

SCONET



Scottish Neuroendocrine Tumour Group

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Consensus Guidelines for the Management of Patients with Neuroendocrine Tumours

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Abbreviations

5-FU, 5-fluorouracil

5-HIAA, 5-hydroxyindoleacetic acid

5-HT, 5-hydroxytryptophan

18F-DOPA/DOPAMINE

68Ga-DOTA, gallium68-DOTATOC/DOTATATE/DOTANOC

ACTH, adrenocorticotrophic hormone

AJCC, American Joint Committee on Cancer

ARSAC, Administration of Radioactive Substances Advisory Committee

BP, bronchopulmonary

CAP, capecitabine

CARB, carboplatin

CAV, cyclophosphamide/DOX/vincristine

CAVE, cyclophosphamide/DOX/vincristine plus etoposide

CD56, cluster of differentiation 56 (also referred to as neural cell adhesion molecule, NCAM)

CEA, carcinoembryonic antigen

CgA, chromogranin A

CgB, chromogranin B

CIS, cisplatin

CK19, cytokeratin 19

CLARINET, Controlled study of Lanreotide Antiproliferative Response in NET

CSF-1R, the receptor for M-CSF

DOX, doxorubicin

DTIC, dacarbazine

ELST, endolymphatic sac tumour

ENETS, European Neuroendocrine Tumour Society

EUS, endoscopic ultrasound

FDG, 18F-Fludeoxyglucose

FLT3, Fms-like tyrosine kinase-3 receptor

FMTC, familial medullary thyroid carcinoma

FNA, fine needle aspiration

FOL, folinic acid

GH, growth hormone

GHRH, growth hormone releasing hormone

HAE, hepatic arterial embolisation

hpf, high-power fields

IASLC, International Association for the Study of Lung Cancer

IFN- α , interferon- α

IGF-1, insulin-like growth factor-1

IRIN, irinotecan

LAR, long-acting release

LCNET, large-cell neuroendocrine tumour

MDT, multidisciplinary team
MEN1, multiple endocrine neoplasia type 1
MEN2, multiple endocrine neoplasia type 2
MGMT, O(6)-methylguanine DNA methyltransferase
MHRA, Medicines and Healthcare Products Regulatory Agency
mIGB, meta-iodobenzylguanidine
MTC, medullary thyroid carcinoma
mTOR, mammalian target of rapamycin

NET, neuroendocrine tumour
NF, non-functioning
NSCLC, non-small-cell lung cancer

OX, oxaliplatin

PDGF, platelet-derived growth factor
PROMID, Placebo controlled, double-blind, prospective, Randomized study on the effect of Octreotide LAR in the control of tumor growth in patients with metastatic neuroendocrine MIDgut tumors
PTH, parathyroid hormone

RE, radioembolisation
RET, ret proto-oncogene
RFA, radiofrequency ablation
RTK, receptor tyrosine kinase

SCLC, small-cell lung cancer
SCONET, Scottish Neuroendocrine Tumour Group
SEPA, Scottish Environmental Protection Agency
SIRT, selective internal radiation therapy
SOP, standard operating procedure
SSRI, somatostatin receptor imaging
SSTR, somatostatin transmembrane receptors
STZ, streptozocin

TACE, transarterial chemoembolisation
TFI, treatment-free interval
TMZ, temozolomide
TNM, tumour, node, metastasis classification of malignant tumours
TSH, thyroid stimulating hormone

UICC, Union for International Cancer Control

VEGF, vascular endothelial growth factor
VHL, Von Hippel-Lindau
VIP, vasoactive intestinal peptide

WHO, World Health Organization

1. Summary of Key Recommendations

General Recommendations

- All patients with NETs should be discussed by a specialist NET MDT to agree definitive management.
- NET multidisciplinary teams should include representation from the following specialities: endocrinology, oncology, pathology, radiology, surgery, gastroenterology, nuclear medicine and clinical nurse specialists.

Diagnosis

- CT and MRI are the initial imaging modalities of choice for staging and monitoring disease progression.
- Octreotide scintigraphy is also helpful in determining the extent of metastatic disease and may help predict response to somatostatin analogue therapy.
- PET scanning should be considered in those patients with suspected disease which has not been demonstrated by conventional imaging.

Biochemical Investigation

- All patients with a confirmed GEP NET should have a baseline CgA, CgB, and 24-hour urine collection for 5-HIAA. Elevated levels of these markers can be used to monitor response to therapy and disease progression.
- A full gut hormone screen should be performed in all pancreatic NETs and consideration given to more detailed endocrine investigation if there are symptoms suggestive of a functioning tumour.
- Pheochromocytoma and paraganglioma should be investigated using plasma or urine metanephrines.

Surgical Management of GEP NETs

- Patients with localised NETs should be considered for surgical resection.
- Surgery should be offered to patients who are fit and have limited disease (i.e. primary tumours and/or disease limited to regional lymph nodes).
- Resection of recurrent or metastatic tumours should be considered for fit patients.
- Resection of locally advanced tumours should be performed to achieve negative margins; this may include en bloc resection of adjacent organs.
- Liver resection or ablative therapies should be considered for patients with metastatic disease.
- The extent of the tumour, its metastases, and secretory profile should be determined as far as possible before planning treatment.

- Incidentally identified lesions that are suspected of being NETs require multidisciplinary assessment before consideration of resection by a surgeon experienced in the management of NETs.
- For patients who are not fit for surgery, the aim of treatment is to improve and maintain an optimal quality of life.
- Octreotide therapy should be commenced prior to resection of primary or metastatic functional NETs.

Pathological Assessment of NETs

- The proliferation index of GEP NETs should be assessed in all tumours using Ki-67 (MIB-1 clone) and mitotic count.
- In pancreatic NETs, CK19 positivity may be of prognostic significance so routine staining for CK19 should be performed.
- GEP and appendiceal NETs should be classified according to current Royal College of Pathologists and WHO guidelines.
- Goblet cell carcinoid tumours of the appendix should be classified using the Royal College of Pathologists guidelines.

Management of Goblet Cell Carcinoids

- Goblet cell carcinoids or adenocarcinoids of the appendix are more aggressive than classical appendiceal NETs and should be managed as colorectal adenocarcinoma.

Management of Bronchopulmonary NETs

- Surgical resection should be considered in all patients who are fit and have limited disease.
- The principal aim is to achieve complete resection with wide and clear resection margins.
- Initial assessment of patients should be identical to that of lung cancer patients. However once a BP NET is confirmed, appropriate specialist investigations are required.
- BP NETs should be classified according to the 2004 WHO classification and staged using TNM7.
- On the rare occasion where the carcinoid does represent a functional NET, octreotide therapy should be commenced prior to surgical resection of the tumour.
- Long term follow is advised in view of the higher risk of late relapse by clinics expert in managing NET cancers.

Medical Therapy and New Drug Treatments

- Somatostatin analogues should be used as first-line agents for the medical management of symptomatic NETs.
- Prior use of short-acting somatostatin analogues and dose titration of sustained-release somatostatin analogues now not required; commence maximal dose of sustained-release somatostatin analogues at treatment initiation. However in very symptomatic patients, short term use of subcutaneous SMS analogues may be necessary.
- INF- α should be reserved as a second-line agent for symptomatic relief in patients who fail to tolerate or show no benefit from somatostatin analogue therapy.
- Everolimus may be considered in patients with progressing pancreatic NETs where the tumour is well or moderately-differentiated and the patient is of PS 0, 1 or possibly 2 with adequate organ function.
- Sunitinib may be considered in patients with progressing pancreatic NETs where the tumour is well-differentiated and the patient is of PS 0 or 1 with adequate organ function.

Chemotherapy

- There is wide variation in the chemosensitivity of different types of NET. Anatomical location, grade and proliferation index help to determine the choice of chemotherapy and timing of interventions.
- Newer agents may offer potential as many traditional chemotherapy approaches have limited activity. More clinical trials are needed to determine the optimal timing of intervention.
- Poorly differentiated (G3) NETs should have chemotherapy with platinum and etoposide combinations.
- The MDT should discuss when to offer chemotherapy as part of the algorithm of treatment options.

Interventional Radiology for Hepatic Metastases

- Interventional radiology techniques such as TACE have a role in the management of symptomatic hepatic metastases that are poorly responsive to hormonal therapies.
- Such procedures are associated with an increased risk of carcinoid crisis and close liaison with an endocrinologist is required before the procedure.

Radionuclide Therapies

- All radionuclide treatments must occur within purpose-built facilities under the supervision of trained staff with expertise in the care of patients undergoing treatment with radiopharmaceuticals.

- ^{131}I -mIBG is first line treatment for metastatic phaeochromocytoma/paraganglioma/neuroblastoma in patients with $^{123/131}\text{I}$ -mIBG-positive disease.
- Radiolabelled somatostatin analogues (DOTATOC and DOTATATE) can be used to treat patients with significant disease demonstrated on ^{111}In -octreotide scintigraphy and acceptable renal function. However, there are currently no Scottish centres that routinely offer this treatment.

Genetics

- Individuals diagnosed with phaeochromocytoma or paraganglioma under the age of 50 years, or at any age if the tumour is bilateral, malignant or there is a family history, should be offered genetic analysis of current known predisposition genes or DNA storage.
- Individuals who have a mutation identified should be referred to the local Clinical Genetics Department.
- As there is no proven screening protocol for familial phaeochromocytoma/paraganglioma it is important to refer to the Regional Service to allow results to be collected and audited with a view to determining the most appropriate regimen.
- A routine surveillance protocol for VHL disease should be conducted at a Regional Service.
- If there is any clinical suspicion of MEN1, samples can be sent for analysis ofmenin. Consider *CDC73* analysis in young patients with hyperparathyroidism and negative menin analysis.
- Individuals with MEN1 should undergo annual screening.

Patient Support

- Patients with NETs can experience a range of physical and psychological challenges, so supporting these patients is a fundamental part of their overall management.
- Patients should be informed about the various organisations that provide support and information for NET patients, their families and carers.

Carcinoid Heart Disease

- This topic has recently gained recognition as an important topic and a separate appendix on CHD will be added later. Clinicians looking after patients with advanced functional small bowel NETs should intermittently screen patients for heart disease as this is best managed by specialist cardiac/thoracic units with interventions including valve replacement and repair.

2. Introduction and Background

The Scottish Neuroendocrine Tumour Group (SCONET), established in 2011, is a Scotland-wide multidisciplinary group involved in all aspects of the neuroendocrine tumour (NET) patient pathway. The principal aim of the group is to ensure equitable care and improve the quality of care for patients with NETs across NHSScotland.

NETs are a relatively rare, heterogeneous group of cancers that occur most commonly in the digestive system, small bowel, appendix, lung and pancreas.¹ While some NETs are aggressive, most are more indolent than other malignancies, which often leads to a significant delay (up to 7 years) between first appearance of symptoms and a NET diagnosis.¹

The annual incidence of NETs is relatively low but increasing. Due to the long survival of patients with NETs, however, the prevalence is amongst the highest of all cancer types.¹ Across Scotland it is estimated that over 150 new cases are seen every year. Data from the USA suggest that NETs are the second most common gastrointestinal malignancy after colorectal cancer.²

Patients with NETs are currently managed locally across Scotland. All patients with NETs should be discussed by a specialist NET multidisciplinary team (MDT) to agree definitive management. NET MDTs should include, but not be restricted to, representatives from endocrinology, oncology, pathology, radiology, surgery, gastroenterology, nuclear medicine and clinical nurse specialists. Due to the complexity of the patient pathway, plus the intricacies of cross-speciality management, SCONET recognised that a Scotland-wide consensus guideline for the management of patients with NETs would be of great value in supporting the delivery of equitable care.

2.1 Methodology

These guidelines have been developed by the multi-disciplinary SCONET Group, following several meetings of the Group where consensus agreement on the management of NETS in NHSScotland was reached. Contributing authors are listed on page 3. The guidelines are not intended to be prescriptive, but form a basis upon which to aim for improved standards in the quality of treatment for patients with NETs across NHSScotland.

2.2 General Recommendations

- **All patients with NETs should be discussed by a specialist NET MDT to agree definitive management.**
- **NET multidisciplinary teams should include representation from the following specialities: endocrinology, oncology, pathology, radiology, surgery, gastroenterology, nuclear medicine and clinical nurse specialists.**

3. Diagnostic Imaging

The optimal imaging of NETs is based on a multimodal approach using a number of different imaging techniques, including CT, MRI, radionuclide imaging (SPECT and SPECT/CT), PET/CT, endoscopic ultrasound (EUS) and occasionally, angiography and venous sampling.

3.1 Diagnosis

Gastric, duodenal and colonic NETs are usually diagnosed by endoscopy and thoracic NETs by CT. Primary midgut NETs can be more difficult to detect until advanced, with CT features including bowel wall thickening and mesenteric desmoplastic reaction. Pancreatic NETs are initially detected using CT/MRI; functioning tumours are usually detected earlier than non-functioning lesions. EUS should be used to localise a pancreatic NET in patients with a functioning syndrome in whom CT/MRI has failed to identify a lesion. EUS has been shown to be more sensitive than CT/MRI and, in skilled hands, allows detailed examination of the whole gland; fine needle aspiration (FNA) of any identified lesion is used to confirm the histological diagnosis.³ Venous sampling and digital subtraction angiography are rarely required for tumour localisation due to the high-resolution images obtained by CT, MRI and EUS.

3.2 Staging and Detection of Metastatic Disease

3.2.1 CT and MRI

CT and MRI are the initial imaging modalities of choice for the detection and assessment of local disease and metastatic spread and should incorporate contrast-enhanced scans of the thorax, abdomen and pelvis. Most NETs are typically arterially enhancing on CT and MRI and may be inconspicuous on portal phase imaging,⁴ so multiphase, contrast-enhanced imaging (including arterial and portal venous phases) is essential for providing maximum accuracy to detect these lesions.⁵

3.2.2 Somatostatin Receptor Imaging (SSRI) (Octreotide Scintigraphy)

SSRI utilising ¹¹¹In-octreotide is currently the first-choice radionuclide imaging investigation to detect metastatic disease. This technique can also be used to predict response to somatostatin analogue therapy. There are five types of somatostatin receptors (I–V); most NETs express type II, and ¹¹¹In-octreotide binds to type II and V. The sensitivity of ¹¹¹In-octreotide scanning is increased with SPECT/CT imaging so this should be used when available.^{6,7}

3.2.3 ¹²³I-mIBG

¹²³I-mIBG imaging is reserved for those patients being considered for ¹³¹I-mIBG therapy. ¹²³I-mIBG is superior to ¹³¹I-mIBG for imaging and accuracy is increased using SPECT/CT.⁸⁻¹⁰

3.2.4 PET/CT

18F-Fludeoxyglucose (FDG), 18F-DOPA/DOPAMINE and gallium68-DOTATOC/DOTATATE/DOTANOC (68Ga-DOTA) are isotopes that are in current clinical use.

At present, PET/CT imaging is used to detect suspected metastatic/recurrent disease in those patients in whom CT/MRI and SSRI is negative. There is increasing evidence that 18F-DOPA/DOPAMINE and 68Ga-DOTA agents are more sensitive than SSRI,¹¹⁻¹⁶ in future these radionuclides may replace SSRI as the radionuclide imaging of choice to detect metastatic disease, with SSRI used to predict response to somatostatin analogue therapy.

FDG

FDG is the most commonly used PET isotope in oncological imaging. It is a glucose analogue and its use is based on the premise that most tumours utilise glucose as their primary energy source. Well-differentiated tumours may be FDG negative. Highly metabolic (FDG-avid) tumours tend to be poorly differentiated and clinically more aggressive.¹⁷ FDG-avid NETs generally demonstrate low or absent octreotide or DOTATOC activity.¹⁵

18F-DOPA/DOPAMINE

18F-DOPA/DOPAMINE is concentrated in NETs by an amino acid transport mechanism that is upregulated in tumour cells. Both agents have been shown to have increased sensitivity and specificity for carcinoid tumours (and pheochromocytoma in particular) compared with other imaging techniques.^{11, 14} The accuracy of F18-DOPA/DOPAMINE for pancreatic NETs is not as high.

68Ga-DOTA

68Ga is a positron emitter that is produced by a generator rather than by a cyclotron (as is the case for 18F) potentially making this isotope more widely available. The different ligands have differing SST receptor avidity as follows: DOTATATE>DOTATOC>DOTANOC. These isotopes have been shown to be of increased sensitivity and specificity compared with ¹¹¹In-octreotide SPECT and SPECT/CT.^{12, 13, 16}

3.3 Monitoring of Disease and Detection of Disease Recurrence

CT and MRI are used for monitoring disease and assessing response to treatment as well as for initial investigation of suspected recurrence. SSRI and PET/CT should be considered in those patients with suspected recurrence where CT and MRI are negative.

3.4 Recommendations

- **CT and MRI are the initial imaging modalities of choice for staging and monitoring disease progression.**
- **Octreotide scintigraphy is also helpful in determining the extent of metastatic disease and may help predict response to somatostatin analogue therapy.**
- **PET scanning should be considered in those patients with suspected disease which has not been demonstrated by conventional imaging.**

4. Biochemical Investigation

From the perspective of biochemical investigation, NETs may be classified as one of three types:

- Pancreatic islet cell tumours
- Carcinoid tumours
- Pheochromocytomas/paragangliomas.

Around 10% of all NETs are functional and therefore secrete hormones; a greater percentage may secrete chromogranin A (CgA).^{18, 19} The site and origin of the tumour will determine which biochemical marker is most likely to be secreted.

A baseline measurement of CgA and chromogranin B (CgB) should be undertaken for all NETs to identify circulating markers that may be used to monitor disease progression and response to treatment. In addition, specific markers may be measured if appropriate and available; a full gut hormone screen, for example, would be appropriate with a pancreatic NET.

Plasma CgA is produced by all neuroendocrine cells and is elevated in foregut, hindgut and most midgut carcinoids, as well as in most well-differentiated NETs. CgA should therefore be measured in all carcinoid tumours, VIPomas (pancreatic tumours secreting vasoactive intestinal peptide, VIP), glucagonomas, insulinomas, gastrinomas and non-functioning pancreatic NETs. Elevation of CgA is correlated with the extent of tumour bulk, though in patients treated with somatostatin analogues, CgA may fall due to biochemical effects that may not reflect a fall in tumour volume.²⁰ Measurement of CgA is most appropriate as a marker of disease progression or response to therapy rather than as a diagnostic tool. Levels correlate with treatment response and may have prognostic significance. However, CgA may also be elevated in other conditions such as renal failure, hepatic failure, systemic inflammatory diseases and in association with the use of proton pump inhibitors, so positive results should be interpreted in context.²¹

Pancreatic polypeptide is secreted by pancreatic polypeptide producing cells in the Islets of Langerhans in the pancreas following a meal. Its roles may include contributing to regulation of gall bladder contraction, gut motility and appetite. Pancreatic polypeptide levels may be elevated in some NETs where a false-negative CgA is seen.

4.1 Pancreatic Islet Cell Tumours

The investigation of specific tumours is detailed below for each subtype. Insulinomas and gastrinomas are the most frequent functioning pancreatic NETs, while approximately 50% of pancreatic NETs are non-functioning.²² It is good practice to consider the possibility of multiple endocrine neoplasia type 1 (MEN1) in all patients with a pancreatic NET, and to enquire about family history as well as measure calcium, parathyroid hormone and prolactin.

4.1.1 Gastrinoma

Fasting serum gastrin should be measured in the investigation of suspected gastrinoma. Modest elevations may also be seen in chronic kidney disease and in association with use of proton pump inhibitors and H₂ receptor blockers. Ideally, gastrin should be measured following withdrawal of anti-secretory agents for at least 1 week (if possible). Where gastrin is elevated but not diagnostic (levels >1000 ng/L) a secretin test should be performed, if available.²³ Secretin will stimulate gastrin

release from a gastrinoma to a far greater extent than from normal gastric G cells. Where there is strong clinical suspicion of gastrinoma (elevated gastrin levels but a negative secretin test) arterial stimulation with calcium infusion may be considered. Following treatment, fasting serum gastrin should be measured 3 and 6 months post-therapy, then every 6–12 months for 3 years, then as clinically indicated.²³

4.1.2 VIPoma

Most VIPomas arise in the pancreas (largely in the tail), though VIP may also be secreted by bronchial carcinomas, phaeochromocytomas, hepatomas, adrenal tumours and colonic carcinomas. Diagnosis is based on the measurement of a high (>75 pg/ml) fasting serum VIP on more than one occasion. Following treatment, serum VIP should be measured 3 and 6 months post-therapy, then every 6–12 months for 3 years, then as clinically indicated.²³

4.1.3 Insulinoma

Insulinomas are NETs of the pancreas that secrete inappropriate insulin in association with either fasting or, less commonly, post-prandial hypoglycaemia. The presence of Whipple's triad (symptoms of hypoglycaemia, low plasma glucose and relief of symptoms as hypoglycaemia is treated) suggests a hypoglycaemic disorder. A plasma glucose of <2.2 mmol/L in an individual without diabetes should raise concern. The investigation is detailed in an Endocrine Society guideline²⁴ and outlined below.

Endogenous insulin production is normally suppressed in the setting of hypoglycemia; a 72-hour fast (supervised in a hospital setting) can be conducted to see if insulin levels fail to suppress in the setting of hypoglycaemia, which is a strong indicator of the presence of insulinoma. A suggested protocol is detailed in Cryer *et al.* 2009.²⁴

The fast is ended when plasma glucose is less than 2.5 mmol/L and the patient has symptoms or signs of hypoglycaemia, or at the end of a prolonged fast (up to 72 hours). The fast may also be ended when plasma glucose is <3 mmol/L with previous documentation of Whipple's triad. At the completion of the test, blood is drawn to measure plasma glucose, insulin, proinsulin, C-peptide and β -hydroxybutyrate, and screen for sulfonyleurea.

Thresholds for diagnosis (confirmation of an endogenous insulin source) are plasma insulin (by immunochemiluminometric assay) ≥ 3 μ U/ml and plasma C-peptide >0.6 ng/mL (0.2 nmol/L) when plasma glucose is <3.0 mmol/L.

4.1.4 Glucagonoma

Glucagonomas originate in the α -cells of the pancreas. Marked elevation in glucagon is generally seen (>500 pg/ml), though some patients may not have such a high level. Mild glucagon elevations may also accompany hypoglycaemia, fasting, sepsis, acute pancreatitis, and renal and hepatic failure. Serum glucagon should be measured 3 and 6 months post-therapy, then every 6–12 months for 3 years, then as clinically indicated.²³

4.1.5 Somatostatinoma

Somatostatinomas are rare NETs of D cell origin, most often in the duodenum or pancreas. Not all secrete somatostatin, although a fasting somatostatin level of >160 pg/ml is suggestive of the diagnosis. Somatostatin levels should be measured 3 and 6 months post-therapy, then every 6–12 months for 3 years, then as clinically indicated.²³

4.2 Carcinoid

Elevated urinary excretion of 5-hydroxyindoleacetic acid (5-HIAA) is seen in serotonin-producing midgut carcinoid tumours, although urinary 5-HIAA may only have around 73% sensitivity for metastatic carcinoid tumours.²⁵ Foregut and hindgut carcinoids seldom secrete serotonin as they lack the enzyme to convert 5-hydroxytryptophan (5-HT) to serotonin, and therefore to 5-HIAA. Urinary serotonin levels may be a more reliable marker in these carcinoids, as 5-HT released into the systemic circulation is converted to serotonin by DOPA decarboxylase inhibitor in the kidney.

False-positive elevations in 5-HIAA may be seen in malabsorption syndromes, with excessive intake of serotonin or tryptophan-rich foods (patients should avoid avocados, bananas, pineapples, plums, tomatoes, kiwi fruit, dates, grapefruit, walnuts for 48h as well as coffee, alcohol and smoking before testing) and in association with paracetamol due to assay interference.

Bronchopulmonary (BP) NETs comprise up to 30% of all NETs²⁶ and may secrete 5-HIAA, as well as adrenocorticotrophic hormone (ACTH) and growth hormone releasing hormone (GHRH) so measurement of urinary free cortisol and insulin-like growth factor-1 (IGF-1) may be of value depending on the clinical picture.

In the follow up of NETs, the use of 5-HIAA for monitoring response to therapy is thought to be less useful than monitoring CgA. In metastatic disease, biochemical monitoring by 5-HIAA and CgA should take place every 6 months indefinitely.

4.3 Pheochromocytoma/Paraganglioma

Suspected pheochromocytoma and paraganglioma should be investigated using 24-hour urinary collection for either metanephrines or plasma metanephrines. In the investigation of sporadic disease, the use of urinary metanephrines may be the best approach as this test has high specificity. When screening for disease in patients with inherited tumour syndromes, the highly sensitive plasma metanephrine test will identify disease at an early stage. False-positives are reduced by drawing blood for plasma metanephrines with the patient supine.²³ Following surgery, metanephrines should be measured at 3 and 6 months, then every 6 months for 3 years, then annually thereafter. In more aggressive and metastatic disease, monitoring may need to be more frequent.

4.4 Recommendations

- **All patients with a confirmed GEP NET should have a baseline CgA, CgB, and 24-hour urine collection for 5-HIAA. Elevated levels of these markers can be used to monitor response to therapy and disease progression.**
- **A full gut hormone screen should be performed in all pancreatic NETs and consideration given to more detailed endocrine investigation if there are symptoms suggestive of a functioning tumour.**
- **Pheochromocytoma and paraganglioma should be investigated using plasma or urine metanephrines.**

5. Surgical Management of Gastroenteropancreatic NETs

5.1 Surgical Principles

The following general principles should be kept in mind when considering the surgical management of gastroenteropancreatic (GEP) NETs.

- Patients with localised NETs should be considered for surgical resection.
- Surgery should be offered to patients who are fit and have limited disease (i.e. primary tumours and/or disease limited to regional lymph nodes).
- Resection of recurrent or metastatic tumours should be considered for fit patients.
- Resection of locally advanced tumours should be performed to achieve negative margins; this may include *en bloc* resection of adjacent organs (e.g. spleen, kidney, pancreas, small or large intestine, vena cava).
- Liver resection or ablative therapies should be considered for patients with metastatic disease.
- The extent of the tumour, its metastases, and secretory profile should be determined as far as possible before planning treatment.
- Incidentally identified lesions that are suspected of being NETs require multidisciplinary assessment before consideration of resection by a surgeon experienced in the management of NETs.
- For patients who are not fit for surgery, the aim of treatment is to improve and maintain an optimal quality of life.

5.2 GEP NETs

Surgery is the only curative treatment for GEP NETs and should be planned under the guidance of a specialised MDT. As with all GEP tumours, surgery aimed at achieving a cure is dependent on presentation and stage of disease.

Specific issues in carcinoid patients include determining the extent of local and distant tumours, identification of synchronous non-carcinoid tumours, recognition of fluid and electrolyte depletion from diarrhoea, and in advanced cases, detection of carcinoid syndrome and of cardiac abnormalities.

5.3 Prevention of Carcinoid Crises

When a functioning carcinoid tumour is found before surgery, a potential carcinoid crisis should be prevented by prophylactic administration of octreotide, given by constant intravenous infusion prior to and for at least 48 hours after surgery. Similar prophylactic measures may be required for pancreatic and periampullary NETs (e.g. glucose infusion for insulinoma, oral or infusion proton pump inhibitor therapy and intravenous octreotide for gastrinoma).

5.4 Surgery for GEP NETs

The surgical approach for GEP NETs depends on a number of factors, including the anatomical site, specific location of the tumour(s), tumour size, type, potential for or actual presence of metastases, and other presenting factors.

A number of other points should also be taken into account when considering surgery for the different GEP NETs. Surgery for appendiceal and small intestinal carcinoids may involve emergency surgery to deal with the acute presentation followed by definitive elective surgery once the diagnosis of carcinoid tumour has been established. The extent of surgery may vary; resections for NETs can range from relatively simple enucleation for well-localised non-malignant tumours to radical resections such as distal pancreatectomy and pancreaticoduodenectomy. Stomach

and pancreatic NETs may take many forms. Stomach NETs, for example, can be divided into distinct types (Type I, Type II and Type III), while pancreatic NETs may be non-functioning or be secreting specific hormones, each requiring different surgical approaches. Surgery for pancreatic nets should be undertaken in specialist hepatopancreatobiliary units, and biochemical diagnosis prior to surgery may provide some indication of the site of the tumour (e.g. gastrinoma triangle) and the risk of malignancy (e.g. low with insulinoma).

The characteristics of the different GEP NETs and associated surgical approaches are outlined in Table 1.

Table 1: Surgical approaches for GEP NETs.¹

Anatomical site	NET size, type or specific location	Surgical approach
Adrenal gland	Phaeochromocytoma: resectable	Laparoscopic or open adrenalectomy
	Phaeochromocytoma: unresectable or with distant metastases	Laparoscopic or open adrenalectomy with maximal cytoreduction +/- medical treatment
Appendix	<2 cm and confined to the appendix	Appendicectomy only
	>2 cm or following excision with incomplete margins	Re-exploration and right hemicolectomy
Pancreas	Pancreas: non-functioning	Laparoscopic pancreatic resection, distal pancreatectomy or pancreaticoduodenectomy
	Gastrinoma: pancreatic head, peripheral location, resectable	Laparoscopic or open enucleation +/- periduodenal lymph node dissection
	Gastrinoma: pancreatic head, deeper location or close to main pancreatic duct	Pancreaticoduodenectomy +/- periduodenal lymph node dissection
	Gastrinoma: pancreatic tail	Enucleation or distal pancreatectomy
	Insulinoma	Laparoscopic or open enucleation, pancreaticoduodenectomy or distal pancreatectomy
	Glucagonoma: usually pancreatic tail	Distal pancreatectomy +/- peripancreatic lymph node dissection
	Vipoma	Pancreaticoduodenectomy or distal pancreatectomy
Rectum	<2 cm	Endoscopic mucosal resection or transanal resection
	>2 cm	Anterior resection or abdominal perineal resection
Small intestine	Jejunum or ileum	Small bowel resection +/- locoregional lymphadenectomy
	Duodenum	Depending on the extent of involvement: <ul style="list-style-type: none"> • Endoscopic mucosal resection • Local excision +/- locoregional lymphadenectomy • Pancreaticoduodenectomy

Anatomical site	NET size, type or specific location	Surgical approach
Stomach	Type I gastric NETs: <ul style="list-style-type: none"> • Related to hypergastrinaemia • Usually small (mms rather than cms) • Multiple • Associated with achlorhydria (chronic atrophic gastritis) • Low frequency of direct invasion into muscle • Low metastatic potential 	<ul style="list-style-type: none"> • In most cases only annual endoscopic surveillance is required • If surgery is required, limited to endoscopic polypectomy, endoscopic mucosal resection or antrectomy, particularly when B12 deficiency anaemia is compounded by iron-deficiency anaemia due to gastric NET bleeding
	Type II gastric NETs: <ul style="list-style-type: none"> • Related to hypergastrinaemia • Usually small • Multiple • Occur in patients with hypergastrinaemia due to Zollinger-Ellison syndrome in combination with MEN1 syndrome • Low metastatic potential 	Small tumours with no extension into muscle on EUS or CT can be resected endoscopically; a combined laparoscopic and endoscopic technique has been described
	Type III gastric NETs: <ul style="list-style-type: none"> • Not associated with elevated gastrin • Often larger than Type I and II gastric NETs (measuring several cms) • Solitary • Usually have malignant potential • Have often metastasised at the time of diagnosis 	Most lesions need resection, regional lymph node dissection and are treated as per gastric adenocarcinomas.

5.5 Recommendations

- **Patients with localised NETs should be considered for surgical resection.**
- **Surgery should be offered to patients who are fit and have limited disease (i.e. primary tumours and/or disease limited to regional lymph nodes).**
- **Resection of recurrent or metastatic tumours should be considered for fit patients.**
- **Resection of locally advanced tumours should be performed to achieve negative margins; this may include *en bloc* resection of adjacent organs.**
- **Liver resection or ablative therapies should be considered for patients with metastatic disease.**
- **The extent of the tumour, its metastases, and secretory profile should be determined as far as possible before planning treatment.**
- **Incidentally identified lesions that are suspected of being NETs require multidisciplinary assessment before consideration of resection by a surgeon experienced in the management of NETs.**
- **Octreotide therapy should be commenced prior to resection of primary or metastatic functional NETs.**
- **For patients who are not fit for surgery, the aim of treatment is to improve and maintain an optimal quality of life.**

6. Pathological Assessment of NETs

6.1 General Principles

There should be at least one nominated histopathologist in each region with an interest in NETs; this individual(s) should also be a member of the local NET MDT. Ideally all NETs, however small, should be notified to the nominated pathologist or MDT coordinator so that a local registry can be maintained, which in turn will allow better assessment of the true incidence of such tumours. Local arrangements may dictate that BP NETs are best managed initially in a lung cancer MDT meeting. Subsequent management will be either by NET or lung cancer MDT determined by local arrangements.

Handling of biopsies and resection specimens should follow the guidelines published by the Royal College of Pathologists for tumours of the GEP tract, including pancreas²⁷ and lung.²⁸ While there is currently no requirement to retain frozen tumour tissue for diagnostic purposes, it would be advantageous to establish a tumour bank of frozen NETs for future research.

Histological recognition of NETs utilises morphological assessment supplemented with immunochemistry with antibodies to CgA, synaptophysin and cluster of differentiation 56 (CD56, also referred to as neural cell adhesion molecule, NCAM); it is recommended that all three antibodies are utilised as variable staining may be seen in some tumours.

The behaviour of GEP and BP NETs differs and the two should be considered separately; GEP NETs are considered here while BP NETs are considered in Section 8.

6.2 Pathological Assessment of GEP NETs

The proliferation index should be assessed in all GEP tumours using the Ki-67 (MIB-1 clone) and mitotic count assessed per 10 high-power fields (hpf, where 1 hpf = 0.2 mm);²⁷ if the tumour sample is large enough, 40 fields should be counted. Opinions vary internationally regarding the utility of assessing the Ki-67 proliferation index. In Europe the Ki-67 is considered an integral part of pathological grading^{29, 30} whereas in North America its use is more controversial.³¹

While immunohistochemical demonstration of specific hormone production by pancreatic NETs may be of some prognostic significance, there is uncertainty and routine staining is currently not recommended.²⁷ There is some evidence that cytokeratin 19 (CK19) positivity is of prognostic significance³² though this finding requires validation. None the less routine staining for CK19 is recommended.

Appendiceal NETs should be classified according to current Royal College of Pathologists²⁷ and World Health Organization (WHO)³³ guidelines. There is uncertainty, however, about the classification of goblet cell carcinoid tumours of the appendix. As arguments exist for these tumours being either NETs or *de novo* mucinous adenocarcinomas,³⁴ these tumours are best considered as an entity distinct from other appendiceal NETs. The classification proposed by Tang *et al.*,³⁵ which separates tumours into three groups based on morphological criteria, should be used (as detailed in the Royal College of Pathologists guidelines²⁷).

There is disagreement between the European Neuroendocrine Tumour Society (ENETS) and the 2009/7th edition of the American Joint Committee on Cancer/Union

for International Cancer Control (AJCC/UICC) tumour, node, metastases (TNM) staging criteria for NETs of the GEP tract and pancreas.³⁶ To avoid confusion and to facilitate interpretation of comparative data it is recommended that the current Royal College of Pathologists guidelines²⁷ are used for staging, not those in the 7th edition of AJCC/UICC TNM.³⁶

6.3 Recommendations

- **The proliferation index of GEP NETs should be assessed in all tumours using Ki-67 (MIB-1 clone) and mitotic count.**
- **In pancreatic NETs, CK19 positivity may be of prognostic significance so routine staining for CK19 should be performed.**
- **GEP and appendiceal NETs should be classified according to current Royal College of Pathologists and WHO guidelines.**
- **Goblet cell carcinoid tumours of the appendix should be classified using the Royal College of Pathologists guidelines.**
- **The Royal College of Pathologists guidelines should be used for staging.**

7. Management of Goblet Cell Carcinoids

Goblet cell carcinoids or adenocarcinoids of the appendix are tumours expressing both neuroendocrine and mucinous differentiation. They have malignant potential following a more aggressive clinical course than classical appendiceal NETs and are associated with a worse prognosis, probably due to the mucinous component.³⁷ Thus for most patients it is appropriate to manage their disease using similar principles to the management of colorectal adenocarcinoma.³⁸ Due to a high incidence of synchronous and metachronous GEP neoplasms, GEP follow-up is also recommended.³⁹

7.1 Localised Disease

If localised disease is diagnosed following an initial appendicectomy, right hemicolectomy should be considered for patients with tumours >1 cm.³⁹ Salpingo-oophorectomy is sometimes recommended for female patients. Although there are no clinical trials, many centres recommend fluoropyrimidine-based adjuvant chemotherapy as for colorectal cancer.³⁹ CgA has not been shown to be a useful marker for follow up in these tumours, but carcinoembryonic antigen (CEA) can be.³⁷

7.2 Advanced Disease

Patients with advanced disease should be considered for surgery or chemotherapy using similar protocols as for colorectal cancer management.³⁹ Hormonal therapies are unlikely to be effective in these patients, although they may be considered in the rare patient in whom receptors are expressed by the tumour on imaging.

7.3 Recommendations

- **Goblet cell carcinoids or adenocarcinoids of the appendix are more aggressive than classical appendiceal NETs and should be managed as colorectal adenocarcinomas.**

8. Management of Bronchopulmonary NETs

8.1 Definition

Bronchopulmonary (BP) neuroendocrine tumours (NETs) encompass a spectrum of lung tumours; classified in four separate categories:⁴⁰

- Typical (or classical) carcinoid tumours
- Atypical carcinoid tumours
- Large cell neuroendocrine tumours (LCNET)
- Small cell lung cancer (SCLC)

LCNET is considered a variant of non-small cell lung cancer (NSCLC). The management of LCNET and SCLC is generally under the auspices of the Lung Cancer service and the healthcare professionals associated with the Lung Cancer MDTs. However the management of LCNET may be either by lung cancer or NET cancer teams depending on local arrangements. From a histological, immunohistochemical and molecular biological perspective, LCNET and SCLC are clearly distinct and will therefore not be discussed in this document.

From SCNET perspective, BP NETs effectively equate with BP carcinoid tumours, both typical and atypical.

8.2 Clinical Features

BP carcinoids can be:

- Central (arising in main or lobar bronchi)
- Peripheral (arising in distal bronchi or lung parenchyma).

Central carcinoids typically present with haemoptysis, cough or with features associated with lobar or segmental collapse. Often evident at bronchoscopy, the macroscopic appearance of central carcinoids tends to be characteristic, with a smooth surface and reddish/tan or cherry appearance. Significant bleeding after biopsy has been described⁴¹ and for that reason, biopsy is sometimes avoided.

Peripheral carcinoids are often incidental findings and their management is that of the undiagnosed solitary pulmonary nodule, with lung cancer being one of the differential diagnoses. Histological diagnosis of peripheral BP carcinoid is often at frozen section and/or at post-resection histology.

8.3 Selection for Surgery

Surgical resection should be considered in all patients who are fit and have limited disease. Assessment of patients should be identical to that of lung cancer patients; guidelines for the radical management of patients with lung cancer have been compiled by the British Thoracic Society.⁴² The value of PET/CT for both characterisation of the primary tumour and nodal/distant metastases in BP carcinoids is the subject of debate; the balance of opinion currently favours the use of PET/CT where the diagnosis of BP carcinoid is proven or suspected.⁴³

Patients with BP carcinoid tumours seldom present with or exhibit features of carcinoid syndrome.⁴⁴ However on the rare occasion when the carcinoid does represent a functional NET, octreotide therapy should be started prior to surgical resection of the carcinoid tumour.

The principles of BP carcinoid resection are similar to that of most tumours, namely to achieve complete resection with wide and clear margins. In most cases this means an anatomical lung resection with systematic nodal dissection. Occasionally, wedge resection may be appropriate. Although BP carcinoid tumours are considered malignant, albeit low-grade, tumours, pneumonectomy should seldom be necessary in uncomplicated cases.⁴⁵ In certain cases, especially in the medically unfit, repeated local ablation with laser or cryotherapy may be an alternative to anatomical lung resection.^{46, 47}

8.4 Staging

While BP carcinoid tumours account for <5% of all lung cancers, they should still be considered as lung cancers and staged accordingly; the International Association for the Study of Lung Cancer (IASLC) Staging Project recommends that TNM be applied to BP carcinoid tumours.⁴⁸

BP NETs should be classified according to the 2004 WHO classification³³ and staged using TNM7. This WHO classification has been criticised for retaining the carcinoid nomenclature⁴⁰ but the term has been retained in part to reflect the difference in behaviour of many of these tumours from their counterparts in the gastrointestinal tract.

8.5 Pathology

BP NETs effectively equate with BP carcinoid tumours, both typical and atypical.⁴⁹

- Typical carcinoids are histologically typified with a carcinoid morphology with <2 mitoses per 2 mm² and no necrosis; these tumours seldom metastasise and 5-year survival is 87–100%.
- Atypical carcinoids have a carcinoid morphology with 2–10 mitoses per 2 mm² and/or necrosis; metastases (nodal or systemic) are relatively common compared with typical carcinoids, and 5-year survival is 25–69%.

Most BP carcinoids are typical. Tumours showing carcinoid morphology and a mitotic count of >10 per 2 mm² are regarded as LCNET and in the WHO classification fall into the large-cell category rather than carcinoids.⁵⁰ It is important to note that the criteria for classification of these lesions in the lung (and thus prognosis) are solely based on the mitotic count and that the Ki-67 proliferation index is not used.

8.6 Follow up

Given that BP carcinoids are considered as part of the spectrum of lung tumours, identification and registration should be under the auspices of the local Lung Cancer MDT. Management following surgery should be by team's expert in managing NETs, depending on local arrangements this maybe either by NET cancer teams or lung cancer teams. Increasingly these patients are being followed up by NET teams who have greater experience in managing these tumours. Given the risk of late relapse; follow up should be for 10 years. Separate registration and referral to any available regional or national Lung Cancer NET clinic/service is highly desirable.

In BP carcinoids where there is evidence of nodal metastases following resection (N1 or N2), referral to a regional or national NET MDT via the Lung Cancer MDT should be considered.

8.7 Recommendations

- **Surgical resection should be considered in all patients who are fit and have limited disease.**
- **The principal aim is to achieve complete resection with wide and clear resection margins.**
- **Initial assessment of patients should be identical to that of lung cancer patients. However once a BP NET is confirmed, appropriate specialist investigations are required.**
- **BP NETs should be classified according to the 2004 WHO classification³³ and staged using TNM7.**
- **On the rare occasion where the carcinoid does represent a functional NET, octreotide therapy should be commenced prior to surgical resection of the tumour.**
- **Long term follow is advised in view of the higher risk of late relapse by clinics expert in managing NET cancers.**

9. Medical Therapy and New Drug Treatments

9.1 Somatostatin

Somatostatin is a peptide hormone produced by the central nervous system and gastrointestinal tract that binds with high affinity to five G-protein coupled transmembrane receptors (SSTR1–5) and inhibit hormone release. Naturally occurring somatostatin is an important regulator of exocrine and endocrine secretion of several hormones (notably glucagon, insulin, gastrin, thyroid stimulating hormone [TSH] and growth hormone [GH]) and exerts an endocrine inhibitory effect by inhibiting GH secretion by the anterior pituitary.

Somatostatin receptors are present in approximately 70–95% of NETs but are found less commonly (<50%) in insulinoma and poorly differentiated NETs.⁵¹ Most gastro-entero-pancreatic NETs over-express SSTR2, which makes this the current major target for medical therapy.⁵²

9.2 Somatostatin Analogues

Somatostatin analogues remain the most effective and commonly used agents in the medical treatment of NETs.⁵¹ Octreotide and lanreotide are the only two synthetic somatostatin analogues currently approved for clinical use; these agents bind with:⁵³

- High affinity to SSTR2 and 5
- Medium affinity to SSTR3
- Low affinity to SSTR1 and 4.

Initially, octreotide was only available as a short-acting preparation requiring two or three daily subcutaneous injections but more recently it has become available as a long-acting (28-day) formulation. Similarly, lanreotide is also available as intermediate (7–14 days) and long-acting (28-day) formulations. Conventional clinical practice has been for patients to be stabilised (and establish tolerability) on short-acting octreotide for 10–28 days before conversion to long-acting somatostatin analogues but there are now safety and tolerability data supporting the use of long-acting analogues at therapy initiation.⁵¹ Although patients with NETs with no ¹¹¹In-octreotide uptake during diagnostic imaging respond less well to somatostatin analogues, a 3-month trial of therapy is usually worthwhile if the patient is symptomatic.⁵⁴

Symptomatic control occurs in most patients in response to somatostatin analogue therapy and biochemical improvement is seen in 30–70% of patients.^{55, 56} Somatostatin analogue therapy is, in general, well tolerated; side effects include gastrointestinal upset, hypo- and hyperglycaemia, headaches and dizziness.⁵⁷ Cholelithiasis has been reported in up to 50% of patients but few (1–3%) develop symptoms severe enough to warrant cholecystectomy.⁵⁸

Until recently, the anti-proliferative and disease-stabilising effects of somatostatin analogues on NETs were unclear; evidence of survival advantages and disease stabilisation came from a series of small retrospective case series and phase II clinical trials.^{59–66} In recognition of this lack of evidence, the PROMID trial was initiated; this is one of the first, phase III, placebo-controlled, randomised studies in patients with metastatic NETs of the midgut.⁶⁷ Clinical trials of the anti-proliferative effect of somatostatin analogues used the maximum licensed dose, Patients in this study were randomised to placebo or long-acting release octreotide (octreotide LAR 30 mg every 28 days) and the primary endpoint was time to disease progression. Trial enrolment was stopped halfway into recruitment (of only 85 patients) after an

interim analysis demonstrated a clear benefit for octreotide LAR. Median time to tumour progression was 14.3 months with octreotide and 6 months with placebo ($p < 0.001$). Similarly, after 6 months of treatment, stable disease was observed in 66.7% with octreotide and 37.2% with placebo. The response was similar in patients with functionally active or functionally inactive tumours. The hazard ratio for overall survival was 0.81 (95% CI: 0.30; 2.18); however, because of the low numbers of observed deaths in both groups (7 with octreotide and 9 with placebo), the survival analysis was not confirmatory.

While the PROMID trial was the first to demonstrate that somatostatin analogue therapy had anti-proliferative and disease-stabilising effects as well as providing symptomatic relief in metastatic grade 1 small intestinal NETs, this result has also recently been confirmed (albeit in a slightly different patient cohort) in the Controlled study of Lanreotide Antiproliferative Response in NET (CLARINET) trial, for patients with grade 1 or 2 gastroenteropancreatic NETs.⁶⁸ This trial included 200 patients with metastatic enteropancreatic NETs (grade 1 or grade 2 tumours; Ki-67 $< 10\%$) who received slow-release lanreotide (lanreotide autogel 120 mg every 28 days). The study was designed with a 2-year treatment period; median time to progression was 18 months with placebo but was not reached with lanreotide ($p < 0.001$). Progression-free survival at 24 months was 65.1% with lanreotide compared with 33% with placebo. Subgroup analyses generally had lower power, but the effect appeared to be consistent for both small intestinal and pancreatic tumours. Although not directly comparable due to clear differences in inclusion criteria and data analysis, the PROMID and CLARINET trials still confirm the anti-proliferative effects of long-acting somatostatin analogues in patients with metastatic NETs. It should be noted that, in both trials, the maximum licensed dose of somatostatin analogue (based on the dose-response curve for the anti-proliferative effects *in vitro*) was used from the time of entry into the trial. Thus, when possible, patients with NETs should be commenced on a maximum somatostatin analogue dosage rather than titrating dose according to clinical response.

9.3 Resistance to Somatostatin Analogues

Unfortunately not all NET patients respond to somatostatin analogue therapy and, even in those who do, the effects of treatment decline over time.⁶⁹ The mechanisms underlying the development of treatment-resistant states are unclear but may be due to altered receptor signalling and/or receptor degradation. SSTR subtypes can undergo heterodimerisation with each other leading to increased binding affinity.⁷⁰ Thus, novel somatostatin analogues that bind to multiple receptor subtypes (e.g. pasireotide, which binds to SSTR1, 2, 3 and 5) may prove to be effective in patients refractory to octreotide or lanreotide.⁷¹ Data supporting the anti-proliferative effects of pasireotide are currently lacking,^{72, 73} but the results from phase II trials are promising in terms of tolerability and symptomatic benefit. Similarly, somatostatin receptors may also heterodimerise with other G-protein coupled receptors such as the dopamine D2 receptor.⁷⁰ There are cases where dopamine agonists have been used in combination with octreotide/lanreotide with a beneficial outcome, although *in vitro* studies are less convincing.⁷⁴ In addition, chimeric compounds incorporating both dopaminergic and somatostatinergic agents have been developed and are undergoing further investigation in NET treatment.⁷⁵

Thus, somatostatin analogues remain the first-line medical treatment of NETs with almost universal clinical benefit, biochemical response in up to 70% of patients and anti-proliferative/tumour-stabilisation effects. However, the development of tolerance to such therapy in most patients over time has resulted in the development of novel

alternative or additional therapies, although further clinical outcome data will be required before these approaches become routine clinical practice.

9.4 Interferon- α (IFN- α)

While somatostatin analogues remain first-line agents in the medical management of NETs, interferon- α (IFN- α) has been recommended as a second-line agent for symptom control in patients who fail to tolerate somatostatin analogues.⁵⁴ Data do not demonstrate an anti-proliferative role for IFN- α in metastatic NET but the possibility that IFN- α may have anti-proliferative activity cannot be excluded as trials were underpowered. This is therefore not yet a recommended first-line treatment approach due to the small numbers of patients included in such studies.⁷⁶ Finally, while there is some evidence that long-acting pegylated IFN- α may be better tolerated and more convenient than IFN- α , pegylated IFN- α is not yet approved for use in NET treatment.⁵⁴

9.5 New and Emerging Drug Treatments

A number of new and emerging drug treatments are currently available or being investigated in the treatment of NETs (www.clinicaltrials.gov/ct2/results?term=neuroendocrine). Of these newer agents, those in current clinical use include:

- Everolimus
- Sunitinib

9.6 Everolimus

Everolimus, a mammalian target of rapamycin (mTOR) inhibitor, is a serine/threonine kinase involved in the integration of signals from numerous growth factor pathways. The activity of everolimus has been investigated in both pancreatic and non-pancreatic NETs.

Evidence for the use of everolimus in progressive pancreatic NET comes from a large, double-blind, placebo-controlled trial.⁷⁷ In this study, 410 patients with progressing low- or intermediate-grade pancreatic NETs (97% of whom had a performance status of 0 or 1) were randomly assigned to everolimus 10 mg daily or placebo.⁷⁷ At the point of radiological progression, patients who had been assigned to placebo were offered open-label everolimus. After a median follow up of 17 months there was a significant improvement in progression-free survival with everolimus versus placebo; progression-free survival was 11.0 months with everolimus versus 4.6 months with placebo (hazard ratio 0.35; 95% CI: 0.27; 0.45, $p < 0.001$). Pre-specified subgroup analyses indicated that the benefit was maintained across subgroups. The most common drug-related adverse events were stomatitis, rash, diarrhoea, fatigue, infections, peripheral oedema and anorexia, and the most common grade 3 and 4 adverse events were stomatitis and anaemia.

Evidence for the use of everolimus in non-pancreatic NET comes from a large, double-blind, placebo-controlled trial.⁷⁸ In this trial, 429 patients with low- or intermediate-grade non-pancreatic NETs with a history of secretory symptoms and disease progression over the previous 12 months were randomised to receive sandostatin LAR (30 mg every 28 days) and everolimus (10 mg daily) or sandostatin LAR (30 mg every 28 days) and placebo. Median progression-free survival was again longer in the everolimus group than in the placebo group; progression-free survival was 16.4 months (95% CI: 13.7; 21.2) with everolimus versus 11.3 months (95% CI: 8.4; 14.6) with placebo. Benefit was observed across all pre-specified subgroups. The toxicity reported in this trial was equivalent to that seen in the pancreatic NET trial.

Everolimus is both licensed and funded for the treatment of unresectable pancreatic NETs in Scotland. It would be appropriate to use the drug in patients who would have fulfilled trial entry criteria, patients with low and intermediate grade advanced pancreatic NETs which had progressed over the previous 12 months.⁷⁸ Patients may be of performance status (PS) 0, 1 or 2; although very few in the trial were of PS 2. At present everolimus is not approved for use in non-pancreatic NETs.

9.7 Sunitinib

Sunitinib is an oral, small-molecule, multi-targeted receptor tyrosine kinase (RTK) inhibitor. Targets include all receptors for platelet-derived growth factor (PDGF) and vascular endothelial growth factor (VEGF) receptors that play a role in angiogenesis and tumour cell proliferation. In addition, sunitinib inhibits other RTKs (e.g. the ret proto-oncogene [RET], the receptor for M-CSF [CSF-1R] and the Fms-like tyrosine kinase-3 receptor [FLT3]).

Evidence for the use of sunitinib in progressive pancreatic NET comes from a double-blind, placebo-controlled phase III trial that demonstrated significant benefit in progression-free survival compared with placebo.⁷⁹ The trial included 171 patients with advanced, well-differentiated, progressing pancreatic NETs who were randomised to receive sunitinib 37.5 mg daily continuously, or placebo. The study was closed early after only 171 patients had been recruited, due to the observation of more serious adverse events and deaths in the placebo group. At this time there was also a significant difference in time to tumour progression between the groups (11.4 months with sunitinib versus 5.5 months with placebo). The study was unblinded at this point and patients on placebo were offered sunitinib. Longer follow up of these patients has not confirmed a significant survival benefit for sunitinib therapy, but these results will be confounded by both small patient numbers and the crossover of patients onto sunitinib when the trial was closed. Sunitinib was associated with moderate toxicity in this trial. The most common toxicity was diarrhoea, although this was only grade 3–4 in 5% of patients. Other toxicities significantly more common with sunitinib than placebo included nausea, vomiting, asthenia, fatigue, hair colour changes, myelosuppression, hypertension, palmar-plantar erythrodysesthesia, stomatitis, dysgeusia and epistaxis.

Sunitinib is both licensed and funded for the management of patients with pancreatic NETs in Scotland. In view of the toxicity of the therapy, however, it should be used in the same way as in the trial, that is, in patients with well-differentiated pancreatic NETs, with good performance status (0–1) and with evidence of disease progression over the previous 12 months.

9.8 Integrating New Drug Therapies into the Management of NETs

The real challenge will be how to integrate new drug therapies into the care of patients with NETs. This is complicated by differences between patients, patient preferences, and differing tumour biology, as well as the lack of data on which to base decisions on systemic therapies for specific NETs. Treatment options for individual patients in Scotland at the current time are therefore likely to depend on drug availability and local expertise until more robust data are available. Due to the relatively long natural history of the disease in some patients, it is likely that during the course of their illness they would be able to receive somatostatin analogues, sunitinib, everolimus and systemic chemotherapy (as appropriate), were these agents all available.

Finally, it is likely that combination therapy may be needed to improve clinical outcomes. Somatostatin analogues, for example, may need to be combined with the molecular-based therapies (e.g. VEGF and mTOR inhibitors). Phase II trials, for example, showed benefit from the addition of the anti-VEGF monoclonal antibody (bevacizumab) or an mTOR inhibitor (everolimus) to octreotide monotherapy in carcinoid and metastatic pancreatic NETs, respectively.^{80, 81}

9.6 Recommendations

- **Somatostatin analogues should be used as first-line agents for the medical management of symptomatic NETs.**
- **Prior use of short-acting somatostatin analogues and dose titration of sustained-release somatostatin analogues now not required; commence maximal dose of sustained-release somatostatin analogues at treatment initiation. However in very symptomatic patients, short term use of subcutaneous SMS analogues may be necessary.**
- **INF- α should be reserved as a second-line agent for symptomatic relief in patients who fail to tolerate or show no benefit from somatostatin analogue therapy.**
- **Everolimus may be considered in patients with progressing pancreatic NETs where the tumour is well or moderately-differentiated and the patient is of PS 0, 1 or possibly 2 with adequate organ function.**
- **Sunitinib may be considered in patients with progressing pancreatic NETs where the tumour is well -differentiated and the patient is of PS 0 or 1 with adequate organ function.**

10. Chemotherapy

NETs represent a diverse group of cancers with different responses to chemotherapy. Many tumours are slow growing and never reach the stage where chemotherapy is required. However, there is a subgroup of NETs that is aggressive and that requires chemotherapy at an early stage or as the definitive treatment.

10.1 General Considerations

A number of factors need to be borne in mind when considering chemotherapy for NETs:

- High-grade (G3) tumours (Ki-67 index >20%) should be distinguished from intermediate-grade (G2) and low-grade (G1) tumours (Ki-67 <20%)
- Pancreatic NETs should be considered separately from small intestinal NETs
- While in the older literature NETs of all subtypes were considered together, differential response types with differing sites of origin are now recognised.

Furthermore:

- Carcinoids and well-differentiated NETs tend to be relatively chemoresistant
- Poorly differentiated G3 tumours are often highly chemosensitive although remissions are often of short duration
- Pancreatic NETs are moderately chemosensitive (response rates 20–60%) with remissions that may last at least 12 if not 24 months.

The response to chemotherapy of different NETs is summarised in Table 2.

Table 2: Summary of the response to chemotherapy of different NETs.

Characteristic	Response to chemotherapy
Pancreatic NETs	Moderately chemosensitive with remissions of relatively long duration
Well-differentiated NETs (non-pancreatic) (G1 and G2; Ki-67 index <20%)	Chemoresistant
Poorly differentiated NETs (G3)	Highly chemosensitive but for a short duration

10.2 Choice of Chemotherapy Agents

Different chemotherapy agents are used for different tumour types.

10.2.1 Well-Differentiated and Pancreatic NETs

At present, streptozotocin (STZ)-based regimes are central to the management of well-differentiated and pancreatic NETs. For well-differentiated NETs, for example, STZ combined with doxorubicin (DOX), 5-fluorouracil (5-FU), or dacarbazine (DTIC) or varying combinations of these agents have been used with responses generally between 15–30%. Relatively few clinical trials have been conducted but one of the earliest trials compared STZ/DOX with STZ/5-FU.⁸² In reality there is probably little to choose between the different combinations, and individual clinicians or treatment centres will have their preferred regimen.

Relatively recently, a number of other chemotherapy agents and regimens have been assessed for the treatment of well-differentiated and pancreatic NETs. Capecitabine (CAP; a prodrug that is converted to 5-FU in the body) was introduced in the last 5 years and may be used as an alternative to 5-FU as shown by the phase II study that demonstrated a response rate of about 30% to single-agent CAP.⁸³ The place of cisplatin (CIS) was assessed in the UK NET01 study that compared STZ/CAP with CIS/STZ/CAP.⁸⁴ The results of this study showed little difference in outcome with slightly more toxicity in the three-drug arm. Other schedules that have been investigated recently include temozolomide (TMZ)/CAP in pancreatic NETs. While essentially a variant of a 5-FU/DTIC regimen, this TMZ/CAP regimen resulted in a 70% response rate in a single retrospective case series in the USA.⁸⁵ If confirmed, this could become a significant schedule and may even become the first-choice regimen for well-differentiated NETs. It has been noted that patients with O(6)-methylguanine DNA methyltransferase (MGMT) deficiency have a differential response rate to TMZ. Although routine testing is not always available, this may be considered and help with tailoring therapy for individual patients.

Other agents that have been investigated for well-differentiated and pancreatic NETs include other platinum (e.g. oxaliplatin [OX]) as well as irinotecan (IRIN) and gemcitabine⁸⁶. However, none of these drugs has achieved any routine place in treatment to date.

Platinum- and etoposide-based regimens tend to be favoured for high-grade (G3) tumours.

10.2.2 Poorly Differentiated NETs

The first-line chemotherapy used for poorly differentiated NETs of lung and gastrointestinal origin will normally be platinum and etoposide. It is debatable whether there is any difference between carboplatin (CARB) and CIS and local preference is commonly used. High response rates are seen but the duration of response is usually less than 12 months.⁸⁷ A recent study suggested that TMZ (with or without CAP) had activity in this situation.⁸⁸ For poor performance patients, the cyclophosphamide/DOX/vincristine (CAV) or CAV plus etoposide (CAVE) regimen or even single-agent oral etoposide may be considered. Another recent report suggested that the FOLFIRI combination may be active in G3 NETs.⁸⁹

10.3 Relapsed NETs and Second-Line Therapy

Choice of chemotherapy agents for second-line therapy and relapsed NETs is difficult, particularly when the treatment-free interval (TFI) is less than 12 months. Rechallenge with platinum and etoposide may be given if the TFI is over 12 months, otherwise other schedules, or clinical trials, should be considered.

10.4 Sequencing

Other biological agents (somatostatin analogues and interferons) and novel targeted agents (the mTOR pathway inhibitors such as everolimus and temsirolimus, small-molecule TK inhibitors such as sunitinib, and the anti-VEGF monoclonal antibody, bevacizumab) may also be used in the treatment of NETs; these agents are discussed in detail in Section 9. The issue of the sequence of therapy – whether to use chemotherapy before a targeted agent versus initial therapy with a targeted agent – is under review. The SEQTOR study, which opened in late 2014, will compare upfront chemotherapy with a STZ-based regimen versus everolimus initially, with the alternative schedule given at the time of relapse.⁹⁰ At the current time there is debate as to whether chemotherapy remains the first-line choice treatment; the available regimens are summarised in Table 3.

Table 3: The chemotherapy regimens, and biological and novel agents for treatment of NETs

Agents, regimens and indications	
Chemotherapy	
<ul style="list-style-type: none"> • STZ/5-FU • STZ/DOX • STZ/5-FU/DOX +/- DTIC • TMZ/CAP 	Pancreatic NETs
<ul style="list-style-type: none"> • STZ/5-FU • CAP • CAP/STZ • CIS/CAP/STZTMZ +/- CAP 	Well-differentiated GEP NETs
<ul style="list-style-type: none"> • CIS/etoposide • CAV(E) • TMZ/CAP • FOL/F/IRIN 	Poorly differentiated GEP and BP NETs
Biological agents	
<ul style="list-style-type: none"> • Somatostatin analogues (e.g. octreotide and lanreotide) 	First-line medical treatment of symptomatic NETs
<ul style="list-style-type: none"> • Interferons 	Second-line for symptom control in patients who fail to tolerate somatostatin analogues
Novel agents	
<ul style="list-style-type: none"> • Everolimus and other mTOR pathway inhibitors 	G1 and G2 pancreatic NETs
<ul style="list-style-type: none"> • Sunitinib 	G1 pancreatic NETs

10.5 Mixed Tumours

Chemotherapy for goblet cell or mixed endocrine/exocrine tumours (adenoneuroendocrine carcinomas) is being re-evaluated. The contemporary view is that these are not NETs but are of gastrointestinal origin and that they should be treated using gastrointestinal chemotherapy regimens.³⁹ Expert pathology review is important to establish whether these tumours behave as endocrine or non-endocrine tumours, and there are rare examples of collision tumours containing both components. For appendiceal and colonic goblet cell tumours, schedules such as CAPOX, FOLOX or FOLFIRI have been used with modest response rates.

10.6 Scheduling Chemotherapy and Alternative Options

Probably the most difficult issue when treating NETs is when to schedule chemotherapy within the treatment programme. For metastatic disease there are often multiple options that reflect the interest, experience and expertise within a

treatment centre. The MDT should discuss when to offer chemotherapy as part of the algorithm of treatment options.

Alternatives to chemotherapy include radiofrequency ablation, hepatic artery embolisation with or without chemotherapy, peptide receptor radionuclide therapy, surgical resection and novel agents; ideally these options should be incorporated into existing local protocols so that useful information can be learned from their use for specific NETs. SCONET also supports patient entry into clinical trials in this area.

10.7 Recommendations

- **There is wide variation in the chemosensitivity of different types of NET. Anatomical location, grade and proliferation index help to determine the choice of chemotherapy and timing of interventions.**
- **Newer agents may offer potential as many traditional chemotherapy approaches have limited activity. More clinical trials are needed to determine the optimal timing of intervention.**
- **Poorly differentiated (G3) NETS should have chemotherapy with platinum and etoposide combinations.**
- **The MDT should discuss when to offer chemotherapy as part of the algorithm of treatment options.**

11. Interventional Radiology for Hepatic Metastases

The following techniques are currently used to provide locoregional treatment of hepatic metastases:

- Transarterial chemoembolisation (TACE)/hepatic arterial embolisation (HAE)
- Radiofrequency ablation (RFA)
- Radioembolisation (RE).

11.1 TACE/HAE

TACE/HAE is now relatively standard in most medium-to-large centres and should be considered in the symptomatic treatment of neuroendocrine metastases confined to the liver.

On the whole, use of TACE as a locoregional therapy is a third-line option following systemic therapy with somatostatin analogues. Data are limited; a small-scale retrospective study suggested good results for TACE used as a first-line treatment,⁹¹ but there are no prospective, head-to-head data comparing systemic chemotherapy versus TACE/HAE. Good symptom relief of between 70–90%^{91, 92} was demonstrated in retrospective studies when all other therapies were shown to be ineffective. Symptom relief included both hormonal effects and secondary to tumour load (i.e. relief of capsular stretching). No significant difference was demonstrated between the use of TACE versus HAE. However, studies to date have been with conventional TACE (chemoagent and lipiodol) rather than drug-eluting beads, which have a better side effect profile.⁹³ Mean survival with TACE/HAE is reported to be 3.5 years with a mortality rate of 2–4%.⁹⁴ These figures are partly attributable to the fact that this approach is typically considered in patients with large-volume metastatic disease. Consideration of staged procedures should be given in high-volume disease, and careful patient selection involving liver function and performance status is important.

11.2 RFA

Few data are available on the use of RFA; this locoregional approach is often used as an adjunct to surgical resection, although there are data suggesting that RFA can be used as symptom-modifying procedure even in high-volume disease.⁹⁵

11.3 RE

This is an innovative locoregional therapy comprising intra-arterial radiotherapy to the tumour using pure β -emitting ⁹⁰Y microspheres. Promising results in the treatment of metastatic NETs have been described in retrospective and small-volume prospective studies; partial response rates of 50–60% and a median survival of 70 months have been reported,^{96, 97} which are comparable to systemic treatment response rates. RE is not, at present, available on the NHS in Scotland. However relatively large-scale randomised multicentre trials are under way for use of RE in first-line treatment of colorectal metastases, which may pave the way for more widespread use.

11.4 Octreotide Cover for Locoregional Therapy

Severe ischaemia/necrosis of carcinoid liver metastases can initiate a potentially life-threatening carcinoid crisis. Prior to any locoregional therapy, therefore, the administration of long-acting somatostatin analogue sub-cutaneous infusions or intravenous octreotide is recommended, although there is little evidence to guide a regimen and liaison with an endocrinologist is important to set up a local protocol.

11.5 Recommendations

- **Interventional radiology techniques such as TACE have a role in the management of symptomatic hepatic metastases that are poorly responsive to hormonal therapies.**
- **Such procedures are associated with an increased risk of carcinoid crisis and close liaison with an endocrinologist is required before the procedure.**

12. Radionuclide Therapies

12.1 ¹³¹I-mIBG Therapy

Meta-iodobenzylguanadine (mIBG) is a noradrenaline analogue, which, when labelled with ¹³¹I, can be used as a radiotherapeutic agent for the treatment of NETs, including phaeochromocytomas, paragangliomas, neuroblastomas, carcinoids and medullary thyroid cancers in adults. Indications for ¹³¹I-mIBG therapy include:

- As an adjuvant after primary surgery
- Metastatic disease
- Occasionally as primary therapy in patients unfit for surgery.

¹³¹I is a β -emitting radionuclide with a half-life of 8 days; it also has a relatively high photon emission (364 keV), which causes significant radiation protection issues. As a result of this, patients need to be nursed in dedicated, purpose-built, inpatient rooms for several days post-administration by suitably trained and experienced nursing staff. Similarly, there is a requirement for close supervision of the whole procedure by a Medical Physics Expert.

Suitability for ¹³¹I-mIBG therapy takes into account the patient's age, fitness, urinary and faecal continence and ability to give informed consent. Adult patients requiring ¹³¹I-mIBG therapy must be reasonably independent and self-caring to avoid excessive radiation exposure to nursing and other staff on the ward. Suitable patients are identified and counselled about the risks and benefits of the procedure. Appropriate discussions of contraception prior to treatment, during treatment and in follow up must be performed. On the day of the procedure, female patients of child-bearing age (12–55 years) undergo a pregnancy test and are requested to sign to indicate that they are not pregnant. Treatment is not performed if there are any doubts about pregnancy status.

Due to the risk of a hypertensive response to the mIBG, the material is infused slowly over a period of up to 60 minutes. A typical adult treatment dose is 7500–10000 MBq. Much of the ¹³¹I is excreted in the urine in the first day or two, with tumour uptake being only a small percentage of the administered activity. There is some natural localisation of activity in the liver and salivary glands, and a small amount of hepatobiliary excretion.

It is important to block thyroid uptake of any free ¹³¹I iodide released as a breakdown product by administering potassium iodate. For adults this consists of 170 mg potassium iodate daily for 1 day prior to and 14 days after therapy. Alternative blocking agents may be used. To minimise the bladder radiation dose, the patient should be well hydrated and have satisfactory renal function. Certain drugs impair the uptake of mIBG by the tumour (e.g. tricyclic antidepressants, antihypertensives, sympathomimetics, calcium channel blockers) so these treatments should be discontinued prior to therapy.⁹⁸

12.2 Radiopeptide Therapy

Radiolabelled somatostatin analogues can be used to treat somatostatin receptor-positive NETs. The main peptides in use are DOTATOC and DOTATATE, which can be labelled with either of the radionuclides ⁹⁰Y or ¹⁷⁷Lu.^{99, 100}

⁹⁰Y is a pure β -emitter (energy 2.27 MeV) with a half-life of 2.7 days. ¹⁷⁷Lu is a lower energy β -emitter (energy 0.498 MeV) with a half-life of 6.7 days. ¹⁷⁷Lu also emits

photons of energy (208 keV and 113 keV). These are suitable for imaging with a gamma camera which allows post-therapy dosimetry measurements to be made.

Centres tend to use ^{177}Lu rather than ^{90}Y radionuclide as the lower β -particle energy of ^{177}Lu makes it less nephrotoxic. The facility to image after therapy to calculate the delivered radiation dose is also an advantage. However, the higher energy β -emission from ^{90}Y may make this radionuclide more effective for the treatment of larger tumours.

The ^{177}Lu and the DOTATATE can be purchased separately. They are processed to produce ^{177}Lu -DOTATATE in a radiopharmacy; this is a procedure that should be performed or supervised by a radiopharmacist. A commercially produced, pre-formulated ^{177}Lu -DOTATATE has also recently become available.

A dose of 5–8 GBq of ^{177}Lu -DOTATATE is usually administered and the patient usually remains in hospital for at least 1 night. If repeat administrations are performed, radiation dosimetry measurements and calculations are required to ensure that the bone marrow dose remains below 2 Gy and the renal dose remains below 23 Gy. Prophylactic amino acid infusions are also administered to minimise renal toxicity. On the day of the procedure, female patients of child-bearing age (12–55 years) undergo a pregnancy test and are requested to sign to indicate that they are not pregnant. Treatment is not performed if there are any doubts about pregnancy status.

Unlike ^{131}I -mIBG therapy (which has high-energy γ emission), there are no significant hazards associated with external radiation exposure to members of the public after the patient has been discharged. Some care is required when dealing with excreta but this would only become an issue if the patient was incontinent. However, there can be significant issues for the staff preparing and administering the radiopeptides, particularly with regard to finger doses. Close supervision of the whole procedure by a Medical Physics Expert is required. In general, significant medical, radiopharmacy and physics staff time is required for radiopeptide therapy.

12.2.1 Licensing of Radiopeptides

None of the available radiopeptide products are licensed by the Medicines and Healthcare Products Regulatory Agency (MHRA). However, several of the radiopharmaceuticals commonly used for nuclear medicine imaging are also unlicensed and, in practice, this lack of licensing should not be an issue. Basically, the prescribing doctor has to indicate that they are aware of the fact that the product is unlicensed and that they are content to take responsibility for the administration.

12.2.2 Facilities and Expertise

With regard to accommodation, there are no specific requirements associated with the administration of radiopharmaceuticals because of the nature of their radionuclide emissions (mainly β particles). However, it is probably best that administration takes place on a ward where radionuclide therapies are regularly performed. It is important to have nursing staff who are familiar with the care of patients who have received radioactive materials (i.e. they have been trained in ionising radiation safety, have film badges, etc.). This would also mean that suitable equipment (contamination monitors, decontamination kits, etc.) would be present and appropriate documentation (local rules, standard operating procedures [SOPs], etc.) would be in use.

12.2.3 ARSAC Certification

There are no Administration of Radioactive Substances Advisory Committee (ARSAC) certificate holders for radiopeptide therapy in Scotland. These certificates are site specific. Centres that perform ^{131}I -MIBG therapy should have most of the necessary components in place, and so should be better placed to apply for certification. However there will need to be some discussion on how many centres in Scotland should be carrying out these procedures to maintain expertise.

12.2.4 SEPA Authorisation and Registration

Special approval is required from the Scottish Environmental Protection Agency (SEPA) to hold and dispose of radionuclides. For example, Gartnavel General Hospital in Glasgow can hold 20 GBq and dispose of 30 GBq of ^{177}Lu to sewer per month, permitting the performance of four to six therapies per month.

12.3 SIRT for Hepatic Disease

Selective internal radiation therapy (SIRT) for hepatic disease consists of the administration of radiolabeled ^{90}Y microspheres via a catheter that has been placed into an appropriate location in either the common hepatic artery or the right/left hepatic artery. The procedure exploits the dominance of hepatic arterial blood flow to the tumour tissue. The microspheres lodge preferentially within the vasculature of liver tumours, with minimal amounts going to normal liver parenchyma and smaller amounts again going to other organs, particularly the lung.

The treatment is planned using the diagnostic radiopharmaceutical $^{99\text{m}}\text{Tc}$ -MAA. The catheter is positioned into the treatment location and the $^{99\text{m}}\text{Tc}$ -MAA administered. The patient is then scanned using a gamma camera to assess its distribution (which should mimic that of the therapeutic agent). The presence of activity in other organs supplied by the hepatic artery may indicate the need to reposition the catheter or to perform selective embolisation. An assessment is also made of lung uptake caused by arterio-venous shunting. The $^{99\text{m}}\text{Tc}$ -MAA activity in the volume to be treated is also assessed and used to calculate the amount of ^{90}Y to be administered. The aim is to deliver a radiation dose of around 120Gy to the tumour volume while keeping the calculated and cumulative lung dose below 30Gy and 50 Gy respectively.

Support from an Interventional Radiologist is required for use of this procedure, and there are significant training and radiation protection issues as well as a need for Radiology and Physics input.

12.4 Recommendations

- **All radionuclide treatments must occur within purpose-built facilities under the supervision of trained staff with expertise in the care of patients undergoing treatment with radiopharmaceuticals.**
- **^{131}I -MIBG is first-line treatment for metastatic pheochromocytoma/paraganglioma/neuroblastoma in patients with $^{123}\text{I}/^{131}\text{I}$ -MIBG positive disease.**
- **Radiolabelled somatostatin analogues (DOTATOC and DOTATATE) can be used to treat patients with significant disease demonstrated on ^{111}In -octrotide scintigraphy and acceptable renal function. However, there are currently no Scottish centres that routinely offer this treatment.**

13. Genetics

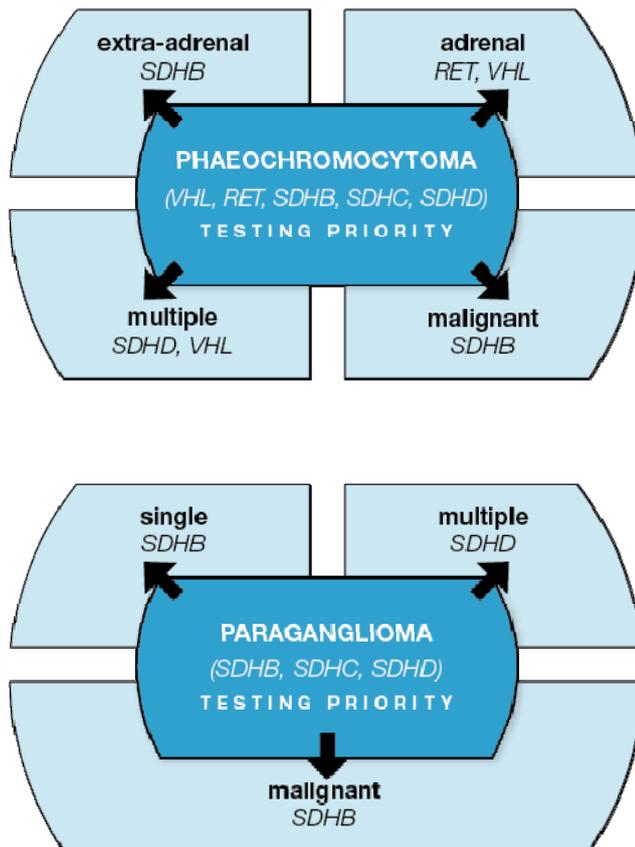
13.1 Pheochromocytoma/Paraganglioma

13.1.1 Genetic Analysis

At present, anyone affected with a pheochromocytoma or paraganglioma under the age of 50 years, or at any age if the tumour is bilateral, malignant or there is a family history, is eligible for genetic analysis. An EDTA blood sample can be sent (with clinical details) to the DNA laboratory. DNA will then be extracted and sent to the Scottish Consortium Laboratory in Dundee for analysis of the appropriate gene. If a mutation is identified, referral to a local Clinical Genetics Department to organise family cascade testing is recommended.

The Scottish Consortium Laboratory can offer analysis of mutations in the following genes *VHL*, *RET*, *SDHB*, *SDHC* and *SDHD*. The following testing priorities have been suggested (Figure 1).¹⁰¹

Figure 1: Testing priorities for genetic analysis in patients with pheochromocytoma or paraganglioma.¹⁰¹



If clinically relevant (i.e. samples from a young patient with pheochromocytoma, bilateral and/or family history but no mutation identified), samples can also be analysed for *TMEM127* mutation and any further genes identified which are shown to increase risk of pheochromocytoma.

It is important that patients with familial pheochromocytoma/paraganglioma are referred to the Regional Service to allow results to be collected and audited with a view to determining the most appropriate regimen.

13.2 Identification of *SDHB*, *SDHC*, *SDHD* and Familial Paraganglioma due to Unknown Genes

To date there is no evidence to support a specific screening protocol for *SDHB*, *SDHC*, *SDHD* and familial paraganglioma due to unknown genes. Most centres use a variation of the approach currently used in the West of Scotland:

- 24-hour urine collection and/or plasma metanephrines and normetanephrines from around 10 years of age (or if there is a very young diagnosis in the family this age can be lowered to 5 years younger than youngest diagnosis in the family).
- MRI every 3 years with ultrasound of abdomen in the intervening years from mid-teens.

13.3 Identification and Management of MEN2

Identification and management of multiple endocrine neoplasia type 2 (MEN2) due to mutations in the *RET* oncogene should be performed as described in Table 4.¹⁰²

Table 4: MEN2 consensus summary statements (modified from Brandi *et al.*, 2001).¹⁰²

- 1) MEN2 has distinctive variants. MEN2A and MEN2B are the MEN2 variants with the greatest syndromic consistency.
- 2) Familial medullary thyroid carcinoma (FMTC) is the mildest variant of MEN2. To avoid missing a diagnosis of MEN2A with its risk of pheochromocytoma, physicians should diagnose FMTC only from rigorous criteria.
- 3) Morbidity from pheochromocytoma in MEN2 has been markedly decreased by improved recognition and management. The preferred treatment for unilateral pheochromocytoma in MEN2 is laparoscopic adrenalectomy.
- 4) Hyperparathyroidism (HPT) is less intense in MEN2 than in MEN1. Parathyroidectomy should be the same as in other disorders with multiple parathyroid tumours.
- 5) The main morbidity from MEN2 is medullary thyroid carcinoma (MTC). MEN2 variants differ in aggressiveness of MTC, in decreasing order as follows: MEN2B>MEN2A>FMTC.
- 6) MEN2 carrier detection should be the basis for recommending thyroidectomy to prevent or cure MTC. This carrier testing is mandatory in all children at 50% risk.
- 7) Compared with *RET* mutation testing, immunoassay of basal or stimulated CT results in more frequent false-positive diagnoses and delays the true positive diagnosis of the MEN2 carrier state. However, the CT test still should be used to monitor the tumour status of MTC. It can be the first index of persistent or recurrent disease.
- 8) *RET* germline mutation testing has replaced CT testing as the basis for carrier diagnosis in MEN2 families. When performed rigorously, it reveals a *RET* mutation in over 95% of MEN2 index cases.

- 9) The *RET* codon mutations can be stratified into three levels of risk from MTC. These three categories predict the MEN2 syndromic variant, the age of onset of MTC, and the aggressiveness of MTC.
- 10) Detailed recommendations about aggressiveness of interventions for MTC are derived from knowledge about the specific *RET* codon mutated and/or from a clear familial pattern.
- 11) Thyroidectomy should be performed before the age of 6 months in MEN2B, perhaps much earlier, and before the age of 5 years in MEN2A. Policies about central lymph node dissection at initial thyroidectomy are controversial and may differ among the MEN2 variants.
- 12) Testing (in blood leukocytes) for germline *RET* mutation should be performed in all cases with apparently isolated and non-familial (i.e. sporadic) MTC or with apparently isolated and non-familial pheochromocytoma. A germline mutation is found only occasionally, but such a discovered mutation is important.
- 13) Tests (in tumour tissue) for somatic *RET* mutation in sporadic MTC or in sporadic pheochromocytoma are generally not recommended for clinical use.
- 14) Periodic screening for tumours in MEN2 carriers is based on the MEN2 variant, as characterised by the *RET* codon mutation and by manifestations in the rest of the family.

13.4 Von Hippel-Lindau Disease (VHL)

VHL disease has been well described.¹⁰³ Most common manifestations are retinal and central nervous haemangioblastomas but in many families there is also a high risk of renal cancers. Visceral cysts (renal, pancreatic and epididymal) are common but rarely compromise organ function. Less frequent tumours include adrenal and extra-adrenal pheochromocytomas, non-functioning pancreatic endocrine cancers, endolymphatic sac tumours (ELSTs) and, occasionally, head and neck paragangliomas.

Routine surveillance for VHL disease should be conducted at a Regional Service, following a protocol such as that shown in Table 5.¹⁰³

Table 5: A routine surveillance protocol for VHL disease.¹⁰³

Screen	Modality	Timing
Retinal angioma	Ophthalmic examinations (direct and indirect ophthalmoscopy)	Annually, beginning in infancy or early childhood
CNS haemangioblastoma	MRI scans of the head	Every 12–36 months, beginning in adolescence
Renal cell carcinoma and pancreatic tumours	MRI (or ultrasound) examinations of the abdomen	Every 12 months, beginning at 16 years
Pheochromocytoma	Blood pressure monitoring and 24-hour urine studies	Annually

Screen	Modality	Timing
	for catecholamine metabolites	
Families at high-risk for pheochromocytoma	More intense surveillance (e.g. measurement of plasma normetanephrine levels, adrenal imaging)	Annually, beginning at 8 years

Additional investigations may be instigated in response to symptoms or signs of specific complications (e.g. ELSTs).

13.6 MEN1-MENIN Gene Analysis

The clinical features of MEN1 are outlined in Table 6. If there is any clinical suspicion of MEN1, samples can be sent for analysis of menin.¹⁰²

Table 6: Expressions of MEN1 with estimated penetrance (in parentheses) at the age of 40 years.

Endocrine features	Non-endocrine features
Parathyroid adenoma (90%)	Lipomas (30%)
Enteropancreatic tumour	Facial angiofibromas (85%)
Gastrinoma (40%)	Collagenomas (70%)
Insulinoma (10%)	
Non-functioning, including pancreatic polypeptide (20%)	Rare, maybe innate, endocrine or non-endocrine features
Other: glucagonoma, VIPoma, somatostatinoma, etc. (2%)	
Foregut carcinoid	
Thymic carcinoid (NF) (2%)	Pheochromocytoma (<1%)
BP carcinoid (NF) (2%)	Ependymoma (1%)
Gastric enterochromaffin-like tumour (NF) (10%)	
Anterior pituitary tumour	
Prolactinoma (20%)	
Other: GH + prolactin, GH (NF) (each 5%)	
ACTH (2%), TSH (rare)	
Adrenal cortex (NF) (25%)	

NF, Non-functioning. May synthesise a peptide hormone or other factors (such as small amines), but does not usually oversecrete enough to produce hormonal expression.

In the case of young patients who have hyperparathyroidism and in whom menin analysis is negative, samples can also be forwarded to Oxford University Hospital NHS Accredited Genetics Laboratory for analysis of the *CDC73* gene and to identify hyperparathyroidism jaw tumour syndrome (there are cost implications and specific forms to complete; this is organised through the DNA laboratory).

The following test schedule can be used to guide for screening for tumour expression in an individual who is highly likely to be a carrier of a *MEN1* mutation:^{101, 102, 104}

Tumour	Age to begin (years)	Annual biochemical tests	Imaging tests every 3 years
Parathyroid adenoma	8	Calcium (especially Ca ⁺⁺), PTH	None
Gastrinoma	20	Gastrin, gastric acid output, ¹⁰¹ secretin-stimulated gastrin ¹⁰¹	None
Insulinoma	5	Fasting glucose, insulin	
Other enteropancreatic	20	CgA, glucagon, proinsulin	¹¹¹ In- octreotide scan, CT or MRI
Anterior pituitary	5	Prolactin, IGF-I	MRI
Foregut carcinoid ¹⁰⁴	20	None	CT

13.7 Recommendations

- **Individuals diagnosed with pheochromocytoma or paraganglioma under the age of 50 years, or at any age if the tumour is bilateral, malignant or there is a family history, should be offered genetic analysis of current known predisposition genes or DNA storage.**
- **Individuals who have a mutation identified should be referred to the local Clinical Genetics Department.**
- **As there is no proven screening protocol for familial pheochromocytoma/paraganglioma it is important to refer to the Regional Service to allow results to be collected and audited with a view to determining the most appropriate regimen.**
- **A routine surveillance protocol for VHL disease should be conducted at a Regional Service.**
- **If there is any clinical suspicion of MEN1, samples can be sent for analysis of menin. Consider *CDC73* analysis in young patients with hyperparathyroidism and negative menin analysis.**
- **Individuals with MEN1 should undergo annual screening.**

14. Patient Support

Patients with NETs can experience a range of physical and psychological challenges, so supporting these patients is a fundamental part of their overall management. Common symptoms caused by hormone producing tumours (e.g. flushing and diarrhoea) can be particularly difficult for patients to live with and impact negatively on daily life. Collecting information about the experiences of patients with NETs to understand the issues they face is important in ensuring appropriate and timely support.

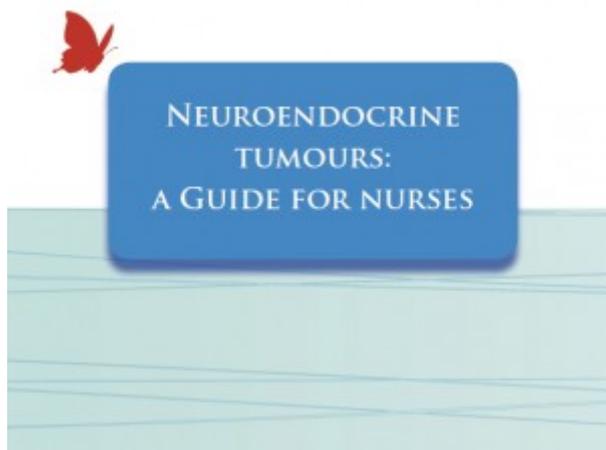
Until objective data are available on the management of specific symptoms, however, collecting and sharing information on clinical expertise and experience remains the only way to disseminate 'best' practice in supporting patients.

There are a variety of organisations that provide support and training for nurses, a means of sharing this information, and support and information for NET patients, their families and carers, as outlined below.

14.1 NET Nurse Europe

In 2011 a task force was established to support nurses in the management of patients with all types of NETs. Initially an educational tool was developed by an expert group at Oslo University Hospital, Norway, covering diagnosis through to treatment, symptom management and psychological support. The tool has since been edited for a European audience, and there are plans to keep the tool updated (Figure 2). It can be accessed from the following website: <http://www.netnurse.eu/nurse-resources-neuroendocrine-tumours-a-guide-for-nurses/>.

Figure 2: The NET Nurses Europe Educational Tool.



In addition, an online European NET Nurses Europe group has been formed (www.netnurse.eu) (Figure 3), with the aim of 'promoting awareness and best nursing practice for neuroendocrine cancer care'. The group continues to develop and will be facilitating research studies as well as ongoing practical guidance for nurses caring for patients with NETs.

14.2 NET Nursing Course

An online NET nursing course is available for nurses new to the role of caring for NET patients (www.cancernursing.org). The site provides general information on nursing cancer patients, as well as specific NET-focused learning, including the aetiology and epidemiology of the disease, how it is diagnosed, staged and treated, and the impact of the disease and its treatment on patients and their families.

14.3 The Ann Edgar Charitable Trust

The Ann Edgar Charitable Trust (www.theannedgarcharitabletrust.org.uk) is Scotland's charity for patients with carcinoid syndrome or other NETs. The Trust was established in 2011 by Ann Edgar, herself a carcinoid patient.

The aims of the Trust are as follows:

- To promote awareness of carcinoid syndrome, a relatively little known condition, in order to improve the speed and accuracy of patient diagnosis.
- To improve quality of life for carcinoid patients in Scotland and North England.
- To work in partnership with other cancer support groups for the benefit of patients.
- Potentially aim to invest in clinical research improvement programmes.
- Become the leading supporting charity in Scotland for carcinoid syndrome.

The Trust shares common aims and works in partnership with the Net Patient Foundation.

14.4 The NET Patient Foundation

The NET Patient Foundation (www.netpatientfoundation.org) is a UK and Ireland Charity Commission dedicated to providing support and information for people affected by NETs. Established in 2006, it has the following aims:

- To provide support, education and information to anyone affected by neuroendocrine cancers.
- To advocate for neuroendocrine cancer patients so they may achieve the best possible outcomes.
- To encourage standardised care for all NET cancer patients.
- To provide community supportive care to patients and their carers or family members.
- To raise awareness of NET cancers throughout the UK.
- To raise funds for clinical and translational research projects.

The Charity produces a range of patient materials and patient videos, runs NET Natter groups throughout the UK and holds patient educational meetings. There is also an active international forum available for patients to communicate with one another. Raising awareness, political lobbying and being the voice of the NET patient in the research process, and within the medical community are also vital aspects of the Charity's work. Current activities include a project on quality of life to help define NET patient needs and formulate tools for evaluation and monitoring.

The Charity shares common aims and works in partnership with the Ann Edgar Charitable Trust, and is part of the International Neuroendocrine Cancer Alliance (www.netcancerday.org).

14.5 Recommendations

- **Patients with NETs can experience a range of physical and psychological challenges, so supporting these patients is a fundamental part of their overall management.**
- **Patients should be informed about the various organisations that provide support and information for NET patients, their families and carers.**

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