SCONET

Scottish Neuroendocrine Tumour Group

Consensus Guidelines for the Management of Patients with Neuroendocrine Tumours

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Contents

Table of figures

Abbreviations

5-FU, 5-fluorouracil
5-HIAA, 5-hydroxyindoleacetic acid
5-HT, 5-hydroxytryptophan
18F-DOPA/DOPAMINE
68Ga-DOTA, gallium68-DOTATOC/DOTATATE/DOTANOC

ACTH, adrenocorticotropic hormone
AJCC, American Joint Committee on Cancer
ARSAC, Administration of Radioactive Substances Advisory Committee
ATA, American Thyroid Association

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

GEP, gastroenteropancreatic
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
mIBG meta-iodobenzylguanadine
MTC, medullary thyroid carcinoma
mTOR, mammalian Target Of Rapamycin

NEC, Neuroendocrine Carcinoma,
NET, neuroendocrine tumour
NEN, Neuroendocrine Neoplasm
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 tumour growth in patients with metastatic neuroendocrine MIDgut tumours
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
SINENS, Small Intestine Neuroendocrine Neoplasm
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 registered and 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. *Additional specialist services include cardiology/cardiac surgery and thoracic surgery.*

Diagnosis

- CT and MRI are the initial imaging modalities of choice for staging and monitoring disease progression.

- Somatostatin receptor scintigraphy (SSTR) is currently indicated for staging and detection of metastatic disease and to predict response to somatostatin analogue therapy. *It is also used to select potential patients for PRRT*.

- During 2021 Gallium PET imaging will become standard of care for G1 and G2 tumours, ^{68}Ga DOTAPET scanning should replace octreotide scintigraphy for staging (but continue to be used to predict response to somatostatin analogue therapy) and should also be used to assess suitability for PRRT with ^{177}Lu-DOTATATE. FDG-PET is preferable for G3 tumours (NEC) and in G3 NET it may be advised to use both radionuclide imaging modalities.

Biochemical Investigation

- All patients with a confirmed GEP NET should have a baseline CgA, CgB, and/or 24-hour urine collection for 5-HIAA. Elevated levels of these markers can be used to monitor response to therapy and disease progression. The introduction of plasma 5HIAA is under discussion.

- 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. *All newly diagnosed SINETS should also have initial full gut hormone profile but for follow up CgA and B may be sufficient*

- Phaeochromocytoma and paraganglioma should be investigated using plasma or urine metanephrines.

Surgical/Endoscopic Management of GEP NETs

- Patients with localised NETs should be considered for surgical resection or endoscopic resection when appropriate.

- 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. *Palliative resection may be considered in metastatic patients after discussion at MDT.*

- 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 especially when liver dominant.

- 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 MINENS (Goblet Cell Carcinoids)

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

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[43] and staged using TNM8.

- On the occasions where the carcinoid does present as a functional NET, octreotide therapy should be considered prior to surgical resection of the tumour. This may be more applicable if there are delays in arranging surgery.

- Long term follow up is advised in view of the higher risk of late relapse in clinics expert in managing NET cancers, or via shared care where appropriate.

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 are no longer 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 considered 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, small intestinal and broncho-pulmonary 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.

- Telotristat ethyl is now available for severe diarrhoea (> 4 stools per day) induced by carcinoid disease after exclusion of reversible or other treatable causes.

SACT (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. New molecular markers and profiling is likely to have a major impact in next 5 years and will show differential responses rate to platinum and non platinum schedules.

- 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 plain hepatic artery embolisation or 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 $^{123/131}$I-MIBG positive disease.

- Radiolabelled somatostatin analogues (DOTATOC and DOTATATE) are now approved for the treatment of GEPNETs patients with progressive disease demonstrated on somatostatin receptor scintigraphy and acceptable renal function. A national service was established at Beatson West of Scotland Cancer Centre in April 2019.

Carcinoid Heart Disease

- Patients with carcinoid syndrome should be screened every 6-12 months with clinical assessment for cardiac murmurs, and evidence of right heart failure (peripheral oedema in particular). In addition, measurement of serum NT-pro BNP is recommended as an initial screening test. If abnormally elevated proceed to echocardiography.

- Efforts should be made to ensure that classical echo features of carcinoid heart disease on echo, should trigger referral for NET work up including CT, Octreotide scan, Chromogranin and 5HIAA check. Early discussion with the local NET team and cardiology would be advised.

- Carcinoid heart disease (CHD) may have a rapid progressive course. Therefore, early referral for Cardiology opinion is appropriate to allow surveillance and consultation about the need and timing of surgery.

- When PRRT is being considered it may be necessary to refer for cardiac assessment prior to commencing PRRT or after 2 cycles.

Genetics

- The possibility of a monogenic tumour syndrome should be considered in all patients presenting with NETs.

- Individuals who have a germline pathogenic/likely pathogenic variant in one of the monogenic endocrine tumour genes should be referred to the local Clinical Genetics Department

- Cascade genetic testing of ‘at-risk’ relatives of patients with known pathogenic/likely germline variants in moderate and high penetrance monogenic endocrine tumour genes is recommended

- The majority of individuals diagnosed with phaeochromocytoma or paraganglioma (PPGL) should be offered genetic analysis of current known predisposition genes (Phaeochromocytoma/Paraganglioma panel).

- Individuals identified to be at risk of PPGL (i.e. those harbouring a pathogenic/likely pathogenic variant in a PPGL monogenic disease gene)

should enter a disease-specific surveillance program (e.g. MEN2/VHL). Although there is little evidence to guide the optimal screening of individuals at risk of familial PPGL (e.g. due to *SDHx* mutation), interval clinical, biochemical and radiological screening is recommended.

- A routine surveillance protocol for patients with VHL should be conducted at a Regional and/or Specialist Service.

- Patients with a clinical or genetic diagnosis of MEN1 should undergo regular clinical, biochemical and radiological surveillance.

Patient Support

- Patients and their families should have access to a Clinical Nurse Specialist in NET to provide information, support, symptom management and co-ordination of care between healthcare settings.

- Patients with NET can experience a range of physical and psycho-social challenges, so information and support is a fundamental part of their overall management and care.

- Patients should be informed about the various organisations that provide support and information for them, their families and carers.

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 term NET is likely to replaced by Neuro-endocrine Neoplasm (NEN) in the near future to reflect the very different behaviour of low grade NETs and high grade Neuro-endocrine carcinomas (NECs). The principal aim of the group is to ensure equitable care and improve the quality of care for patients with NETs across NHSScotland.

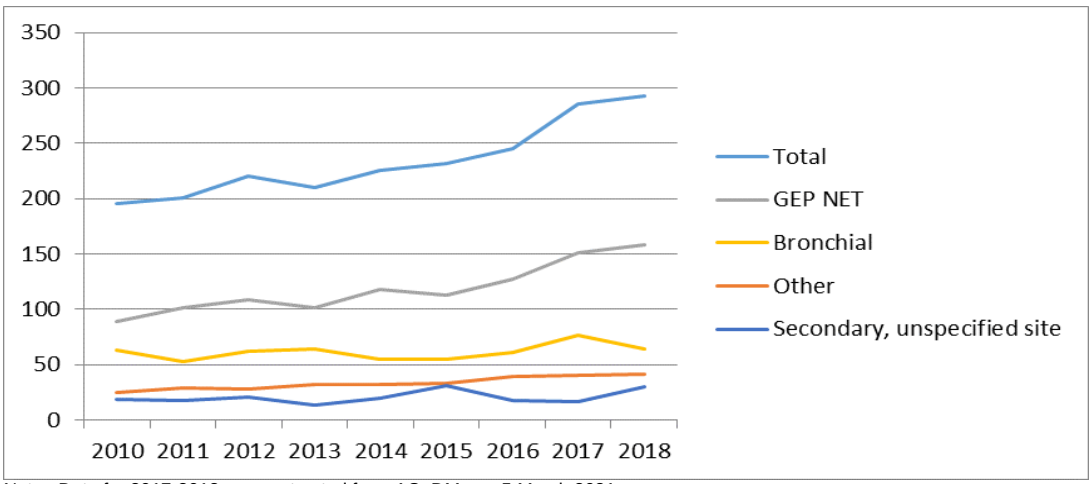
Individually NETs are a relatively rare, heterogeneous group of cancers that occur most commonly in the digestive system, small bowel, appendix, lung and pancreas.[1] While some NETs are aggressive, most are more indolent than other malignancies, which often lead to a significant delay (up to 7 years)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

The annual incidence of NETs was relatively low but increasing. Recent data suggest about 7 cases per 100,000 population. Due to the long survival of patients with NETs, however, the prevalence is amongst the highest of all cancer types.[1] In 2019 a total of 526 patients were diagnosed with a NET in Scotland, an increase of 31% since 2010. The majority (51%) were GEP NETs.[2]

Table 1: NET Incidence in the West of Scotland 2010 - 2018[2]

Cancer Site	2010	2011	2012	2013	2014	2015	2016	2017	2018
GEP NET	89	101	109	101	118	113	127	151	158
Bronchial*	63	53	62	64	55	55	61	77	64
Secondary, unspecified site	19	18	21	13	20	31	18	17	30
Other^	25	29	28	32	32	33	39	40	41
Total	**196**	**201**	**220**	**210**	**225**	**232**	**245**	**285**	**293**

The following Cancer morphology ICD(O)3 codes were selected: 8013, 8041, 8042, 8043, 8044, 8045, 8150, 8151, 8152, 8153, 8154, 8155, 8156, 8157, 8158, 8240, 8241, 8242, 8243, 8244, 8245, 8246, 8247, 8249, 8574, 9091.
* ICD 03 Code 8041/3 with ICD 10 Code as Lung/Bronchus have been excluded from the analysis
^ Other includes: head & neck, skin, breast, gynaecological and urological sites



Note: Data for 2017-2018 were extracted from ACaDMe on 5 March 2021

Figure 1: NET Incidence in the West of Scotland 2010 - 2018

Patients with NETs are currently managed locally across all 14 Boards in NHSScotland. 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. Additional input will be sought from thoracic surgery, cardiology and cardiac surgery, hepatobiliary and liver surgery where indicated.

NETs present numerous clinical problems, principally due to relatively rare occurrence and patterns of disease presentation. 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 were developed in 2015 by the multi-disciplinary SCONET Group, following several meetings of the Group where consensus agreement on the management of NETS in NHSScotland was reached. Original contributing authors are listed in appendix 1. The guidelines were reviewed and updated in 2018/19 by contributing authors and peer reviewed by the core SCONET group with representatives from across specialities and Boards (see appendix 1).

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. An increasing number is picked up incidentally when imaging done for other purposes, these are usually asymptomatic and sporadic. A further small number will be identified through family screening of established hereditary pedigrees. 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 can be 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 ^{111}In-octreotide or ^{99m}Tc Tektrotyd are currently still the first-choice radionuclide imaging investigations in Scotland and are used for staging of metastatic disease in selected patients, detection of occult primary disease in patients with histologically proven metastatic NET disease and detection of occult disease in patients with biochemical or suspected clinical relapse. These techniques 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 ^{111}In-octreotide and ^{99m}Tc Tektrotyd bind to type II and to a lesser extent types III and V. The sensitivity of SSRI scanning is increased with SPECT/CT imaging and should be used when available.[6, 7]

^{68}Gallium PET/CT will be introduced to the Scottish PET centres during 2021-2 and will replace the above given the superior quality of information obtained, see section 3.2.4. ^{18}FDG PET is preferred for high grade tumours, G3 NEC and probably for G3 NET. There is currently debate about whether it is indicated in other NETs to look for mis-match with Gallium as this may have prognostic value.

3.2.3. ^{123}I-mIBG

^{123}I-mIBG imaging is reserved for those patients being considered for ^{131}I-mIBG therapy. ^{123}I-mIBG is superior to ^{131}I-mIBG for imaging and accuracy is increased using SPECT/CT.[8,9,10]

3.2.4. Indications for the use of 68Gallium DOTA PET CT (68Ga DOTA) in Neuroendocrine Tumours[11]

Background

Somatostatin Receptor Scintigraphy (SRS) is a well-established imaging tool in the diagnosis and management of Neuroendocrine tumours (NETs). In Scotland, to date, the main radiopharmaceuticals used for this indication are ^{111}Indium Octreotide and more recently ^{99m}Tc-Tektrotyd. The development of PET radiopharmaceuticals offers the benefit of improved resolution capabilities of PET together with the greater receptor affinity of the peptide component resulting in the potential for more accurate staging and disease delineation.

The Scottish Government has approved funding to develop ^{68}Ga DOTA services at all four Scottish PET CT centres. Although it may be preferential to replace SRS with ^{68}Ga DOTA the availability of tracer is likely to remain limited while these services are established. As a result, it is expected that SRS will have a continued role in the management of patients with ^{68}Ga DOTA being considered where it is felt to add additional benefit. Therefore, all referrals should come via (or in discussion with) the regional NET MDTs.

^{68}Ga DOTA, as with all PET referrals, should only be considered where the outcome of the investigation will directly influence individual patient management and treatment.

Routine Indications

- **Gastroduodenal Neuroendocrine Neoplasms (GNENS):**
  - Type 3- GNEN- when staging CT/laparoscopy inconclusive in patients being potentially considered for radical surgery.

- **Jejunal/Ileal NENS**
  - Staging of patients with small bowel NET being considered for surgery
  - Post op staging in patients presenting with small bowel obstruction secondary to small bowel NET
  - Staging of patients with metastatic disease considered for treatment with curative intent e.g. Hepatic metastases.
  - Suspected tumour (clinical/elevated urinary 5-HIAA/serum CgA) with negative conventional imaging.
  - Suspected biochemical recurrence or progressive disease with negative/stable conventional imaging

- **Pancreatic NENS**
  - Localisation of functional (non Insulinoma) NENS not identified on CT/MRI/EUS.
  - Staging of Gastrinoma and other rare functional tumours (RFT).
  - Patients being considered for radical surgery (other than Insulinoma).

- **G1/2 Colorectal NEN**

- When CT/MRI demonstrates possible/definite metastatic disease which would be suitable for treatment with curative intent.

- **Appendiceal NEN**
  - G1/2 disease with suspected/ definite metastatic disease on CT/MRI in patients with tumours >2cm and or with deep mesoappendiceal infiltration or angioinvasion.

- Metastatic NET of unknown primary being considered for treatment with curative intent

- Patients being considered for PRRT

- Staging of bronchial carcinoids in patients being considered for radical surgery

- Medullary thyroid cancer with increasing calcitonin and negative/equivocal conventional imaging

- Clinically or biochemically suspected paraganglioma/phaeochromocytoma with negative or equivocal imaging including MIBG

Non-routine

- Somatostatin receptor status should, in the first instance, be assessed using SRS with ^{68}GA DOTA only be considered in exceptional cases (unless in conjunction with the indications above).

Future Considerations

It is the aim, that as services become more established, ^{68}Ga DOTA will become the routine investigation of choice for NETs. However, the availability of tracer may remain limited and ongoing assessment of resource availability and clinical need will be required to guide service development. There is currently insufficient evidence to support the use of ^{68}Ga DOTA in the follow up of patients treated with PRRT at present but will be subject to further review in future. The ongoing development of other ^{68}Ga labelled tracers as well as ^{18}F fluorinated versions will also be kept under review.

3.3. Recommendations

- **CT and MRI are the initial imaging modalities of choice for staging and monitoring disease progression.**

- **Octreotide/Tektrotyd scintigraphy until recently have been indicated for staging and detection of metastatic disease and to predict response to somatostatin analogue therapy. It is also required before considering PRRT.**

- **When routinely available, ^{68}Ga DOTAPET scanning should replace octreotide scintigraphy for staging (but continue to be used to predict response to somatostatin analogue therapy) and should also be used to assess suitability for PRRT with ^{177}Lu or ^{90}Y DOTATATE.**

4. Biochemical Investigation

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

- Pancreatic islet cell tumours
- Carcinoid tumours usually of gastro-intestinal, rectal or bronchial origin
- Phaeochromocytomas/paragangliomas.

Around 10% of all NETs are biochemically functional and therefore secrete hormones; a greater percentage may secrete chromogranin A (CgA).[12,13] The site and origin of the tumour will determine which biochemical marker is most likely to be secreted. Chromogranin B is more frequently seen to be elevated in bronchial and rectal well differentiated NETs and less frequently in pancreatic NETs.

A baseline measurement of chromogranins CgA and B 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.[13] 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.[14]

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.

Neurone specific enolase (NSE) is found elevated in many large cell/high grade G3 tumours. It should be measured at baseline and maybe used for serial monitoring.

Biochemical testing available within Scotland:

- 5HIAA urine (24hr) – serum assay may be available in 2021
- Metadrenalines – urine (24hr) and plasma
- CgA
- Gastrin
- Insulin

Biochemistry tests analysed outside Scotland:

- Fasting full gut hormone profile (VIP, Pancreatic Polypeptide, Glucagon, Somatostatin, Gastrin, CgA and CgB). Either a full profile or individual hormones can be requested.
- NSE

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.[15] 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. A serum gastrin of >1000ng/L and gastric pH <2 is diagnostic. Modest elevations of gastrin may be seen in chronic kidney disease, H Pylori associated gastritis, atrophic gastritis 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, off PPI therapy, if available.25 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.[16]

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 pmol) 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.[16]

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 guideline[17] 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[17 above17].

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 sulfonylurea.

Thresholds for diagnosis (confirmation of an endogenous insulin source) are plasma insulin (by immunochemiluminometric assay) ≥21pmol/l and plasma C-peptide >200 pmol/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 pmol), 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.[16]

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 pmol 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.[16]

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.[18] 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 NETs[19] and may secrete 5-HIAA but less than 10% as well as adrenocorticotropic 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. Phaeochromocytoma/Paraganglioma

Suspected phaeochromocytoma 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.[16] 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. Serum 5HIAA is expected to become available during 2021.**

- **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.**

- **Phaeochromocytoma and paraganglioma should be investigated using plasma or urine metanephrines.**

5. Endoscopic and Surgical Management of Gastroenteropancreatic NETs

5.1. 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 or endoscopic resection where appropriate.
- 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 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, 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).

5.5. Endoscopy for GEP NETs

Endoscopic resection using either Endoscopic Mucosal Resection (EMR) or Endoscopic Submucosal Dissection (ESD) of GE NETs is appropriate in specific cases. Decisions regarding endoscopic versus surgical resection should be made within a multidisciplinary setting taking into account the wishes and comorbidities of the patient as endoscopic resection is associated with a risk of perforation and bleeding.

Endoscopic ultrasound can be used to assess submucosal / involvement in upper GI and rectal lesions to aid decision making about method of resection.

Please refer to the ENETS Consensus Guidelines 2016 for associated endoscopic and surgical approaches.

5.6. Recommendations

- **Patients with localised NETs should be considered for surgical resection or endoscopic resection when appropriate.**
- **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 NENs

6.1. General Principles

There should be at least one histopathologist within each region with an interest in neuroendocrine neoplasms (NENs) and who attends the local NEN MDT. It is strongly recommended that all diagnosed NENs are highlighted to this pathologist or MDT coordinator in order that a local registry can be maintained.

The core data items from the Royal College of Pathologists guidance for GEP-NENs[20] should be followed, as should the site specific guidance and advice on specimen handling. Creation of a frozen tissue tumour bank would be helpful for future NEN research.

Assessment, classification and management of bronchopulmonary NENs is distinct from GEP-NENs. Bronchopulmonary NENs should be assessed following the specific Royal College of Pathologists guidelines[21], with input from pathologists with an interest in bronchopulmonary pathology, and should be discussed and initially treated under the local lung MDT but subsequent management of lower grade NENs should also be discussed and registered at NEN MDT.

6.2. Pathological Assessment of GEP-NENs

It was recognised in 2010 that well differentiated NENs are distinct from poorly differentiated NENs, with differences in underlying molecular biology, behaviour and treatment modalities. At that time, the European Neuroendocrine Tumour Society (ENETS) three tier grading system (G1-G3) was also adopted and recommended for use by the Royal College of Pathologists (RCPath). As a result of these developments, there have been significant changes to the classification of GEP-NENs, as outlined in the 2017 WHO classification for pancreatic neuroendocrine neoplasms (PanNENs)[22] and 2019 classification for GEP-NENs[23] (see table 1). These WHO classification systems and the ENETS three tier grading system are recommended for use by the RCPath when assessing GEP-NENs.

The term neuroendocrine neoplasm (NEN) is used to identify all tumours of neuroendocrine origin regardless of degree of differentiation[20,23]:

- Neuroendocrine tumours (NETs) are well-differentiated NENs with a strong resemblance to non-neoplastic neuroendocrine tissues, and can be low-grade (G1), intermediate-grade (G2) or high grade (G3). The importance of recording ki 67 score is discussed below.
- Neuroendocrine carcinomas (NECs) are poorly differentiated NENs which morphologically resemble either small cell or large cell NEC of the lung. NECs are, by definition, high grade and are not assigned a specific numerical grade.
- Mixed neuroendocrine–non-neuroendocrine neoplasms (MiNEN) are composed of a neuroendocrine component and morphologically and immunohistochemically recognisable non-neuroendocrine component. This has replaced the term MANEC previously used in PanNENs, as it is recognised that the non-neuroendocrine component does not have to be an adenocarcinoma.

Table 2: Comparison of the WHO 2019 GI-NEN classification, the WHO 2017 PanNEN classification and the WHO 2010 GEP-NEN classification. Adapted from RCPath Dataset for histopathological reporting of neuroendocrine neoplasms of the gastroenteropancreatic tract[1]

WHO 2019 GI-NEN classification	**WHO 2017 PanNEN classification**	**WHO 2010 GEP-NEN classification**
Well differentiated NETs: • NET G1 • NET G2 • NET G3	Well differentiated NETs: • NET G1 • NET G2 • NET G3	Well differentiated NETs: • NET G1 • NET G2
Poorly differentiated NECs: • NEC (large cell or small cell NEC)	Poorly differentiated NECs: • NEC G3 (large cell or small cell NEC)	Poorly differentiated NECs: • NEC G3 (large cell or small cell NEC)
MiNEN	MiNEN	MANEC
Abolished, but recognised in gastric NENs	Abolished preneoplastic category because PanNEN precursor changes have not been clearly identified in association with sporadic neoplasms	Hyperplastic and preneoplastic lesions

6.3. Immunohistochemistry

RCPath advises that to confirm diagnosis of NEN it is best practice to have positive staining with at least two neuroendocrine markers[20]. We advise the use of three markers to allow for variability in tumour expression, with chromogranin A, synaptophysin and cluster of differentiation 56 (CD56) being most useful in diagnostic practice. In addition, pancytokeratins should be used to differentiate GEP-NENs from non-epithelial NENs.

Immunohistochemical staining for specific peptide hormones may be carried out if there is a clinical need to demonstrate production of this hormone by the tumour. It is not, however, required in routine practice[20].

There is evidence that expression of CK19 in pancreatic NENs has been associated with more aggressive tumours and reduced survival[24,25.] We therefore recommended routinely staining for CK19 in assessment of PanNENs.

6.4. Grading and staging

Tumour grade and stage are the most important predictors of prognosis[20].

Grading (G1, G2, G3) is based on tumour proliferation[20,22,23,] therefore the mitotic count and Ki-67 index should be assessed for all NENs. Mitotic count should be given as number of mitoses per $2mm^2$ after assessment of 50 high power fields (HPFs)[20]. $2mm^2$ is likely to be equal to 10 HPFs at 40x magnification, but should be calculated for each microscope specifically for maximum accuracy. Ki-67 index should be calculated following assessment of at least 500 tumour cells in the area of highest nuclear labelling[20]. The cut-off value for Ki-67 index between G1 and G2

NETs has increased since previous guidelines, with G1 tumours having a Ki-67 index of <3% and G2 tumours 3-20%[20,22,23] (see table 2).

We recommend clearly stating the precise value of the Ki-67 index in the pathology report, and to avoid the use of broad statements such as ">20%" for G3 neoplasms. This value is of particular use for treatment planning, as it has been shown in the NORDIC NEC study that GEP-NENs with Ki-67 index of <55% have a less aggressive clinical course and respond less well to platinum-based chemotherapy agents than those with a Ki-67 index in excess of 55%[26].

Grading should also be attempted on small biopsies of NENs to guide treatment decisions. Ki-67 index may be of more use in this setting than mitotic count due to often small volumes of material present for assessment[20].

Table 3: Grading system for GEP-NENs and PanNENs. From RCPath Dataset for histopathological reporting of neuroendocrine neoplasms of the gastroenteropancreatic tract[20]

Grade	Mitotic count (10 HPFs)*	Ki-67 index (%)**
G1	<2	<3***
G2	2-20	3-20
G3	>20	>20

*10 HPF =2mm^2 based on each HPF being 0.2mm^2 with at least 50 consecutive fields evaluated in areas of highest mitotic density (hot spots).
**Ki-67 proliferation index is based on the evaluation of ≥500 tumour cells in the areas of highest nuclear labelling (so-called hot spots). For assessing Ki-67, casual visual estimation (eyeballing) is not recommended; manual counting using printed images is advocated.
***<3 replaces ≤2 in the 2010 WHO classification to include decimal numbers between 2 and 3.
HPF: High power field

Two staging systems are currently in use for GEP-NENs; the ENETS system[27,28] and the Union for International Cancer Control/Tumour Node Metastasis 8th edition (UICC/TNM 8)[29]. For its most recent publication, UICC/TNM 8 generally adopted the ENETS system with the exception of staging of appendiceal NENs. Some site specific differences for T, N and M stages also remain. The ENETS staging system includes both NETs and NECs, however, NECS are excluded from UICC/TNM 8 and should instead be staged as for adenocarcinoma at their respective site[29].

Note that involvement of lymph node(s) by any volume of tumour is considered significant, and the classification of isolated tumour cells is not used in the reporting of GEP-NENs[20].

Serosal deposits found within the surgical field of the primary tumour are not considered metastases as they likely result from exfoliation of cells from serosa-invasive primary tumours[20].

RCPath recommends use of the ENETS staging system[20]. We recommend that the staging system used should be stated clearly in the report to avoid confusion.

6.5. Goblet cell adenocarcinoma of the appendix

Previously called goblet cell carcinoids, goblet cell adenocarcinomas of the appendix have been separated from other appendiceal NENs due to differences in clinical

course[1]. Goblet cell adenocarcinoma comprises a low-grade goblet cell adenocarcinoma component and variable numbers of neuroendocrine cells. These neoplasms are graded based on the relative volume of low and high-grade patterns within the tumour (see table 3) and not on mitotic count or Ki-67 index[1]. They are staged and treated as for colorectal and appendiceal adenocarcinoma[20,23,29].

Table 4: Three-tiered grading system for goblet cell adenocarcinoma. From RCPath Dataset for histopathological reporting of neuroendocrine neoplasms of the gastroenteropancreatic tract[20]

Grade	Tubular or clustered growth (low-grade pattern)	Loss of tubular or clustered growth (any combination of high-grade patterns)
1	>75%	<25%
2	50-75%	25-50%
3	<50%	>50%

6.6. Recommendations

- **GEP-NENs should be classified and graded according to current WHO classification and Royal College of Pathologists guidelines.**
- **The precise value of Ki-67 proliferation index should be stated within the pathology report to help guide treatment decisions.**
- **Staging should preferably be performed using the ENETS system as per RCPath guidance.**
- **Both classification and staging systems adopted should be clearly stated in the pathology report.**
- **Goblet cell adenocarcinomas should be graded as per the current Royal College of Pathologists guidelines, and staged as for colorectal and appendiceal adenocarcinomas.**

7. Management of MINENS {formerly known as MANECS and Goblet Cell Carcinoids}

Mixed Neuroendocrine Non Neuroendocrine Neoplasms (MiNEN), previously termed MANEC have been defined by the association of at least two morphologically different neoplastic components one of which one is neuroendocrine[30].

Each component of a MiNEN must theoretically account for 30 % of the cancer. This cut off value only applies to resected specimens at which time the whole specimen can be reviewed. Thus when evaluating a biopsy there is the potential for sampling bias and therefore caution must be advised. Furthermore the 30% threshold is not supported by evidence and was chosen purely because it was felt that a tumour composing less than 30% was unlikely to influence behaviour[31].

In terms of incidence if we review the data from Surveillance of Rare Cancers in Europe registry (2008), the incidence of MiNENs was below 0.01/100,000 cases per annum. Therefore due to the rarity of data the best management strategy for these tumours is hard to define.

In most cases MiNEN is an aggressive disease with the neuroendocrine component usually being of high grade. The non neuroendocrine component is usually adenocarcinoma, but is not exclusively so.

7.1. Localised disease

The data to support management of both localised and metastatic disease is poor and usually from single centre series and it is therefore very difficult to formulate recommendations

In a recent review by McNamara et al surgery was found to be the treatment of choice in nearly all potentially curable cases. Chemotherapy either as adjuvant treatment or peri-operatively tended to be offered, but in most cases followed the clinical guidelines for the adenocarcinoma component of that particular site[32].

7.2. Advanced disease

Treatment of metastatic MiNEN should be aimed at the neoplastic component responsible for the metastasis which is most commonly the neuroendocrine component. This component is usually the more aggressive component and so platinum based chemotherapy is usually the first line treatment. It has been documented that the neuroendocrine and non neuroendocrine components can metastasise together or separately, but usually only one tumour is present in the distant site. The ENETS guidelines suggest treatment based along similar lines to pure neuroendocrine carcinomas with platinum based chemotherapy[33].

7.3. Recommendations

- **The incidence of MiNEN's is very low and so the evidence base from which to base recommendations is sparse**

- **Surgery should be considered for localised disease. Following surgery adjuvant chemotherapy could be considered, but this is not supported by randomised evidence**

- **Advanced disease is usually due to one or other component and so biopsying the metastatic deposit would be advised.**

- **Treatment of advanced disease should be directed at the metastatic disease type which in most cases will be the neuroendocrine component and so platinum based chemotherapy should be considered.**

- **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:[34]

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

Typical or atypical bronchial carcinoids are relatively uncommon. However they constitute between 20-30% of all NETs. They are often found incidentally. Large Cell Neuroendocrine Carcinomas (LCNEC) are more complex to manage. Pure small cell tumours remain within the domain of lung cancer teams. However LCNEC may have an intermediate behaviour, the recent recognition of the importance of ki 67 with values between 20 and 55% has changed practice. At other sites these are reclassified as G3NETs. These behave more like atypical bronchial carcinoids and should be discussed with NET team. Imaging with both SSTR and FDG PET is usually advised. There is a higher chance of positive SSTR so somatostatin analogues may be considered and again treatment with PRRT has been reported although the licence currently does not include these reporting of the ki 67 has not always been carried out. Repeat biopsies should be considered. Small cell lung cancer is generally not considered to be a NET.

At present platinum and etoposide based chemotherapy is considered as standard of care but new molecular profiling suggests different patterns with differential response rates and recommendations may change in next few years. Imaging with both FDG PET and SSTR should be considered in these patients. Molecular profiling is likely to become more established over next 5 years. At least two different molecular subtypes have been recognised in past few years. Alternative options include temozolomide based regimens and everolimus particularly in tumours with lower ki 67 and clinical behaviour more in keeping with an AC.

LCNEC is considered a variant of non-small cell lung cancer (NSCLC). The initial management of LCNEC 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 SCONET perspective, BP NETs effectively equate with BP carcinoid tumours, both typical and atypical. However if patients with LCNEC or SCLC show unexpected survival, a review of the pathology should be considered.

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 described[35] 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.[36] 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.[37]

Patients with BP carcinoid tumours seldom present with or exhibit features of carcinoid syndrome.[38] 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. Very occasionally Cushing's syndrome may be the presenting symptom, but more often it is a later feature of disease.

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.[39] In certain cases, especially in the medically unfit, repeated local ablation with laser or cryotherapy may be an alternative to anatomical lung resection.[40-41]

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.[42]

BP NETs should be classified according to the 2004 WHO classification[43] and staged using TNM8. This WHO classification has been criticised for retaining the carcinoid nomenclature[35] 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.[44]

- Typical carcinoids are histologically typified with a carcinoid morphology with <2 mitoses per 2 mm^2 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 mm^2 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 mm^2 are regarded as LCNET and in the WHO classification fall into the large-cell category rather than carcinoids.[45] 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 but is expected to be recommended in the next WHO revision and is very useful in clinical day to day practice. The finding of a ki 67 between 20-55% in a LCNEC or SCLC diagnosed on a small fragment raises suspicious of an Atypical Carcinoid or G3NET.

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. Genetics

Up to 10% of BP/Thymic NETS may develop in patients with MEN 1 syndrome. This should always be considered by taking family history and checking calcium and PTH. When proven referral is made to genetics/endocrinology. See section 15.

8.8. 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 classification[34] and staged using TNM 8.**

- **On the rare occasion where the carcinoid does represent a functional NET, octreotide therapy should be considered prior to surgical resection of the tumour.**

- **Long term follow up is advised in view of the higher risk of late relapse by clinics expert in managing NET cancers, or via shared care where appropriate.**

9. Medical Therapy and Newer 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.[46] Most gastro-entero-pancreatic NETs over-express SSTR2, which makes this the current major target for medical therapy.[47]

9.2. Somatostatin Analogues

Somatostatin analogues remain the most effective and commonly used agents in the medical treatment of NETs.[47] Octreotide and lanreotide are the only two synthetic somatostatin analogues currently approved for clinical use in NETs; these agents bind with:[48]

- 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 it is more routinely used in its long-acting (28-day) formulation. Similarly, lanreotide is also available as intermediate (7–14 days) and long-acting (28-day) formulations. Traditional 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.[47] Although patients with NETs with no SSRI uptake during diagnostic imaging respond less well to somatostatin analogues, a 3-month trial of therapy is usually worthwhile if the patient is symptomatic.[49] It is hoped that, with greater accessibility to more sensitive radionuclide imaging such as Gallium-68 DOTATE PET, we may identify more individuals with positive imaging who are more likely to benefit from somatostatin analogue therapy.

Symptomatic control occurs in most patients in response to somatostatin analogue therapy and biochemical improvement is seen in 30–70% of patients.[50,51] Somatostatin analogue therapy is, in general, well tolerated; side effects include gastrointestinal upset, hypo- and hyperglycaemia, headaches and dizziness.[52] Malabsorption and steatorrhoea are probably more common than literature suggests and pancreatic supplements may be useful for symptom control. Cholelithiasis has been reported in up to 50% of patients but more typically around 20%, but few (1–3%) develop symptoms severe enough to warrant cholecystectomy.[53]

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.[54,55,56,57,58,59,60,61] In recognition of this lack of evidence, the PROMID trial was initiated; this was the first, phase III, placebo-controlled, randomised study in patients with metastatic NETs of the midgut.[62] 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 was subsequently 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.[63] 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.

In patients with hormonal symptoms or elevated 5HIAA levels SSA should be considered at diagnosis. In patients with low volume, hormonally asymptomatic disease it may be possible to have a period of observation commencing SSA at symptomatic, radiological or hormonal progression.

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.[64] 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.[65] 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.[66] Data supporting the anti-proliferative effects of pasireotide are currently lacking,[67],[68] but the results from phase II trials are promising in terms of tolerability and symptomatic benefit. The manufacturer has so far not chosen to seek a licence in NETs. Similarly, somatostatin receptors may also heterodimerise with other G-protein coupled receptors such as the dopamine D2 receptor.[66] 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.[69] In addition, chimeric compounds incorporating both

dopaminergic and somatostatinergic agents have been developed and are undergoing further investigation in NET treatment.[70]

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. There would appear to be no significant difference in efficacy between the two agents with very similar activity, efficacy and toxicity. Both are now available in Scotland with home care delivery systems. Lanreotide is more suited for self-administration.

If SSA have been commenced for disease-control, as opposed to symptom control, consideration should be given to discontinuing treatment on disease progression. If patients have hormonal symptoms or elevated HIAA, SSA will likely continue whilst other therapies are considered.

Somatostatin infusions may be need prior to surgery or other interventional procedures. This is best reviewed in the UKINETS bite size guidance[71].

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 or do not derive benefit from somatostatin analogues or who show progression on somatostatin analogues.[50] In practice, however, widespread use of this agent is limited by severe side effects (fatigue, myelosuppresion, myalgia and weight loss, mood disturbance and even increased risk of suicide). There is some limited 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.[50]

Animal data show considerable activity with Interferons but human clinical trials have been less convincing for a reliable 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 a recommended first-line treatment approach due to the small numbers of patients included in such studies.[72] The use of IFN outwith Scandinavia and Germany has rarely been adopted in any large scale.

9.5. Telotristat ethyl

Diarrhoea in some patients with SINETS and carcinoid syndrome can be very disabling and seriously impair quality of life. A careful review and exclusion of other causes of diarrhoea should be investigated and treated. It is recommended that discussions with a friendly gastro-enterologist should be considered. Telotristat ethyl (previously known as Telotristat etiprate) blocks the conversion of 5 hydroxy tryptophan to 5 hydroxy tryptamine. Several clinical trials have been reported which show marked reduction in stool frequency and also reduction in serotonin and urine 5HIAA levels.[73] In July 2018 SMC approved the use of Telotristat for refractory diarrhoea in carcinoid syndrome with patients have in excess of 4 stools per day.

9.6. Sytemic Anti-Cancer Therapies (SACT)

A number of new and emerging drug treatments are available or being investigated in the treatment of NETs (www.clinicaltrials.gov/ct2/results?term=neuroendocrine). Currently available options include targeted agents, everolimus, sunitinib and cytotoxic chemotherapy

9.7. 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 (RADIANT-3).[74] 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.[75] 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. In addition, everolimus has been shown to cause or exacerbate hyperglycaemia (especially if pre-existing) and so may be particularly useful in the management of patients with insulinoma and refractory hypoglycaemia.

Evidence for the use of everolimus in non-pancreatic NET comes from a large, double-blind, placebo-controlled trial (RADIANT 2).[74] 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. However the trial was insufficiently powered to show a statistically significant benefit.

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.[75] Patients may be of performance status (PS) 0, 1 or 2; although very few in the trial were of PS 2.

More recently, the RADIANT-4 placebo-controlled trial provided more definitive evidence of benefit from everolimus in patients with advanced, non-functional lung or small intestinal NETs. In this trial of 302 such patients, everolimus was associated with a significant improvement in progression free survival (11 versus 3.9 months) as well as a disease control rate of 81% compared to 64% for patients assigned to placebo.[76] It is now approved by SMC in Scotland for both these clinical indications. Subset analysis has suggested a better effect in BP NETS however until recently the alternative options in SINETS have been limited. The recent approval of Peptide receptor radionuclide therapy (PRRT) in GEPNETs, see section 12, will change the clinical options and sequencing of treatments.

9.8. 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.[77] 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.

9.9. Other TKIs

Two other TK inhibitors, sorafenib and pazopanib have been evaluated in pancreatic NET in phase II studies and have shown modest efficacy with response rates of 9% and 22% respectively.[78,79] More recent studies have investigated cabozantinib, sulfatinib and lenvatinib. The latter was used in the TALENT study[80] and has shown 29-40% RR.

To date, Sunitinib (in common with sorafenib and pazopanib) has been evaluated in advanced GI NET in phase II trials only. So far, response rates have been low although there are reports of a high rate of disease stabilisation. Currently, there are insufficient data to support their routine use in advanced GI NET.

A number of new TKIs/MKIs are being investigated but data using Lenvatinib was published from the TALENT study[81] (currently in press) and showed 30-40% RR. Other drugs under development include PARP inhibitors.

9.10. Immunotherapy and other approaches

New treatment options are developing quickly. The PDR001 study investigated spartolizumab, a new PDL1 inhibitor. Whilst the overall results were disappointing, there were hints of response in BPNETS and higher grade (G3) NETs. Given the built-in obsolescence of these guidelines, it is anticipated that these new therapeutic approaches will become established in the next 3-5 years. Other new drugs under investigation include durvulumab alone or in combination and ROVA-T.

9.11. 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. The more recent approval of PRRT will impact on the scheduling of these treatment options.

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.[82,83] In addition, a more recent phase II trial of progressive metastatic NET demonstrated benefit of bevacizumab in combination with the cytotoxic agent, capecitabine.[84]

9.12. Liver dominant disease

Initial treatment is usually fairly straightforward with initiation of SMS analogue therapy and either octreotide or lanreotide are selected. The choices become more complex on progression and are determined by the factors listed below together with site of metastatic disease. Management of liver dominant disease is very different from diffuse disease. Surgical options should always be considered, and for liver dominant disease locally ablative treatments may be deployed including liver resections, ablation (RFA and microwave) as well as embolisation.

9.13. Widespread metastatic disease

Factors that are now used to choose therapy include the site of tumour (BP vs pancreas vs. SINETS), the grade of tumour (G1 vs. G2 vs. G3 NET vs. G3 NEC), ki 67 score, SSRI uptake and patient fitness and performance status.

The options in pancreatic NETs are greater and there is much debate as to how to sequence them, and the recent approval of PRRT (see chapter 12) has only added to this whereas for SINETs the choices are simpler where PRRT has emerged as the preferred first choice on progression with SSAs.

9.14. 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 considered 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, small intestinal and broncho-pulmonary 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 1with adequate organ function.**

- **Telotristat ethyl should be used for second-line hormonal control in patients with significant diarrhoea (> 4 stools per day) induced by carcinoid disease after exclusion of reversible or other treatable causes. INF-α may be considered for symptomatic relief in patients who fail to tolerate or show no benefit from somatostatin analogue therapy and Telotristat.**

10. SACT – 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%).
- New revision now separates G3 into G3 NET with ki 67 20-55% and G3 NEC where Ki-67 >55% which have different behavioural characteristics and responses to chemotherapy and PRRT.[85]
- Site of origin of NET: Pancreatic NETs should be considered separately from small intestinal NETs (SINETS) and bronchopulmonary NETS (BPNETS).
- Molecular profiling over the next 5 years will play a key role in treatment planning for both treatment selection and predicting /optimising treatment response.

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 6.

Table 5: 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%)	Moderately Chemoresistant
G3 NETs (ki 67 20-55%)	Moderate chemosensitivity but may show SSTR uptake
Poorly differentiated NECs (G3) (ki 67 >55%)	Highly chemosensitive but for a short duration, usually SSTR negative but ^{18}FDG positive uptake

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.[86] 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.[87] The place of cisplatin (CIS) was assessed in the UK NET01 study that compared STZ/CAP with CIS/STZ/CAP.[88] 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.[89]

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.

Capecitabine-based regimens should not be initiated without testing patients for DPD polymorphisms first.

Other agents that have been investigated for well-differentiated and pancreatic NETs include other platinums (e.g. oxaliplatin [OX]) as well as irinotecan (IRIN) and gemcitabine.[90] However, none of these drugs has achieved any routine place in treatment to date although there in increasing use of FOLFIRI or FOLFIRINOX in higher grade tumours.

Platinum- and etoposide-based regimens tend to be favoured first line for high-grade (G3) tumours but for LCNEC lung new molecular markers may help to identify when to use SCLC schedules or NSCLC regimens.

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.[91] A recent study suggested that TMZ (with or without CAP) had activity in this situation.[92] 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.[93] This has been adopted as one of the arms in the NET02 trial but using liposomal irinotecan.

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. Re-challenge with platinum and etoposide may be given if the TFI is over 12 months, otherwise other schedules, or clinical trials, should be considered. Docetaxel has some activity and FOLFIRI is commonly used in central Europe although with no good clinical supporting data. The NET02 study will compare these two regimens.

There is emerging evidence for clinical activity of PDL1 in inhibitors such as spartolizumab in G3 NETs/NECs and BPNETs. These may be used in combination.

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.[94] At the current time there is debate as to whether chemotherapy remains the first-line choice treatment; the available regimens are summarised in Table 9. Trial now closed and awaiting analysis. The selection further challenged by emerging use of PRRT at earlier stages of disease.

Outside the NET-01 clinical trial there isn't yet a published randomised comparator of chemotherapy regimens. It may be appropriate to select a regimen on the basis of toxicity. The temozolomide-capecitabine combination is usually better tolerated than alternative chemotherapy regimens or TKIs

Table 6: The chemotherapy regimens, and biological and novel agents for treatment of NETs

Agents, regimens and indications	
Chemotherapy	
• STZ/5-FU • STZ/DOX • STZ/5-FU/DOX +/- DTIC • TMZ/CAP	Pancreatic NETs
• STZ/5-FU • CAP • CAP/STZ • CIS/CAP/STZTMZ +/- CAP	Well-differentiated GEP NETs
• CIS/etoposide • CAV(E) • TMZ/CAP • FOL/F/IRIN • Docetaxel	Poorly differentiated GEP and BP NETs
Biological agents	
• Somatostatin analogues (e.g. octreotide and lanreotide)	First-line medical treatment of symptomatic NETs
• Interferons	Second-line for symptom control in patients who fail to tolerate somatostatin analogues

Licenced TKIs	
• Everolimus and other mTOR pathway inhibitors	G1 and G2 pancreatic NETs
• Sunitinib	G1 pancreatic NETs
• Agents in development for NET management	
• Lenvatinib	TALENT study[80] shows considerable activity in PancNETS and SINETs
• Cabozantinib	Early signs of activity similar to lenvatinib
• Sulfatinib	Chinese trial reported at ENETS 2017 shows good activity
• PDL1	Several agents are under investigation
• Palbociclib	Under investigation still

10.5. Mixed Non Neuroendocrine Neoplasms (MINENS)

Chemotherapy for goblet cell or mixed endocrine/exocrine tumours (adenoneuroendocrine carcinomas) is being re-evaluated. They have been re-named and Mixed Non-Neuroendocrine Neoplasms. The contemporary view is that these are not NETs but are of gastrointestinal origin and that they should be treated using gastrointestinal chemotherapy regimens.[95] 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, see tables 8 and 9. 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.

Table 7: Potential Sequences in Pancreatic NETs

1	1st line Chemo	Targeted agent	PRRT	2nd line Chemo
2	Targeted	1st line chemo	PRRT	2nd line chemo
3	Targeted	PRRT	1st line chemo	2nd line Chemo
4	PRRT	1st line Chemo	Targeted	2nd line Chemo
5	PRRT	Targeted	1st line Chemo	2nd line Chemo

Table 8: Sequencing options SI/BP NETs

PRRT	Everolimus	Chemo STZ or Temo/Cap
Everolimus	PRRT	Chemo
Clinical Trials		

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. New molecular markers and profiling is likely to have a major impact in next 5 years and will show differential responses rate to platinum and non platinum schedules.**

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

11. Radionuclide Therapies

11.1. 131I-mIBG Therapy

Meta-iodobenzylguanidine (mIBG) is a noradrenaline analogue, which, when labelled with ^{131}I, 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 ^{131}I-mIBG therapy include:

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

^{131}I 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 ^{131}I-mIBG therapy takes into account the patient's age, fitness, urinary and faecal continence and ability to give informed consent. Adult patients requiring ^{131}I-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 60-90 minutes. A typical adult treatment dose is 7500–10000 MBq. Much of the ^{131}I 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 ^{131}I iodide released as a breakdown product by administering potassium iodate. For adults this consists of 130 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.[96]

11.2. Peptide Receptor Radionuclide Therapy (PRRT)

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 ^{90}Y or ^{177}Lu.[97,98]

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

There is a preference 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 or even in combination.

However NICE only recommend Lutathera and in Scotland only Lutathera is approved. A commercially produced, pre-formulated ^{177}Lu-DOTATATE now known as Lutetium-oxodotreotide Is the preferred format. Other formulations from other manufacturers are currently under development.

The usual activity administered is 7.4 GBq of ^{177}Lu-Oxodotreotide and the patient usually remains in hospital for 1 night. It is currently standard practice to administer 4 activities of 7.4GBq at 8 weekly intervals although both the activity and frequency may be modified if clinical circumstances advise. When 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. Screening for haematological reserve, renal and hepatic function and carcinoid heart disease are performed prior to patients being treated.

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.

SMC approved the use of PRRT for GEPNETs during 2018 and a business case with NHS National Services Division has now been approved and a Scottish national service was established on 1 April 2019. A referral form and pre-screening proforma are attached as an appendix (refs).

11.3. 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 phaeochromocytoma/ paraganglioma/neuroblastoma in patients with $^{123/131}$I-MIBG positive disease.**

- **Radiolabelled somatostatin analogues (Lutathera) are now approved for the treatment of GEPNETs patients with significant disease demonstrated on somatostatin receptor scintigraphy and acceptable renal function. A national service was established at Beatson West of Scotland Cancer Centre in April 2019.**

12. Interventional Radiology for Liver 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).

12.1. 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[99] but there are no prospective, head-to-head data comparing systemic chemotherapy versus TACE/HAE. Good symptom relief of between 70–90%[100,101] 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.[101] Mean survival with TACE/HAE is reported to be 3.5 years with a mortality rate of 2–4%.[102] 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.

12.2. 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.[103]

12.3. RE

This is an innovative locoregional therapy comprising intra-arterial radiotherapy to the tumour using pure β-emitting ^{90}Y 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,[104,105] 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.

12.4. 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.

12.5. 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.**

13. Carcinoid Heart Disease

Excellent international guidelines have been published on the presentation, investigation and management of carcinoid heart disease. These are:

Diagnosis and Management of Carcinoid Heart Disease (2017) Davar et al. Journal of the American College of Cardiology, vol 69, issue 10: 1288 – 1304.[106]

Neuroendocrine tumours are uncommon tumours. Approximately a third of patients with NETs (particularly those with midgut primaries) develop carcinoid syndrome, particularly if there has been metastases to the liver.

Carcinoid syndrome is characterised by intermittent vasomotor symptoms: flushing, diarrhoea, hypotension (or hypertension), and bronchospasm.

Carcinoid heart disease occurs in up to half of the patients with carcinoid syndrome. It is thought that the circulating serotonin causes an endocardial process with thickening of the heart valve tissues that are in contact with the high circulating levels of serotonin. The thickening of the leaflets causes the valve function to reduce. In some occasions thickening causes stenosis of the valves as the leaflets become less mobile. But more commonly the thickening causes the leaflets to thicken, shorten and retract with consequent failure of leaflet coaptation and regurgitation. The valves affected are usually the right sided valves (tricuspid > pulmonary), but if there is an atrial septal defect (including patent foramen ovale) then the left sided valves (mitral > aortic) may also be affected. It is hypothesised that the lungs deactivate the serotonin and associated vasoactive peptides.

Non-valvular carcinoid heart disease: The vasoactive peptides may also cause **coronary artery vasospasm** in patients with non-obstructive coronary artery disease[107]. It has been postulated that in the context of an atrial septal defect, serotonin may contribute to coronary artery stent thrombosis because of platelet activation[108]. **Arrhythmias** are a rare association with carcinoid heart disease. Serotonin has been implicated in both atrial and ventricular arrhythmias possibly by driving sympathetic tone. **Metastatic deposits in myocardium** is an unusual consequence of carcinoid heart disease. If under 1cm in size they may not be identifiable on transthoracic echo, but may be detected by PET-CT. They can be obstructive depending on their location in the heart. They are potentially resectable[109].

The major clinical presentation of carcinoid heart disease is right heart failure. This is best managed with diuretics to manage the volume status. In addition, ensuring that there is optimal management of the NET is critical.

The prognosis of carcinoid heart disease, if left untreated is poor: 31% 3-year survival. If there are significant heart failure symptoms (NYHA III or IV) then median survival is 11 months.

13.1. Screening for carcinoid heart disease

Patients with carcinoid syndrome should be screened every 6-12 months with clinical assessment for cardiac murmurs, and evidence of right heart failure (peripheral oedema in particular). In addition, measurement of serum NT-proBNP is recommended. NT-proBNP is a cardiac biomarker that is used to monitor patients with heart failure. Worsening heart failure is associated with increasing levels of NT-proBNP.

In carcinoid heart disease patients with NETs who have a higher level of urinary 5-HIAA (>300micromol/24hr) are at higher risk of developing carcinoid heart disease.
If the NT-proBNP is <260ng/ml – continue with clinical surveillance and NT-proBNP assay every 6-12 months.

If the NT-proBNP is >260ng/ml and/or there are features suggestive of carcinoid heart disease, then refer for transthoracic echo.

If the transthoracic echo confirms carcinoid heart disease then onward referral to a Cardiologist with an interest in carcinoid heart disease is appropriate. If the echo is normal then continued surveillance is indicated. If non-carcinoid features are seen on echo, then referral to a Cardiologist should be made.

13.2. Imaging diagnosis of carcinoid heart disease

Imaging of the heart to assess for carcinoid heart disease can be achieved with transthoracic echo, transoesophageal echo, MRI and CT. The transthoracic echo (TTE) is diagnostic in the majority of cases.

TTE features of carcinoid heart disease include thickening and shortening of the heart valve leaflets, particularly of the tricuspid valve. Additional assessment should include assessment of biventricular function, and whether there is a septal defect.

Efforts should be made to ensure that classical echo features of carcinoid heart disease on echo, should trigger referral for NET work up including CT, Octreotide scan, Chromogranin and 5HIAA check. Early discussion with the local NET team would be advised.

Cross-sectional imaging with MRI or CT can be performed if the TTE is non-diagnostic. In addition, CT can be used to assess for coronary artery disease in patients proceeding to valve surgery if they are >40 years of age.

13.3. Management of carcinoid heart disease

- ***Symptom control*** of right heart failure

Diuretics can help control peripheral oedema – starting doses include Furosemide 40mg once or twice daily.

Compression stockings can help control symptoms.

- ***Optimisation of carcinoid treatment*** as per guidelines above
- ***Surgical intervention*** to affected heart valves

Surgical management of carcinoid heart disease in current practice is the replacement of affected valves usually with bioprostheses. This is a major undertaking and is appropriate to consider if carcinoid syndrome is controlled and the prognosis is estimated at over 12 months.

The aim of cardiac surgery is to control the symptoms of heart failure. It does not alter the metastatic cancer diagnosis, although it may facilitate treatment options for the primary disease. The surgical valve replacements can be affected by the carcinoid heart disease.

Carcinoid heart disease may have a rapid progressive course. Therefore, early referral for Cardiology opinion is appropriate to allow surveillance and consultation about the need and timing of surgery.

Indications for cardiac surgery include:

- Fatigue and dyspnoea with oedema +/- ascites
- Progressive asymptomatic right ventricular enlargement/dysfunction
- Before hepatic surgery or possibly to facilitate PRRT

All patients with severe TR secondary to carcinoid heart disease should be considered for valve replacement.

Risk factors for poor outcomes in cardiac surgery have been identified as:
- Older age
- Advanced heart failure symptoms
- Elevated creatinine.

Early mortality following cardiac surgery is estimated at 5% from the Mayo group.[110] This has improved over recent eras with improved case selection and perioperative care.

Overall survival was quoted from the Mayo group as:
- 1 year 69%
- 3 years 48%
- 5 years 34%.

The current practice recommends bioprosthetic valve replacement as opposed to mechanical valve replacement. This reflects observational data about recurrence rates and the challenge of mandatory longterm anticoagulation necessitated by mechanical valves. 3-6 months of anticoagulation is considered post-operatively, reflecting preliminary evidence suggesting that this may prevent micro-thrombi developing on the bioprosthetic leaflets which may cause early valve failure. However, this should be individualised to the patient as anticoagulation may be challenging in the post-operative care.

Peri-operative management is challenging. The patient should be managed in collaboration with Oncology, Endocrinology, Cardiology, Cardiac Surgery, Anaesthetics and Critical Care. Pre-optimisation of both volume status and carcinoid is essential. Pre-admission is recommended for intravenous diuretics if required and initiation of IV Octreotide infusion as described in the UKINETS document on the management of perioperative octreotide[71].

The infusion should be commenced 12 hours pre-operation and continued for at least 48 hours before slow and cautious down-titration. Clear protocols on the recognition and management of carcinoid crisis must be in place throughout the peri-operative course.

Post-operatively the patient needs careful continuation of carcinoid care. The cardiology follow-up should be continued with 6-12 monthly clinical examination and monitoring of NT-proBNP, +/- TTE.

If the bioprosthetic valve fails, then re-referral for review with Cardiology is indicated. Re-operation is possible and transcatheter valve-in-valve replacement may be possible.

13.4. Recommendations

- **Patients with carcinoid syndrome should be screened every 6-12 months with clinical assessment for cardiac murmurs, and evidence of right heart failure (peripheral oedema in particular). In addition, measurement of serum NT-proBNP is recommended.**

- **Efforts should be made to ensure that classical echo features of carcinoid heart disease on echo, should trigger referral for NET work up including CT, Octreotide scan, Chromogranin and 5HIAA check. Early discussion with the local NET team would be advised.**

- **Carcinoid heart disease may have a rapid progressive course. Therefore, early referral for Cardiology opinion is appropriate to allow surveillance and consultation about the need and timing of surgery**[111]

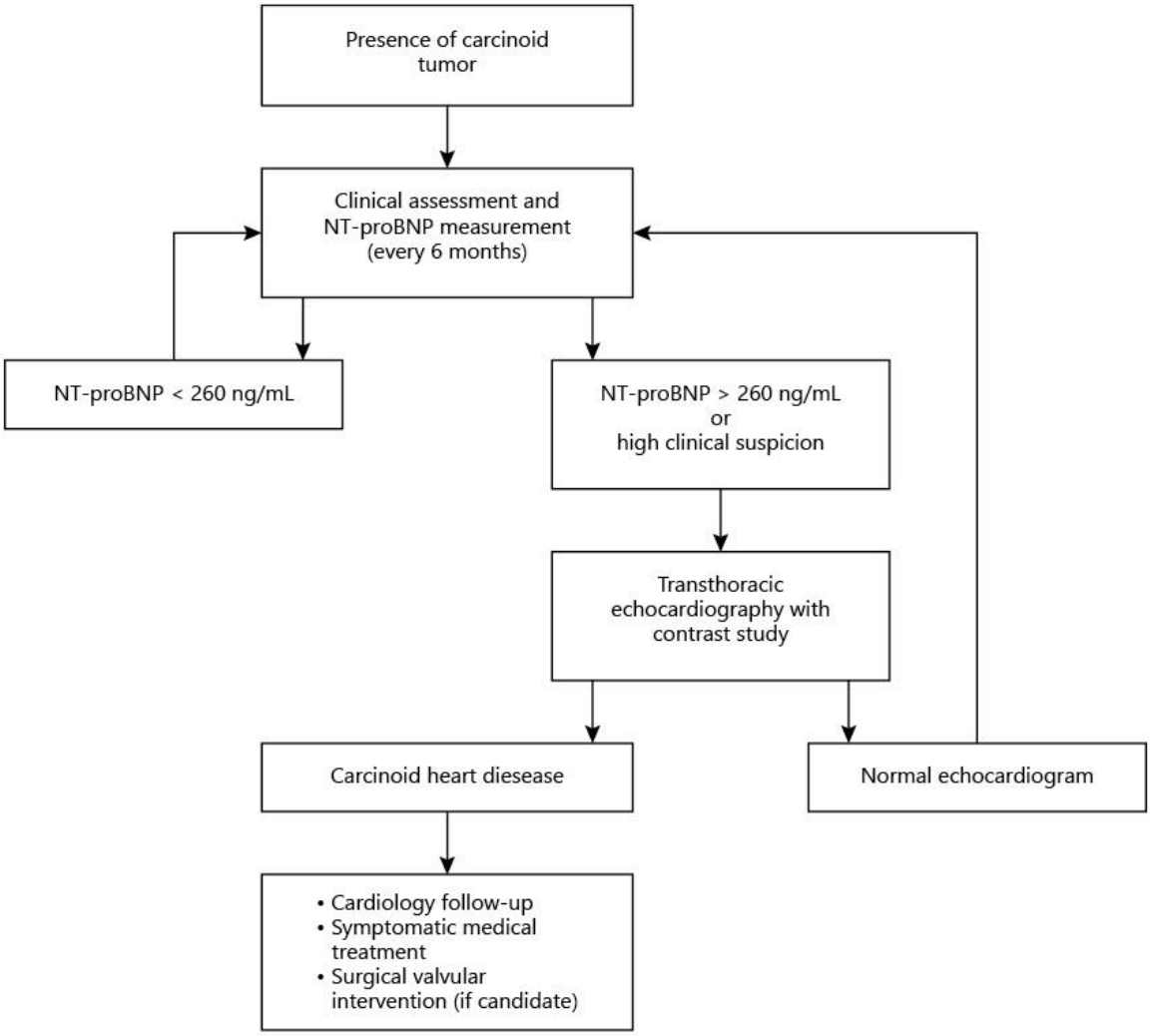


Figure 2: Diagnostic and treatment algorithm for carcinoid heart disease

14. Genetics

14.1. Overview of Genetic Testing

Several monogenic hereditary endocrine tumour syndromes manifest neuroendocrine tumours including pancreatic NETs, foregut NETs, and phaeochromocytoma/paraganglioma (PPGL). Thus, the possibility of a hereditary condition should be considered in those presenting with relevant tumours. Once a genetic diagnosis is established, it is important to consider whether cascade genetic testing of 'at-risk' first-degree family members is indicated (e.g. for autosomal dominant disorders). Close working relationships between the physician and clinical genetics team are required and specialist input may be needed for pre-conception genetic counselling, pre-implantation or pre-natal genetic diagnosis.

The potential indications for undertaking genetic testing in those presenting with NETs are specific to the clinical presentation. However, potential indicators of a hereditary monogenic syndrome may include, young age of disease onset, tumour multiplicity, and presence of a relevant family history (e.g. affected first-degree relatives). Indeed, establishing whether there is a relevant family history is an essential component of the clinical evaluation, although the absence of such history does not exclude the possibility of a monogenic disorder. For example, a family history may be absent due to: the presence of a *de novo* pathogenic variant in the affected patient; reduced or variable age-related disease penetrance for the familial mutation; inadequate knowledge of the medical history or incomplete clinical evaluation of relatives; or geographical or social separation of kindreds.

Genetic testing may be performed for diagnostic purposes in an index case, or for predictive testing in symptomatic or asymptomatic relatives of an affected patient. Some indications for genetic testing relevant to NETs are provided in Table 6 and highlight the more frequent situations in which genetic testing may be appropriate. Any uncertainties regarding genetic testing should be discussed with the clinical genetics team.

Genetic testing for the majority of hereditary endocrine disorders is performed using a disease-targeted gene panel (see appendix 2). All relevant information (diagnosis, age of onset, relevant family history) should be provided on the request proforma. Consent for genetic testing should be obtained prior to diagnostic testing according to local protocols. Whilst the majority of monogenic disorders associated with NETs result from either single nucleotide variants (SNVs) or small insertions or deletions (indels), it is important to note that larger scale genetic abnormalities (e.g. *partial or whole gene deletions)* may not identified by gene panel testing. Where this remains a possibility, alternate testing strategies may be required (e.g. multiplex ligation-dependent probe amplification (MLPA) analysis). Likewise, when initial genetic testing is negative but a strong clinical suspicion persists for a given disorder, discussion with the clinical or molecular genetics team is appropriate to consider alternate genetic testing strategies.

For penetrant autosomal dominant monogenic endocrine tumour syndromes (e.g. MEN1, MEN2, Familial PPGL) predictive genetic testing of asymptomatic first-degree relatives is recommended and should be undertaken by the clinical genetics team following appropriate counselling. The suggested age to undertake predictive genetic testing in asymptomatic first-degree relatives is disease-specific, but is usually recommended around the time that clinical, biochemical and/or radiological surveillance would commence. For several disorders associated with early-onset disease (e.g. MEN1/MEN2), genetic testing is recommended in early childhood with appropriate parental consent.

DNA sequence variants (e.g. SNVs, indels) identified in the relevant gene(s) under test are evaluated according to the American College of Medical Genetics & Genomics (ACMG) recommendations, and are classified into one of 5 groups: pathogenic (class 5), likely pathogenic (class 4), variant of uncertain significance (VUS) (class 3), likely benign (class 2), or benign (class 1)[112]. Typically, only VUS, likely pathogenic and pathogenic variants (i.e. classes 3-5) are reported to the clinician. Cascade/predictive genetic testing of first-degree relatives is typically recommended for pathogenic/likely pathogenic variants in genes associated with penetrant autosomal dominant disorders. In contrast, genetic testing of asymptomatic relatives of a patient with a VUS is not usually recommended, although the testing of additional symptomatic family members may aid a more definitive variant categorisation (i.e. by increasing or decreasing support for pathogenicity).

Table 9: Examples of potential indications for germline genetic testing relevant to NETs and PPGL

Indication/Clinical Setting	**Appropriate genetic test(s)**
In an index case with clinical features indicating a specific monogenic disorder	
- ≥2 typical clinical manifestations of MEN1/MEN4 (e.g. pituitary, parathyroid, pancreatic NET)	MEN1/4 gene panel ± MLPA*)
- Isolated or combined clinical features suspicious for VHL (e.g.retinal or CNS haemangioblastoma, PPGL, early onset renal cell carcinoma)	*VHL* gene panel + MLPA
- Features consistent with MEN2A (e.g. MTC + hyperparathyroidism and/or PPGL)	*MEN2A/B* gene panel
- Clinical features suspicious of MEN2B (e.g. mucosal neuroma, marfanoid appearance)	*MEN2A/B* gene panel
- Features consistent with Neurofibromatosis type 1 (e.g. ≥6 café-au-lait patches, ≥2 neurofibromas, axillary freckling, optic gliomas, Lisch nodules, relevant bone lesion	*NF1* Single gene test + MLPA
In an index case with apparently single and/or sporadic endocrine tumours	
Majority (if not all) patients with PPGL Some indications for genetic testing in PPGL patients may include; - PPGL at young age (e.g. <60 years) - Head and Neck PPGL - Sympathetic PPGL - Metastatic PPGL - Bilateral or multiple PPGL - PPGL and history Renal cell carcinoma (RCC) - Clinical features suggestive of a specific disorder (e.g. VHL, MEN2, NF1) - PPGL with loss of staining for SDH protein by IHC - PPGL at any age with ≥1 relative with PPGL or RCC	PPGL gene panel + MLPA (*VHL* and *SDHB/C/D*)
- All patients with MTC irrespective of age or family history	*MEN2A/B* gene panel
- All patients with sporadic gastrinoma	*MEN1/4* gene panel
- All patients with single endocrine tumours but family history suggestive of a relevant monogenic endocrine disorder	Appropriate gene panel
In an index case with early onset endocrine tumours or tumour multiplicity	
- Primary hyperparathyroidism: <30 years of age and/or multi-gland parathyroid disease	Hyperparathyroidism gene panel
- Pituitary adenoma presenting in children and young people (e.g. ≤21	FIPA/Pituitary

years of age)	adenoma gene panel
- Patients with multiple pancreatic NETs	*VHL/MEN1 gene panel /NF1 + MLPA**
- Classic/non-classic combinations of endocrine tumours (i.e. ≥2 tumours that are not exclusively limited to the main diagnostic groups (e.g. parathyroid + adrenal tumour)	Relevant endocrine tumour gene panel
Predictive testing: all symptomatic and asymptomatic first-degree relatives of patient with known moderate or high penetrance NET-associated mutation	
- Examples include first-degree relatives of those with *MEN1*, *RET, VHL*, *CDKN1B*, *SDHB, SDHC, SDHD* + others	Variant-specific testing
Examples of situations in which genetic testing not typically indicated	
- sporadic solitary non-functioning or functioning pancreatic NET in absence of additional clinical features/family history of associated monogenic disorders (e.g. MEN1, VHL, NF1 (with exception of gastrinoma and MEN1)	NA
- sporadic bronchial carcinoid in absence of additional clinical features/family history	NA
- sporadic thymic carcinoid in absence of additional clinical features/family history suggestive of MEN1	NA
- Predictive testing in asymptomatic first-degree relatives of index case with a VUS in monogenic endocrine disease gene	NA

*MLPA analysis may be appropriate for genes in which partial or whole gene deletions have been reported in association with disease particularly where there is a high index of suspicion and initial Gene panel/DNA sequencing does not identify a causative variant.

14.2. Phaeochromocytoma/Paraganglioma (PPGL)

14.2.1. Genetic Analysis

Approximately 30% of PPGL cases are familial[113-114]. Germline genetic testing should be considered in the majority of patients affected with a PPGL (Table 6). An EDTA blood sample can be sent (with all relevant clinical details) to the local molecular genetics laboratory. DNA will then be extracted and sent to the Scottish Consortium Laboratory in Dundee for panel analysis. The current PPGL panel employed by the Scottish Consortium Laboratory is consists of VHL, MAX, RET (exons 5, 8, 10, 11, 13-16), SDHA, SDHB, SDHC, SDHD, SDHAF2, TMEM127, FH, and NF1 (see appendix 2). It is strongly recommended that patients identified to harbour pathogenic/likely pathogenic variants in disease-relevant genes are referred to the local clinical genetics team for further management (e.g. discussion of predictive testing of first-degree relatives).

The clinical management of the patient will be determined by the disorder implicated. The most common hereditary disorders associated with PPGL include the Familial PPGL syndromes due to succinate dehydrogenase enzyme complex variants (SDHx), Multiple Endocrine Neoplasia type 2 (MEN2), and von Hippel Lindau (VHL) disease. Specific guidance for the management of these disorders is provided elsewhere [113,115,116,117,118,119,120]. Patients with pathogenic/likely pathogenic variants in genes associated with hereditary PPGL are likely to benefit from clinical follow up in specialist and/or regional clinics with access to clinical genetics and endocrine services. Here, a very brief overview of the more common monogenic PPGL disorders is provided, including a summary of suggested clinical surveillance schedules for those identified to be at risk (e.g. known pathogenic/likely pathogenic variant carriers)

14.2.2. Surveillance monitoring for individuals at risk of hereditary PPGL including those harbouring pathogenic/likely pathogenic SDHx variants

Germline mutations in the succinate dehydrogenase (SDH) enzyme complex genes account for 30-40% of hereditary PPGL cases and are inherited in an autosomal

dominant manner[113,117,121]. PPGLs occurring in patients with germline *SDHB* mutations are reported to have an increased malignant potential, with a 5-year mortality of ~50%[113,117]. Mutations in the *SDHx* genes are also associated with additional tumours including gastrointestinal stromal tumours (GISTs) and renal cell carcinomas (RCCs). The penetrance of *SDHx* mutations is reduced such that ~20% and ~40% of *SDHB* and *SDHD* mutation carriers will express disease by 50-years of age, respectively.[117,122] In addition, *SDHD* and *SDHAF2* mutations display parent of origin effects and clinical surveillance is usually only recommended for those with pathogenic/likely pathogenic variants inherited from their father. The lifetime penetrance of PPGL in those with pathogenic *SDHA* and *SDHC* variants is reported to be lower at 1-4% and 8%, respectively[122,123].

There is general agreement that clinical, biochemical and radiological surveillance should be offered to individuals with pathogenic/likely pathogenic *SDHx* variants, with the aim of the early detection and treatment of associated tumours (Table 7). However, evidence supporting the optimal approach has not been established. Tumour development is unusual in first decade of life but has been reported in small numbers of cases[113]. Although the majority of suggested surveillance programs do not differentiate between the SDH subunit affected, the increased risk of malignancy and early-onset disease observed for *SDHB* mutations, indicates that implementation of surveillance is most important for patients harbouring this group of variants[112]. When employing interval imaging surveillance programs it is important to acknowledge the potential for incidental findings using whole body MRI. Likewise the frequency and content of surveillance schedule should also consider the potential psychological impact of such screening[114].

Table 10: Example of a suggested surveillance program for SDHx mutation carriers

Recommended surveillance	Interval	Age to begin*
Clinical review to include history for relevant symptoms and clinical examination	Annual	10-years (5-years for *SDHB*[§])
Blood pressure monitoring	Annual	10-years (5-years for *SDHB*[§])
Plasma fractionated metanephrines and/or 24-hour urine fractionated metanephrines	Annual	10-years (5-years for *SDHB*[§])
Whole-body MRI (skull-base to pelvis) with possible dedicated neck MRI protocol	2-3 years	15-years (10-years for *SDHB*[§])
Ultrasound for children for whom MRI is not tolerated	2-3 years	15-years (10-years for *SDHB*[§])

*Earlier imaging may be appropriate if there is evidence of symptoms/signs of disease or abnormal relevant biochemistry. Furthermore, where tumours have occurred at a very young age in a kindred, it may be appropriate for surveillance to commence at an earlier age than recommended above.
[§]The age-related penetrance of 'clinical PPGL' in *SDHB* mutation carriers is 1% and 5% at age 10 years and 16 years, respectively, and hence the earlier recommended age of screening commencement
A similar surveillance program may be suitable for individuals harbouring *MAX* and *TMEM127* mutations. *MAX* related PPGLs frequently display a paternal inheritance pattern.

14.2.3. Multiple Endocrine Neoplasia Type 2 (MEN2)

Multiple endocrine neoplasia type 2 is an autosomal dominant disorder characterized by the occurrence of medullary thyroid cancer (MTC) in association with phaeochromocytoma and parathyroid tumours[116]. MEN2 comprises two syndromes, MEN2A and MEN2B. MEN2A accounts for >95% of cases of MEN2 and itself has 4 clinical variants: classical MEN2A; MEN2A with Hirschsprung disease, MEN2A with cutaneous lichen amyloidosis (CLA) and familial MTC-only (FMTC). MEN2B, is characterized by the occurrence of MTC and phaeochromocytoma, without PHPT, but in association with a marfanoid habitus, mucosal neuromas, medullated corneal fibers, and intestinal autonomic ganglion dysfunction. The leading cause of morbidity

and mortality in MEN2 is metastatic MTC, which is typically the first manifestation of disease. Guidelines for the specialist management of MTC in the context of MEN2 are provided elsewhere[116].

MEN2 displays a strong genotype-phenotype correlation Approximately ~95% of MEN2-associated *RET* variants involve the cysteine-rich extracellular domain, whereas ~95% of MEN2B *RET* mutations are due to the p.Met918Thr variant, which is located in the intracellular tyrosine kinase domain. The American Thyroid Association (ATA) defines 3 categories of germline *RET* mutations based on the age-of onset/aggressiveness of MTC, and these comprise: Highest risk (MEN2B associated p.Met918Thr mutation); High risk (p.Cys634 and p.Ala883Phe mutations associated with MEN2A and MEN2B, respectively); and Moderate risk (all other MEN2A-associated *RET* mutations) (Table 12)[116].

Table 11: Clinical relationships and MTC risk level associated with common RET variants in MEN2A and MEN2B[116]

Exon	*RET* mutation	ATA MTC risk level	Penetrance of PHAEO	Penetrance of Primary HPT
8	Gly533Cys	Moderate	c.10%	c.10%
10	Cys609Phe/Gly/Arg/Ser/Tyr	Moderate	c.10%-20%	c.10%
10	Cys611Phe/Gly/Ser/Tyr/Trp	Moderate	c.10%-20%	c.10%
10	Cys618Phe/Arg/Ser	Moderate	c.10%-20%	c.10%
10	Cys620Phe/Arg/Ser	Moderate	c.10%-20%	c.10%
11	Asp631Tyr	Moderate	c.50%	-
11	Cys634 Phe/Gly/Arg/Ser/Trp/Tyr	High	c.50%	c.20-30%
11	Lys666Glu	Moderate	c.10%	-
13	Glu768Asp	Moderate	-	-
13	Leu790Phe	Moderate	c.10%	-
14	Val804Leu	Moderate	c.10%	c.10%
14	Val804Met	Moderate	c.10%	c.10%
15	Ala883Phe (MEN2B phenotype)	High	c.50%	-
15	Ser891Ala	Moderate	c.10%	c.10%
16	Arg912Pro	Moderate	-	-
16	Met918Thr (MEN2B phenotype)	Highest	c.50%	-

PPGL is reported in 40-50% of MEN2 cases but its prevalence is influenced by genotype (Table 12). It is most commonly observed in association with the MEN2B associated mutations (p.Met918Thr, p.Ala883Phe) and the p.Cys631/634 codon mutations associated with MEN2A. PPGL is the first clinical presentation in only a small minority of MEN2A cases and childhood presentations are rare. MEN2-associated PPGLs are predominantly located within the adrenal gland and typically display benign behaviour. Bilateral PPGLs, occurring either synchronously or metachronously, are common in MEN2.

The possibility of MEN2 should be considered in all patients presenting with adrenal PPGL. *RET* genetic testing using the endocrine PPGL gene panel limits analysis to exons known to harbour recurrently pathogenic variants. If a MEN2-associated *RET* mutation is identified patients should be evaluated for presence of MTC (clinical examination, neck USS and serum calcitonin level). Cascade genetic testing should be offered to all relevant family members by the local clinical genetic team following appropriate genetic counselling. Patients found to harbour *RET* mutations should be

managed according to current guidelines (Table 13)[116]. The majority of MEN2B mutations occur *de novo* and a high index of suspicion is required for early diagnosis.

Table 12: Suggested Screening and Treatment Guidelines for Individuals at Risk of MEN2A/MEN2B[116]

		***ATA MTC Risk Category of *RET* Mutation**		
		Highest	**High**	**Moderate**
	Relevant *RET* Mutations	p.Met918Thr	Codon 634 and p.Ala883Phe mutations	All other validated pathogenic *RET* variants
Recommended age for screening or intervention	***RET* Genetic testing**	As early as possible and by <1 year	<3 years	<3-5 years
	Medullary thyroid cancer (MTC)			
	First serum calcitonin/neck USS	<0.5-1 year	3 years	5 years
	Prophylactic thyroidectomy	<1 year (first few months of life may be appropriate with MDT discussion)	≤5 years (based on serum calcitonin levels)	>5 years (based on serum calcitonin levels)
	Phaeochromocytoma	11 years	11 years	16 years
	Primary HPT	-	11 years	16 years

*Risk category of *RET* mutation and screening and treatment schedule based upon the 'Revised American Thyroid Association Guidelines for the Management of Medullary Thyroid Carcinoma'

14.2.4. Von Hippel-Lindau Syndrome (VHL)

VHL disease is an autosomal dominant disorder characterized by haemangioblastoma of the retina and central nervous system, as well as a range of benign and malignant tumours and/or cysts involving the: kidneys (RCC, renal cysts); pancreas (cysts, cystadenomas, non-functioning pancreatic NETs); adrenal glands and sympathetic ganglia (i.e. PPGL); epididymis (cysts, cystadenomas); and endolymphatic sac (endolymphatic sac tumours (ELSTs)). VHL disease is classified into two main categories[118,119,120,122]. Type 1 includes those with typical manifestations including haemangioblastoma and RCC, but not PPGL. Type 2 describes those with PPGL and is further subdivided according to the presence or absence of additional manifestations (Table 14).

The clinical presentation of PPGL in VHL disease is similar to that in sporadic cases, except that there is a higher frequency of bilateral or multiple tumours. The majority of VHL associated PPGL occur within the adrenal gland but may involve extra-adrenal sites, although malignancy is rare. Pancreatic lesions in VHL disease include multiple cyst-adenomas which rarely cause clinical manifestations, and non-functioning pancreatic NETs, which are reported in ~10% of VHL patients. Affected individuals are frequently asymptomatic and tumours are often detected by radiological screening. Pancreatic NETs frequently become malignant, and surgical resection is recommended although the optimal timing of surgery has not been established.

Genotype-phenotype correlations are reported in VHL and recent studies indicate that amino acid substitutions affecting the surface of the VHL protein are associated with a higher risk of phaeochromocytoma. Patients identified to harbour pathogenic/likely pathogenic *VHL* variants should be under specialist care and

undergo regular surveillance following a protocol such as that shown in Table 11[118,120].

Table 13: Genotype-Phenotype correlations in von Hippel Lindau (VHL)

VHL subtype	*VHL* variant type	Clinical Manifestations
1	Deletions, nonsense, frameshift, missense	CNS / Retinal Haemangioblastoma Clear Cell Renal Cell Carcinoma
2A	Missense (e.g. p.Tyr112His)	CNS / Retinal Haemangioblastoma Phaeochromocytoma
2B	Missense (e.g. p.Arg167Gly)	CNS / Retinal Haemangioblastoma Clear Cell Renal Cell Carcinoma Phaeochromocytoma
2C	Missense (e.g. p.Leu188Val)	Phaeochromocytoma

The majority of individuals with gene deletions or variants resulting in premature protein truncation develop type 1 disease, whereas >80% of kindreds with type 2 disease harbour missense variants, and the majority of these, the 2B variant.

Table 14: An example of a surveillance protocol for VHL disease

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 of age
Phaeochromocytoma/ paraganglioma	Blood pressure monitoring and 24-hour urine or fractionated plasma metanephrines	Annually
Families at high-risk for phaeochromocytoma	More intense surveillance (e.g. measurement of fractionated plasma metanephrines, adrenal imaging)	Annually, beginning at 8 years of age

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

14.2.5. Neurofibromatosis Type 1 (NF-1)

Neurofibromatosis type 1 (NF1) is an autosomal dominant disorder affecting 1:3000 individuals[124,125]. The diagnosis of NF1 is typically a clinical one made by the identification of at least 2 of the following NIH diagnostic criteria: ≥ 6 café-au-lait macules >5mm in diameter in pre-pubertal individuals or >15mm in diameter post-puberty; ≥2neurofibromas of any type of a plexiform neurofibroma; freckling in the axillary or inguinal regions; optic glioma; ≥2 Lisch nodules (iris) hamartomas); a distinctive osseous lesion such as sphenoid dysplasia or tibial pseudoarthrosis; and a first-degree relative with NF-1 as defined by the previous criteria.

Patients with NF1 have a 1-5% lifetime risk of developing phaeochromocytoma. The features of phaeochromocytomas in NF1 are similar to those in non-NF1 patients, and the majority of tumours are benign. Bilateral disease may occur. Primary carcinoid tumours occur in ~1% of NF1 patients and are often in the peri-ampullary region of the duodenum and symptoms may relate to biliary dilatation and pancreatitis. In those with advanced disease (i.e. hepatic metastases), the carcinoid syndrome may be present. Gastrinoma, non-functioning pancreatic NETs and insulinoma have also been observed in patients with NF1.

Routine screening of asymptomatic patients with NF1 mutations for phaeochromocytoma or other endocrine manifestations is not routinely

recommended although a high index of suspicion should be maintained with regular clinical evaluation.

14.3. Pancreatic NETs

Pancreatic NETs may occur as part of one of several hereditary monogenic endocrine disorders including MEN1 (see below), VHL and NF1 (see above). The diagnosis of a hereditary disorder may be indicated by: the presence of specific combinations of clinical features; tumour multiplicity; and/or a relevant positive family history. In the absence of a relevant family history or additional clinical findings suggestive of a monogenic disorder, germline genetic testing in those with a solitary pancreatic NET is not usually indicated (Table 6). An exception to this is for those with gastrinoma in whom *MEN1* testing is appropriate. In contrast, germline genetic testing is recommended for those with multiple pancreatic tumours, or those with clinical features indicative of a specific monogenic disorder (e.g. VHL, MEN1). Whilst recent studies have indicated that germline mutations in a number of additional genes may be present in pancreatic NETs (e.g. *MUTYH*, *CHEK2* and *BRCA2*)[126], routine genetic testing for these genes is not currently recommended.

14.3.1. Multiple Endocrine Neoplasia Type 1 (MEN1)

MEN1 is an autosomal dominant disorder with an estimated prevalence of 1:30,000, characterized by the combined occurrence of parathyroid, pituitary and duodenopancreatic NETs[127]. In addition, patients may manifest other endocrine tumours (e.g. adrenal cortical tumours, carcinoids of the thymus and bronchus) as well as non-endocrine tumours (e.g. meningiomas, facial angiofibromas, collagenomas, and cutaneous lipomas) (Table 16). In MEN1, malignant duodenopancreatic NETs and thymic carcinoid tumours account for the leading cause of premature MEN1-related deaths.

MEN1 genetic testing should be offered to: all patients with a clinical diagnosis of MEN1 (i.e. manifesting ≥2 relevant endocrine tumours); all first-degree relatives of affected individuals (both symptomatic and asymptomatic); and individuals with an increased likelihood of disease (e.g. multiple PNETs, sporadic gastrinoma, recurrent or multi-gland parathyroid disease). Notably, ~5-10% of patients with a diagnosis MEN1 do not have mutations in the *MEN1* coding-region, and these individuals may harbour mutations in non-coding regions or have mutations in other genes. For example, a small number of kindreds with a MEN1-like phenotype have been identified to harbour mutations in the cyclin-dependent-kinase inhibitor 1B (*CDKN1B*) gene, a condition referred to as MEN Type 4 (MEN4)[125]. Genetic testing for *MEN1* mutations is performed locally using the NGS-based disease-targeted gene panel. Partial or whole gene deletions of the *MEN1* gene currently require alternate means of detection (e.g. MLPA) and should be considered when initial *MEN1* sequencing is negative.

Current guidelines recommend that individuals at high risk of disease (i.e. individuals harbouring germline pathogenic/likely pathogenic *MEN1* variants) undergo periodic clinical, biochemical and radiological screening as per current guidelines. A summary of suggested surveillance is provided in Table 17[127].

Table 15: Clinical Features of MEN1

Primary Hyperparathyroidism (>95%)
• Parathyroid adenoma/hyperplasia (>95%)
• Parathyroid carcinoma (very rare)
Pancreatic Neuroendocrine Tumours (PNET) (30-80%)
• Gastrinoma* (30-40%)
• Insulinoma (10-30%)
• Glucagonoma (<3%)
• VIPoma (very rare)
• Non-functioning PNET (30-60%)
Pituitary adenoma (30-40%)
• Prolactinoma (20%)
• Somatotropinoma (<10%)
• Corticotropinoma (<5%)
• Non-functioning adenoma (10-25%)
Foregut Neuroendocrine Tumours
• Thymic NET (2-8%)
• Bronchial NET (<5%)
• Gastric NET ('ECLoma'[§]) (10%)
Adrenocortical Tumours (10-20%)
• Conn's adenoma (~1%)
• Cortisol-secreting adenoma (~1%)
• Phaeochromocytoma (very rare)
• Non-functioning adenoma (10-20%)
• Adrenocortical carcinoma (~1%)
Miscellaneous Tumours
• Lipomas (30%)
• Angiofibromas (85%)
• Collagenomas (70%)
• Meningiomas (~5%)
• Ependymomas (<5%)
• Breast cancer (increased relative risk reported)

* The majority of gastrinomas are located in the duodenal mucosa

[§] 'ECLoma" refers to tumours arising from enterochromaffin-like cells, which are observed in patients with hypergastrinaemia due to the Zollinger-Ellison syndrome

Table 16: Suggested Screening Guidelines for Individuals at Risk of MEN1[127]

MEN1-Associated Tumour	Age to Begin Screening (year)	Biochemical Screening Test (Annually)	Imaging Screening Test (time interval)
Parathyroid	8	Calcium, PTH	None
Pancreatic			
- Gastrinoma	20	Fasting gastrin	None
- Insulinoma	5	Fasting glucose (± insulin)	None
- Other Pancreatic NET (e.g. Non-Functioning)	10	Chromogranin A, GI hormone profile* (e.g. glucagon; pancreatic polypeptide vasoactive intestinal peptide)	MRI abdomen, EUS (annually)
Pituitary			
- Prolactinoma	5	Prolactin	None
- Somatotropinoma	5	Insulin-like growth factor 1 (IGF1)	None
- Other Pituitary adenoma	10[§]	None, unless signs or symptoms of functioning tumour (e.g. corticotroph adenoma)	MRI pituitary (every 3 years)
Adrenocortical	<10	None, unless signs or symptoms of functioning tumour or tumour >1cm on imaging	MRI abdomen (annually)
Thymic / Bronchial Carcinoid	15	None	Consider CT[#] or MRI chest (every 1-3 years)

*Although chromogranin A, pancreatic polypeptide and glucagon levels may be elevated in individuals with NF-pancreatic NETs, they have low sensitivity and specificity.
[§]Although pituitary tumours are reported in MEN1 patients as young as 5-years of age, in the absence of symptoms, signs or biochemical evidence of a pituitary adenoma, pituitary imaging may be delayed until >10-years of age to coincide with pancreatic imaging. Abbreviations: GI, gastrointestinal; CT, Computer tomography; MRI, magnetic resonance imaging; EUS, endoscopic ultrasound.
[#] CT scanning has been suggested for the detection of thymic and or bronchial carcinoids, but there is a concern over the potential for high cumulative doses of ionizing radiation, such that some have advocated utilizing 'low-dose' CT protocols or MRI.

14.4. Relevance of primary hyperparathyroidism to NETs

The finding of primary hyperparathyroidism (HPT) in a young patient (i.e. <30 years of age), in association with other endocrine tumours, and/or a positive family history of relevant endocrine disease, substantially increases the likelihood of an underlying genetic diagnosis which includes MEN1, MEN2A, and the Hyperparathyroidism-Jaw Tumour (HPT-JT) syndrome. Genetic testing should be targeted to the specific endocrine disorder using the appropriate gene panel request. Where the differential diagnosis remains wide, the Hyperparathyroidism/FHH gene panel should be employed, which includes testing of *MEN1, CASR, CDC73, RET, CDKN1B, AP2S1 GNA11* and *GCM2*. MLPA analysis for relevant genes (e.g. *MEN1, CDC73*) may be appropriate if a high index of suspicion for the disorder persists if initial genetic testing is negative.

Germline genetic testing may be appropriate for patients with primary hyperparathyroidism in a number of clinical settings, which include:

- Multigland parathyroid disease (e.g. increased risk of MEN1)

- Positive family history of relevant clinical manifestations (e.g. HPT, MTC, PPGL)
- Young age of HPT onset (i.e. children and young adults <30 years of age)
- Additional clinical features diagnostic for a monogenic endocrine disorder (e.g. 'classic' manifestations of MEN1, MEN2, Hyperparathyroidism Jaw-tumour syndrome)
- Additional clinical features suspicious for a monogenic endocrine disorder (e.g. 'non-classic features of MEN1 (e.g. HPT + adrenal adenoma)

14.5. Small intestinal NETs

Germline genetic testing for small bowel NETs is not routinely recommended unless clinical features indicate a particular genetic diagnosis

14.6. Thymic and Broncho-Pulmonary NETs

Germline genetic testing for thymic and broncho-pulmonary NETs is not routinely recommended unless clinical features indicate a particular genetic diagnosis (e.g. MEN1).

14.7. Recommendations

- **The possibility of a monogenic tumour syndrome should be considered in all patients presenting with NETs.**

- **Individuals who have a germline pathogenic/likely pathogenic variant in one of the monogenic endocrine tumour genes should be referred to the local Clinical Genetics Department**

- **Cascade genetic testing of 'at-risk' relatives of patients with known pathogenic/likely germline variants in moderate and high penetrance monogenic endocrine tumour genes is recommended**

- **The majority of individuals diagnosed with phaeochromocytoma or paraganglioma (PPGL) should be offered genetic analysis of current known predisposition genes (Phaeochromocytoma/Paraganglioma panel).**

- **Individuals identified to be at risk of PPGL (i.e. those harbouring a pathogenic/likely pathogenic variant in a PPGL monogenic disease gene) should enter a disease-specific surveillance program (e.g. MEN2/VHL). Although there is little evidence to guide the optimal screening of individuals at risk of familial PPGL (e.g. due to *SDHx* mutation), interval clinical, biochemical and radiological screening is recommended.**

- **A routine surveillance protocol for patients with VHL should be conducted at a Regional and/or Specialist Service.**

- **Patients with a clinical or genetic diagnosis of MEN1 should undergo regular clinical, biochemical and radiological surveillance.**

15. Patient Support

Patients with NET can experience a range of physical and psycho-social challenges so support is a fundamental part of their overall management and care. Many will have had symptoms for considerable time, even years, resulting in delayed diagnosis. A significant number of patients have metastatic disease at diagnosis meaning they cannot be cured. In addition 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 NET to understand the issues they face is vital in ensuring appropriate and timely support, treatment and service development.

Guidelines on the management of symptoms specific to neuroendocrine tumours are not available however collecting and sharing information on clinical expertise and experience does provide 'best' practice in supporting patients. The Scottish Palliative Care Symptom Management Guidelines are an excellent source of information and management https://www.palliativecareguidelines.scot.nhs.uk

There are two specific 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.

15.1. The Ann Edgar Charitable Trust

The Ann Edgar Charitable Trust (www.taect.scot) is Scotland's charity for patients with NETs. The Trust was established in 2011 by Ann Edgar, herself a patient who had a NET.

The aims of the Trust are as follows:

- To support and provide information to people with Neuroendocrine Tumours and their families;
- To advance the knowledge and understanding of Neuroendocrine Tumour and associated syndromes by raising public awareness of these rare cancers;
- To support new research into Neuroendocrine Tumours and associated syndromes

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

15.2. Neuroendocrine Cancer UK

Neuroendocrine Cancer UK, formerly known as The NET Patient Foundation, is the leading dedicated UK charity for NETs. Its website is: www.NCUK.org.uk

It 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 tumours.
- To advocate for NET patients so they may achieve the best possible outcomes.
- To encourage standardised care for all NET patients.
- To provide community supportive care to patients and their carers or family members.

- To raise awareness of NET 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. Previous, current and future projects can be found on the website.

Work is currently underway to create an evidence based Competency Framework specifically for nurses caring for patients and their families with NET.

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).

15.3. Recommendations

- **Patients and their families should have access to a Clinical Nurse Specialist in NET to provide information, support, symptom management and co-ordination of care between healthcare settings.**

- **Patients with NET can experience a range of physical and psycho-social challenges, so information and support is a fundamental part of their overall management and care.**

- **Patients should be informed about the various organisations that provide support and information for them, their families and carers.**

Appendix 1: Contributing Authors

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Appendix 2 – Molecular Genetic Testing for Endocrine Disorders

Molecular Genetic Testing for Endocrine Disorders by NGS

Please send EDTA blood *(min. 4ml adults; 2-4ml children; 1ml neonates) or DNA extracted from Blood EDTA to:*
East of Scotland Regional Genetics Laboratory, Level 6 Ninewells Hospital, Dundee DD1 9SY

Clinical Leads: Dr Paul Newey (Endocrinology paul.newey@nhs.scot) & Dr David Goudie (Genetics david.goudie@nhs.scot)
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Lab enquiries: 01382 740533 Tay.esrg@nhs.scot (website www.esrg.scot.nhs.uk)

Please complete all fields as fully as possible and tick boxes where appropriate.

Patient Details:

SURNAME:	REQUESTING CONSULTANT:
FORENAME:	TELEPHONE:
D.O.B. / CHI NUMBER	NHS E-MAIL ADDRESS (Reports are sent to NHS accounts as default)
PATIENT'S POSTCODE:	REPORT ADDRESS:
GENDER & ETHNIC ORIGIN:	

Consent: In submitting this sample, the clinician confirms that CONSENT has been obtained: (a) for testing and storage, (b) for the use of this sample and the information generated from it to be shared with members of the patient's family and their healthcare professionals (if appropriate).
I confirm I have obtained consent for testing, storage and sharing of information:

……..
……..
Clinician name Clinician signature

*It is recommended that a 'Record of Discussion' or suitable alternative is completed.

Clinical Details: Please also provide the additional panel-specific clinical information over the page

CLINICAL DIAGNOSIS:	AGE AT DIAGNOSIS:
CLINICAL HISTORY:	
AFFECTED FIRST OR SECOND DEGREE RELATIVE(S) : YES ☐ NO ☐ DETAILS OF RELEVANT FAMILY HISTORY: If a variant is known in the family please provide details of the variant and the name and DOB of the affected family member. Please provide a family tree if appropriate	

Endocrine Panels: Please select only one panel. Turnaround time is 56 days unless indicated.

☐ Hyperparathyroidism/Familial Hypocalciuric Hypercalcaemia (FHH):
AP2S1, CASR, CDC73, CDKN1B, GCM2, GNA11, MEN1, RET (relevant exons)

☐ Hypoparathyroidism/Autosomal Dominant Hypocalcaemia (ADH):
AIRE, CASR, GATA3, GCM2, GNA11, PTH, TBCE

☐ Multiple Endocrine Neoplasia Type 1/4 (MEN1/MEN4)/Familial Isolated Pituitary Adenoma (FIPA): *AIP, CDKN1B, MEN1*

☐ Phaeochromocytoma/Paraganglioma (turnaround time 112 days):
FH, MAX, NF1, RET* (relevant exons), *SDHA, SDHB, SDHC, SDHD, SDHAF2, TMEM127, VHL.*

*Features to suggest NF1? YES ☐ / NO ☐ (If 'NO' analysis will not include *NF1)*

Single gene tests: Please select only one test. Turnaround time is 56 days unless indicated.

☐ Hyperparathyroidism-Jaw Tumour Syndrome/Parathyroid Carcinoma: *CDC73*

☐ Multiple Endocrine Neoplasia Type 2 (MEN2A/MEN2B) / Medullary Thyroid Cancer (MTC):

RET exons *5, 8, 10, 11, 13 to 16*

☐ Von Hippel Lindau**:** *VHL*

☐ Carney Complex: *PRKAR1A*

☐ Thyroid Hormone Resistance: *THRB*

☐ Albright's Hereditary Osteodystrophy/PseudoHypoPara/PseudoPseudoHypoPara: *GNAS*

Phenotype/Clinical Information: Please provide the relevant clinical information for the requested panel

Hyperparathyroidism/Familial Hypocalciuric Hypercalcaemia (FHH) Panel;

c.Ca = PTH =	25OH vit. D =	24hr U. Ca = or U.CCR = (provide local FHH cut off):
Condition suspected: FHH HPTH		Previous HPTH Surgery: Yes / No
Pathology: Adenoma / Hyperplasia glands		Single gland / Multiple

Hypoparathyroidism/Autosomal Dominant Hypocalcaemia (ADH) Panel

Baseline Biochem: cCa^{2+} = Mg^{2+} = 25OH-VitD= PTH = $PO4^{-}$ =	Condition suspected?
Any associated clinical features?	

Multiple Endocrine Neoplasia Type 1/4 / Familial Isolated Pituitary Adenoma (FIPA) Panel

HPTH: Yes / No Details:	Gastro/Pancreatic - NET: Yes / No Details:
Pit. Tumour: Yes / No Details:	Other relevant tumour type(s): Yes / No Details:

Multiple Endocrine Neoplasia 2A/2B / Medullary Thyroid Cancer (MTC)

MTC: Yes / No Details:	HPTH: Yes / No Details
Phaeo: Yes / No: Details:	Features of MEN2B: Yes / No Details:

Phaeochromocytoma/Paraganglioma (PPGL):

Features of clinical syndrome?: Yes / No / Not known If Yes: NF1 VHL MEN2A/B other: Details:
Location of PPGL: Adrenal / Extra-adrenal If Adrenal: Unilateral / Bilateral If Extra-Adrenal: Single / Multiple If Extra-Adrenal: Head & Neck Sympathetic chain/intrabdominal

Other: Details: Evidence of malignancy? Yes / No / Not known
Family history of PPGL, RCC or GIST; Yes / No Details:

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