver remnant, and, for a tumour-negative margin)* |
| Hepatic metastases[23-26,29,33] | Localised to liver with no extrahepatic disease and primary completely resected | Hepatic resection ± ablation |
| | Localised to liver with no extrahepatic disease and primary completely resected with clear margins, age < 55 years, low-grade NET (low Ki-67 index), stable disease during 6 months prior to transplant | Liver transplantation in highly selected patients with prolonged disease stability |
| | NET related functional syndrome | Debulking surgery |
| **Other surgeries in GEP-NET** | | |
| Other surgeries[23,29] | Planned adjuvant treatment with octreotide or lanreotide | Prophylactic cholecystectomy |

*Table 7: Surgical options for GEP-NETs based on tumour site, size, type and presence of metastases including hepatic metastases. GEP-NETs: gastroenteropancreatic neuroendocrine tumour; NET: neuroendocrine tumour.*



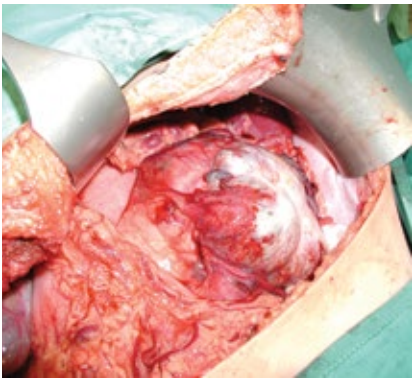


*Figure 7: Pancreatic neuroendocrine tumour*

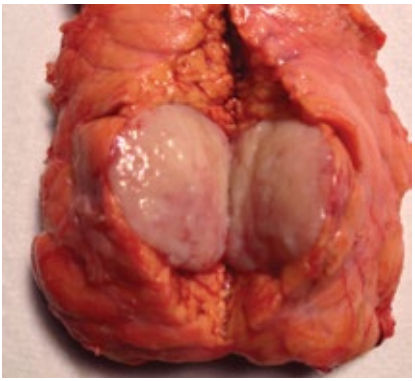


*Figure 8: Surgical specimen of resected distal pancreas with pancreatic-NET.*

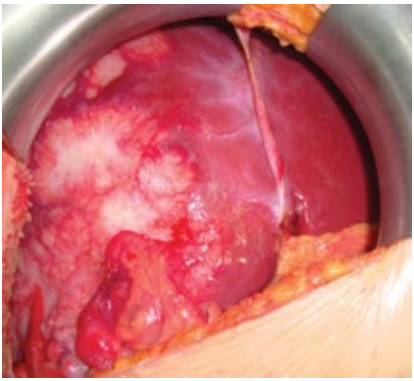


*Figure 9: Right lobe liver metastases from rectal NET.*

## 5.3 Medical (systemic) therapy

Systemic therapy of GEP-NETs is dependent on their differentiation.

Well-differentiated NETs are usually treated with targeted therapies as these tumours do not respond well to chemotherapy while poorly differentiated NETs are treated with chemotherapy.

## 5.3.1 Somatostatin analogues

The currently available **somatostatin analogues** (SSA) in Malaysia are:

- short/immediate acting SSAs
  - octreotide 50, 100 mcg/ml either by SC injection twice/thrice daily or IV injection/infusion
- depot formulations
  - octreotide LAR IM injection every 4 weeks (20, 30mg available in Malaysia)
  - lanreotide autogel SC injection every 4 weeks (120mg available in Malaysia)

| Role of SSA in functioning GEP-NETs | Role of SSA in non-functioning GEP-NETs |
|---|---|
| • **SSA is standard therapy in functioning NETs of ANY site as an anti-secretory treatment.**<br>  ▸ However, in specific functioning pNETs, other therapies should be considered as 1st line therapy:<br>  ◦ gastrinoma – high dose proton pump inhibitors<br>  ◦ insulinoma – diaxozide, verapramil, phenytoin, prednisolone and everolimus (in malignancy)<br>• As first-line therapy for carcinoid symptoms arising from tumour sites:<br>  ▸ jejuno-ileal and pancreas – common<br>  ▸ gastroduodenal and colorectal – rare<br>  ▸ liver and distant metastases from GEP-NETs<br>• In glucagonoma, as it is very effective for necrolytic migratory erythema (NME).<br>• In VIPoma as 1st line treatment as it is very effective for diarrhoea;<br>  ▸ 80-90% have clinical response<br>  ▸ 60-80% have reduction in VIP and glucagon levels | • SSAs have anti-proliferative/growth effects on NETs that stabilise tumour growth rather than reduce tumour size.<br>  ▸ Delays time to tumour progression (TTP)[33]<br>  ▸ Improves/prolongs progression-free survival (PFS)[35]<br>• SSAs in non-functioning NETs:<br>  ▸ are usually started with evidence of high tumour burden, tumour progression or local effect<br>  ▸ may be started in newly diagnosed, treatment naïve patients without prior observation period for tumour growth<br>  ▸ are not recommended in G3 metastatic NETs<br>  ▸ are not recommended if curative resection of liver metastases and/or loco-regional therapies are feasible |

*Table 8: Role of SSA in functioning and non-functioning NETs.*

Initiation of SSAs:

Depending on the indications, either short/immediate or long-acting SSAs may be used.

| For anti-secretory effect | For anti-proliferative effect | Role of SSAs as RESCUE medication |
|---|---|---|
| • Start with SC octreotide 100-600 mcg/day in 2-3 divided doses for a few days<br>• Switch to either IM octreotide LAR 20-30 mg every 4 weeks or SC lanreotide autogel 120 mg every 4 weeks | • Start with either IM octreotide LAR 30 mg, every 4 weeks or SC lanreotide autogel 120 mg every 4 weeks | • Administered in acute situations such as pre-operatively and during a crisis<br>• Administer a bolus SC octeoride and/or IV infusion at 50-100 mcg/hour |

*Table 9: Initiation of SSA for different indications.*

Monitoring patients on long-term SSA:

| For safety | For efficacy |
|---|---|
| • Baseline gallbladder ultrasound, repeated at intervals (6-12 monthly)<br>• Blood for vitamin B12 levels and thyroid function test | • Blood for CgA<br>• Urine for 5-HIAA<br>• Imaging – either CT, MRI or Somatostatin Receptor Scintigraphy (SRS) |

*Table 10: Recommendations for monitoring of patients on long-term SSA.*

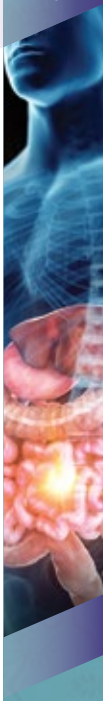
Note: Newer SSAs such as pasireotide have been used for patients with refractory carcinoid syndrome who are already on optimised dose of current SSAs or who have failed other treatment options.

## 5.3.2 Interferon

Interferon alpha is a form of systemic therapy for metastatic GEP-NETs but it is not used frequently due to its perceived limited efficacy and associated toxicities.[36] However, it has a role in certain situations:

- small volume diffuse disease
- syndromic patients with resistance to SSAs
- as a bridge to other therapies

Interferon alpha may be used in combination with SSAs such as octreotide in the treatment of metastatic GEP-NETs.[37,38]



## 5.3.3 Targeted therapies

There are currently two targeted therapies approved for GEP-NETs:

- Everolimus - a mammalian Target of Rapamycin (mTOR) inhibitor
- Sunitinib – a multikinase inhibitor

Therapy is based on the tumour site. Everolimus has shown improvement in progression-free survival (PFS) in well-differentiated non-functioning GI-NETs,[39] whilst both everolimus and sunitinib improve PFS in pNETs.[40-42] The effect of treatment on overall survival is uncertain as many patients are salvaged with further therapies upon progression.

Pazopanib has also shown similar efficacy in a phase II trial and may be considered as an option in patients intolerant to everolimus or sunitinib.[43]

## 5.3.4 Chemotherapy

The role of chemotherapy in GEP-NETs is not well studied in phase III trials.

Patients with **poorly differentiated (PD) NETs** are generally treated with standard chemotherapy regimes.[44] Cisplatin-etoposide (EP) combination is considered standard for PD NETs.

In the **metastatic setting**, palliative chemotherapy is recommended, as survival with best supportive care is only 1-3 months. Chemotherapy with EP regime should be started as soon as possible while the patients are fit. The response rate to chemotherapy is about 50-70% with a median survival of 1 year.[45,46] For patients with **poor renal function**, cisplatin can be substituted with carboplatin. An alternative first line therapy of irinotecan-cisplatin (IC) yields similar results to EP.[47,48]

Data for second line chemotherapy is extremely limited and is based on small cohorts of patients. These regimes with response rates of 20-40% may be considered.[44,49,50]

- capecitabine-temozolamide (CAP-TEM)
- oxaliplatin with fluorouracil (5FU) and folinic acid (FOLFOX)
- folinic acid (leucovorin)-fluorouracil-irinotecan (FOLFIRI)
- paclitaxel-carboplatin

## CHAPTER 5: TREATMENT

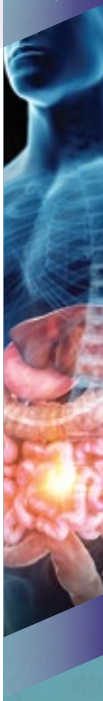
The choice of chemotherapy is dependent on the previous response, performance status of patient and residual toxicity from chemotherapy, namely peripheral neuropathy.

The role of chemotherapy in **well-differentiated GEP-NETs** is not established. However, in fit patients with progressive disease following other standard therapies, the same regimes used in PD NETs should be considered. Streptozocin based regimes are reported to have a higher response rate in G1/2 tumours of pancreatic origin versus other sites (38% vs. 25%) with a disease control rate of 72% at 6 months.[51]

| Drug | Functionality | Grading | Primary site | SSTR status | Special considerations |
|---|---|---|---|---|---|
| Octreotide | +/- | G1 | midgut | + | Low tumour burden |
| Lanreotide | +/- | G1/G2 (- 10%) | midgut, pancreas | + | Low and high (> 25%) liver tumour burden |
| IFN-alpha 2b | +/- | G1/G2 | midgut | | If SSTR is negative |
| CAP/TEM | +/- | G2 | pancreas | | Progressing in short-term* or high tumour burden or symptomatic; if STZ is contraindicated or not available |
| Everolimus | +/- | G1/G2 | lung | | Atypical carcinoid and/or SSTR negative |
| | | | pancreas | | Insulinoma or contraindication for CTX |
| | | | midgut | | If SSTR negative |
| Sunitinib | +/- | G1/G2 | pancreas | | Contraindication for CTX |
| PRRT | +/- | G1/G2 | midgut | + (required) | Extended disease; extrahepatic disease such as bone metastasis |
| Cisplatin$^{\delta}$/ etoposide | +/- | G3 | any | | All poorly differentiated NEC |

IFN-alpha: interferon alpha; CAP: Capecitabine; TEM: temozolomide; PRRT: peptide receptor radionuclide therapy; SSTR: somatostatin receptor subtypes; STZ: streptozocin, CTX: chemotherapy; NEC: neuroendocrine carcinoma.
* ⩽ 6-12 months; δ Cisplatin can be replaced by carboplatin.

*Table 11: Medical, systemic and chemotherapy treatment modalities for GEP-NETs. Adapted from ENETS 2016 Guidelines.*[52,53]



## 5.4 Interventional radiology

Advances in radiology have expanded its role to include minimally invasive image guided diagnostic and therapeutic techniques in the management of various cancers including gastrointestinal and pancreatic NETs and complications arising following their surgery.

Interventional radiology plays an important role in diagnosis, treatment and palliation of the various cancers. In view of the limited number of interventional radiologists in Malaysia, its availability is limited to hospitals with expertise and appropriate facilities.

The role of interventional radiology in the management of GEP-NETs is evolving and the interventional procedures currently available in Malaysia include, but are not limited to,

**I: Diagnosis**

- Image-guided biopsy.
- Localisation of occult primary lesions as in the case of gastrinoma and insulinoma through digital subtraction angiography and venous sampling of portal blood.
- Transjugular biopsy of liver tumours.

**II: Treatment**

Loco-regional treatments include those for control of tumour growth or control of secretory syndrome.

- Image guided ablative therapy uses image guidance (ultrasound, CT or MRI) to insert the probe into the targeted tumour to deliver energy (radiofrequency, microwave, cryoablation and electroporation) to ablate it.
- Percutaneous ablation can be undertaken for tumours in the liver, lung and bones.
  *NB: Percutaneous RFA may be curative for tumours up to 3 cm that are confined to the liver.*
- Intra-arterial therapies[54-56]
  a. Hepatic intra-arterial therapies for GEP-NET liver tumours/metastases entails occlusion of the tumour arterial supply, with or without chemotherapy or internal radiation therapy.
  b. Common treatment of GEP-NET liver metastases include:[57-59]
     - Trans-arterial chemoembolisation (TACE),
     - Trans-arterial embolisation (TARE) or selective internal radiation therapy (SIRT).

c. Indications[58,60]
- Cytoreduction of liver tumour mass (including bilobar disease) in patients who are not candidates for surgical resection.
- Down-staging of liver tumours prior to surgical resection.
- Uncontrolled secretory symptoms.

d. Contraindications[60]
- Liver insufficiency (Child Pugh C).
- Obstructive jaundice.
- Portal vein thrombosis (not a contraindication for TARE/SIRT).
- Renal insufficiency.
- Extensive extrahepatic metastatic disease.

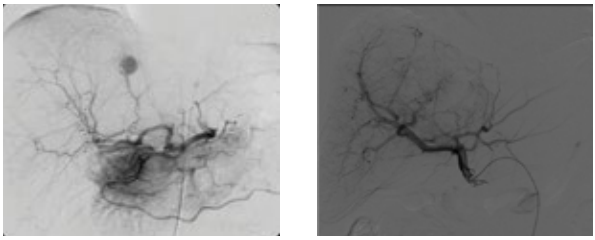


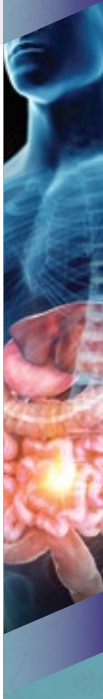
*Figure 10: Hepatic Angiography showing tumour blush of a metastatic lesion from a pancreatic neuroendocrine tumour.*

### III: Support
Interventional procedures that facilitate the provision of appropriate treatments but do not in themselves affect the tumour.

- Image guided peripheral insertion of central catheters for medium term venous access for cytotoxic chemotherapy or nutritional support.
- Image guided placement of enteral feeding tube.
- Image guided aspiration/drainage of pleural effusion, ascites and fluid collection.

### IV: Palliation
Management of disease related and surgical complications to provide symptomatic relief without modifying the course of the disease.

- Post-operative drainage of intra-abdominal fluid collection or abscesses.
- Mesenteric angiography with or without coil embolisation or endovascular stenting for tumour related post-operative bleeding.
- Percutaneous transhepatic cholangiography with internal or external biliary drainage and stenting for biliary strictures or obstruction.
- Dilatation and stenting of bowel stenosis or strictures.



**Note: There are no randomised trials comparing each of these treatment interventions; most data, however, is retrospective and derived from cohort studies.**

## 5.5 Peptide receptor radionuclide therapy (PRRT)

- PRRT is a molecularly targeted radiation therapy involving intravenous administration of a specific radiopharmaceutical composed of a β-emitting radioisotope yttrium-90 ($^{90}$Y-) or lutetium-177 ($^{177}$Lu-) chelated to a DOTA-peptide such as [DOTA$^0$-1-Nal$^3$]octreotide (DOTA-NOC), [DOTA$^0$, tyrosine-3 (Tyr$^3$)]octreotate (DOTA-TATE) or [DOTA$^0$, Tyr$^3$]octreotide (DOTA-TOC) for the purpose of delivering cytotoxic radiation to tumoural sites that express somatostatin receptors (SSR).[61]

- The safety and efficacy of PRRT ($^{90}$Y- and $^{177}$Lu-DOTA-peptide) for both secretory and non-secretory GEP-NETs are supported by large sample size phase I and II data.[62-68] The recent phase III NETTER-1 trial (Neuroendocrine Tumors Therapy trial) in patients with advanced midgut NETs demonstrated that $^{177}$Lu-DOTA-TATE ($^{177}$LuTate) has a significantly longer PFS and higher response rate compared to high-dose octreotide long-acting repeatable (LAR) therapy.[69]

- The United States Food and Drug Administration (US FDA) has recently approved$^{177}$ Lu-Tate as an option for patients with SSR expressive NETs (including fore-, mid- and hind-gut) who have progressed on standard dose SSA therapy regardless of secretory status.[70] Hence, in these cases, PRRT should be considered as an option.

- Pre-treatment assessment with somatostatin receptor imaging, preferably Ga-DOTA-peptide PET/CT, with/without FDG PET/CT should be performed to establish somatostatin receptor subtypes (SSTR) expression tumours.[71]

- Combination of PRRT with radiosensitising chemotherapy (capecitabine and temozolamide) to synergistically improve therapeutic efficacy with no increase in toxicity, especially in G2 and G3 NETs, has been reported in several phase II trials.[72-75] This deserves further evaluation.

## 5.6 Supportive care

The primary purpose of an early diagnosis of GEP-NETs is to enable a cure. However, the majority of patients often present with advanced disease when treatment options are limited. Throughout the course of the illness, patients and their families face a multitude of challenges which may affect them physically (symptoms and side effects related to the neoplasm and its treatment), emotionally and socially.

Management of patients with GEP-NETs thus encompasses not only physical treatments but also various aspects of supportive care to improve the quality of life and optimise outcomes.

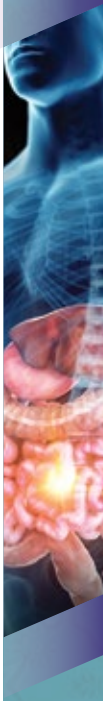
Supportive care is an integral component of the comprehensive management of patients with GEP-NETs and includes:

- emotional support and counselling
- alleviating symptoms and complications associated with GEP-NETs
- reducing or preventing side effects of treatment
- nutritional support
- palliative care including advanced care planning and end-of-life care

Supportive care can be provided by:

- Primary Care Team in liaison with the Multidisciplinary NET Team.
- Palliative Care Team
  - Palliative care units are currently available in a number of public and private hospitals in Malaysia.
  - In addition there are various non-governmental organisations providing community palliative care throughout the country. Hospis Malaysia is amongst the most established organisation providing free professional community palliative care within the Klang Valley.
- NET support groups help people cope with the emotional aspects of being diagnosed with GEP-NETs by sharing their own experiences.
  - Unfortunately there are no specific NET support groups in Malaysia to date though patients often link up with the various international online NET support groups and with individual NET patients to share their experiences and learn from each other.
- The National Cancer Society of Malaysia has peer support groups for cancer in general and these may be able to provide support to NET patients.
- 'Living with NETs' is an online patient support group for people living with NETs. It provides online information about the various aspects of NETs, an online forum and links to other people living with NETs, as well as details of NETs related events that patients can attend.

# CHAPTER 6:
# FOLLOW-UP



GEP-NETs are a heterogeneous group of neoplasms with a wide spectrum of biological behaviour. However, all GEP-NETs have malignant potential depending on their site of origin, degree of differentiation and stage.

In principle all patients with GEP-NETs should be maintained on long-term follow-up, individualised to the needs of each patient and the tumour kinetics (Ki-67 proliferative index).

There is currently **no standard follow-up policy** for patients after diagnosis and treatment of GEP-NETs. It is based only on expert opinion and consensus. The ESMO[76] and ENETS[51,52,77] guidelines recommend follow-up between 3-12 months depending on the site of NETs. **We recommend that follow-up should be done every six months after curative surgery of G1-G2 GEP-NETs; and every three months for G3 GEP-NETs.**

Minimal examinations during follow-up should include:

- clinical history and physical examination
- laboratory investigations including serum biomarker (serum CgA)

Radiological evaluation with contrast enhanced CT scan or MRI and/or somatostatin receptor imaging should be performed if suspicious of recurrence, and for restaging prior to repeat surgery.[78,79]

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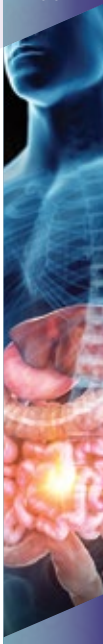

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