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Trust Guideline for the Management of Adult Patients with Neuroendocrine Tumours

For Use in:	All departments
By:	Medical and Surgical staff
For:	Adult patients with suspected/confirmed neuroendocrine tumours
Division responsible for document:	Medical Division
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This guideline has been approved by the Trust's Clinical Guidelines Assessment Panel as an aid to the diagnosis and management of relevant patients and clinical circumstances. Not every patient or situation fits neatly into a standard guideline scenario and the guideline must be interpreted and applied in practice in the light of prevailing clinical circumstances, the diagnostic and treatment options available and the professional judgement, knowledge and expertise of relevant clinicians. It is advised that the rationale for any departure from relevant guidance should be documented in the patient's case notes.

Version and Document Control:

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3.2	25/05/2021	3 month extension given to review date.	Dr Frankie Swords Dr Gaurav Kapur
4	12/10/2021	Neuroendocrine neoplasm table added	Dr Khin Swe Myint Dr Gaurav Kapur

Glossary and abbreviations

Child PUGH Score – This scoring system uses measurement of albumen, bilirubin and INR, and the presence or absence of ascites and hepatic encephalopathy to assess the prognosis of chronic liver disease. Lower scores correspond to better prognoses.

GEP NET – Gastro-entero-pancreatic NET.

Ki 67 – Antigen KI67 is a nuclear protein used as a cellular marker for proliferation, and is absent in resting cells.

MIB1 is a commonly used antibody to stain for the cell proliferation antigen Ki 67, and is suitable for use in formalin-fixed paraffin-embedded sections.

MIBG – Meta iodo benzyl guanidine. Radiolabelled MIBG is used as a tracer for a nuclear medicine uptake scan. This is highly sensitive for neuroendocrine tumours, and is used to define metastases. MIBG Therapy is a treatment for neuroendocrine tumours also using radioactive MIBG.

NET – neuroendocrine tumour.

Octreotide – somatostatin analogue, radiolabelled versions available for alternative uptake scan and NET therapy.

Octreotide LAR – a depot form of octreotide therapy.

pT staging – Primary tumour staging assesses the local extent or spread of a primary tumour on a histological specimen. The radial extension of the primary untreated tumor at its deepest point of invasion is used.

SSRS – Somatostatin receptor scintigraphy also known as octreotide scanning above.

UKINETS – UK and Ireland neuroendocrine tumour group.

TSH- Thyroide stimulating Hormone
FDG – Fluorodeoxyglucose
aFP alpha feto protein
5HIAA – 5 Hydroxy indoleaceticacid
MEN1- Multiple Endocrine Neoplasia Type 1
MEN2 Multiple Endocrine Neoplasia Type 2
ACTH- Adrenocorticotropic hormone
PRRT – Peptide Receptor Radionuclide Therapy
CgA- Chromogranin A

Quick Reference guidelines

Objectives

The safe and consistent management of patients with suspected and confirmed neuroendocrine tumours (NET) using validated, evidence based data. These guidelines have been developed from the national NET guidelines (1) and the report from the Promid study group (2), and adapted for local use.

Rationale

Neuroendocrine tumours are rare tumours: incidence 3-6 per 100 000, though this is thought to be rising. However, there are currently 80 patients with NETs under regular follow up by the departments of oncology and endocrinology at NNUH, and new referrals and diagnoses are being made all the time.

In line with national Improving Outcomes Guidance (IOG), all patients should be discussed at a specialist MDT. This is particularly important since there have been many advances including clearer characterisation, more specific and therapeutically relevant diagnosis, and improved treatments in the last few years.. This guideline has been developed for use by the proposed new MDT, and to aid prompt recognition, diagnosis and referral for these tumours.

This guideline draws heavily on the previously published UK NETs guidelines of 2005, and the latest guidelines in preparation by the United Kingdom and Ireland Neuroendocrine Tumour Group (UKINETS) with endorsement from the clinical committees of the British Society of Gastroenterology, the Society for Endocrinology, the Association of Surgeons of Great Britain and Ireland (and its Surgical Speciality Associations), the British Society of Gastrointestinal and Abdominal Radiology (BSGAR) and others.

NETs are usually classified according to their embryological origin into tumours of the foregut (bronchi, stomach, pancreas, gall bladder, duodenum), midgut (jejunum, ileum, appendix, right colon), and hindgut (left colon, rectum). These guidelines apply to NETs arising from the gut including the pancreas and liver (gastroenteropatic GEPNETs), as well as those originating elsewhere including the lung (or with an unknown primary) which have metastasized to the liver or abdominal lymph nodes.

Since these tumours arise from the neuroendocrine cells, they may have secretory characteristics, and present with distinct clinical syndromes. Historically, one such syndrome (of diarrhoea and flushing associated with elevated circulating 5-HT levels) was named carcinoid syndrome, and various NETs with or without liver metastases, and with or without 5-HT secretion were frequently referred to as carcinoid or Apud tumours. This nomenclature is confusing and the term NET now preferred.

Broad recommendations

I - Genetics: (all grade C evidence)

1. Thorough history and examination is mandatory to exclude complex cancer syndromes, although the majority of NETs are sporadic. The commonest association is with MEN1 (typified by pituitary, parathyroid and pancreatic tumours). However, NETs may also occur in association with MEN2 (typified by medullary cell carcinoma of the thyroid, phaeochromocytomas and parathyroid disease), Neurofibromatosis 1 (neuromas and neurofibromas, very rarely phaeochromoctyomas), Carney Complex (adrenal, gonadal and skin lesions), von Hippel Lindau (renal cell carcinoma, phaeochromocytoma, angiomatosis, haemangioblastomas, pancreatic cysts), and Succinate Dehydrogenase B and D mutations (paraganglioma and phaeochromocytoma).
2. Consider referral to genetics service for MEN1 screening for all patients with bronchial and gastric NETs, and for all other cases with a suggestive family history. Where a syndrome is confirmed, family screening should also be undertaken, and the appropriate surveillance programme initiated for associated tumours (detailed surveillance protocols on www.endobible.com).
3. Evaluate all patients for second endocrine or gut cancers: 20% of patients with a carcinoid tumour may develop another synchronous cancer, typically affecting the gastrointestinal tract.

II - Diagnosis: Biochemical tests (grade C/D)

1. Where clinical symptoms are suggestive of NET: perform 2 X 24 h urinary collections for 5HIAA, and fasting chromogranin A in all cases (grade C). Chromogranin A (CgA) is a large protein produced by all cells deriving from the neural crest including NETs, regardless of their secretory status. It is the most useful plasma tumour marker for NETs and may predict 5 year survival (High CgA 22%, low CgA 63%). False positives can be seen in renal and hepatic failure, and in inflammatory bowel disease. In selective cases with a normal Chromogranin A but confirmed disease, Chromogranin B, Neurokinin A or pancreastatin should also be tested. Beta HCG may also be useful in rectal carcinoids.

2. Certain foods including banana, avocado, aubergine, pineapple, plums, tomatoes, kiwi fruit, chocolate, caffeine and walnuts give false positive results and should be avoided for several days prior to urine testing.

3. Multiple drugs also affect urinary 5HIAA excretion, giving either false negatives or false positives. Written instructions to avoid these agents must be given. The list includes alcohol, over the counter medicines: aspirin, paracetamol, naproxen, glycerol, guafenesi , ephedrine; antidepressants: tricyclics, and MOA inhibitors; and other drugs: heparin, Levodopa, methyldopa, chlorphenylalanine, diazepam, melphalan, metamphetamine, fluorouracil, methysergide, adrenocorticotropic hormone (ACTH), and phenothiazines.

4. If clinical suspicion is high, also send fasting gut hormones (Gastrin, Glucagon, Somatostatin, Pancreatic Polypeptide and VIP) in all cases (grade D).

5. Proton pump inhibitors and to a lesser extent histamine 2 antagonists lead to gastric achlorhydria and a rise in serum gastrin and chromogranin A. Proton pump inhibitors should be stopped for 7 days prior to testing under supervision. infection must also be eradicated if present, and intrinsic factor antibodies checked to rule out other causes.

6. In other cases, consider tests for other diagnoses: FBC, U+E, Bone profile, Thyroid function, IGF-I, Growth hormone. Alpha Fetoprotein, CEA, hCG should be sent if other GEP malignancy is suspected. Calcium, prolactin and PTH should be sent if a familial syndrome is suspected, and always to screen for MEN when a gastrinoma has been confirmed. Calcitonin should also be considered when MEN2 or medullary thyroid cancer are suspected, though this also needs to be taken in a lithium heparin tube, and taken immediately to the biochemistry for spinning, before being frozen and sent to the Hammersmith reference laboratory.

7. In certain cases where ectopic hormone secretion is suspected, consider testing Growth hormone releasing hormone, ACTH, and human chorionic gonadotophin (hCG). Rectal tumours do not tend to secrete Chromogranin A. Send beta HCG, enteroglucagon and PP as these may be useful markers.

8. Where an insulinoma is suspected, arrange to test insulin antibodies, a urinary screen for sulphonylurea and simultaneous glucose, insulin, C peptide in the fasting state. If an episode of hypoglycaemia has not been documented, arrange supervised 72 hour fast according to 72 Hour Fast for Investigation of Spontaneous Hypoglycaemia in Adults Trustdocs Id 1460

9. If a glucagonoma is suspected, arrange a biopsy of the characteristic rash.

III - Diagnosis: Histology Histological diagnosis should be confirmed in all cases where possible to confirm the diagnosis, and provide further prognostic information. Specimen handling, gross and microscopic assessment should be according to the Royal College of Pathologists data set for NETs of the gastrointestinal tract and pancreas, and all specimens should be reviewed by the upper GI/NET pathologist team (3).

Core data items in the macroscopic description include the specimen type, the site and three-dimensional size of the tumour, extension of the tumour within the primary organ and into neighbouring tissues, relationship to other key anatomical structures and the specimen resection margins, and the number and site of lymph nodes retrieved from the main specimen and/or from separately submitted samples.

Core data items to be reported of the microscopic features include: histological type, specific hormone immunostaining, if indicated, histological grade (including the mitotic rate and/or proliferation index), maximum extent of local invasion (primary tumour staging: pT stage), serosal involvement, lymph node status, vascular invasion, perineural invasion, histologically confirmed distant metastases and site, and background abnormalities present e.g. Enterochromaffin-like (ECL) cell or G cell hyperplasia in stomach, gastritis.

Reports should include classification according to both WHO and TNM systems, since these offer complementary information.

All NET pathology reports should be copied to the NET MDT for data collection.

WHO Classification

This classification is particularly useful in predicting possible malignant potential in patients whose tumours have not metastasised at the time of diagnosis.

1. Well differentiated endocrine tumour of probable benign behaviour.
2 Well differentiated endocrine tumour of uncertain behaviour.
3 Well differentiated endocrine carcinoma.
4 Poorly differentiated endocrine carcinoma.

TNM Classification

A TNM staging and grading system for gastrointestinal and pancreatic endocrine tumour has also recently been introduced (4,5). The TNM system indicates the prognostic impact of specific characteristics of the primary tumour (which is always regarded as malignant, irrespective of tumour size and extent) and the presence of lymph node or distant metastasis. This allows prognostic sub-stratification of patients whose tumours would fall into the WHO category of (poorly or well-differentiated) endocrine carcinoma irrespective of the presence or absence of metastasis.

Staging of the primary tumour (pT) is based on the evaluation of tumour size and extent only, whereby the exact criteria and cut-off values depend on the anatomical site of the tumour. Grading is then performed separately, following a 3-tier system based exclusively on proliferative activity. Grades 1 and 2 are low grade (well differentiated), while Grade 3 is poorly differentiated, based on the mitotic count and proliferative activity of the tumour.

The assessment of the proliferative activity should be done on Ki-67 or MIB-1 add to glossary immunostained slides. Estimate quantification of ki67 is needed for the estimation of proliferative activity. The mitotic count may also provide comparable and more reproducible grading information. Immunohistochemical studies using neuroendocrine markers will also be performed to confirm the diagnosis, and to complement the biochemical assays, based on the discretion of the reporting pathologist, and discussion with MDT.

Table 1: Grading of gastroenteropancreatic Neuroendocrine neoplasia (NEN)

Grade	Mitotic count, 10 HPF	Ki-67 index[a], %
G1	=2	<3[b]
G2	2 – 20	3 – 20
G3	>20	>20

HPF, high-power field = 2 cm^2, at least 40 fields evaluated in areas at highest mitotic density. [a] MIB1 antibody; percent of 500 – 2,000 cells in areas of highest nuclear labeling. If less cells, the number of assessed cells should be noted. [b] <3 could replace =2 in the 2010 WHO classification in order to include decimal numbers between 2 and 3.

IV - Diagnosis: Imaging (grade B/C)

1 Staging CT in all cases of biochemically or histologically confirmed NET, or as appropriate according to clinical presentation (grade B/C). Multidetector and arterial phase CT imaging may increase the sensitivity of CT scanning dramatically, and CT enteroclysis is optimal to demonstrate the primary tumour in patients strongly suspected of a midgut NET. Detailed CT protocols are given in an appendix to the latest UKINETs guidelines.

2 Suspected bronchial NETs should also be assessed by bronchoscopy, which may facilitate tissue diagnosis.

3 Somatostatin receptor scintigraphy (SSRS or octreotide scan) should be performed in all cases, and is the best screen for metastatic disease (grade B). A sensitivity of up to 90% has been reported for foregut, midgut and hindgut tumours, although it is less useful in the assessment of insulinomas (50% sensitivity (6)). It also positively predicts response to therapeutic somatostatin analogue therapy, and led to revised staging and altered management when performed preoperatively in one series. Ideally, these scans should be performed in patients prior to starting somatostatin analogue therapy, as these may reduce the sensitivity of the scans. Short acting sc therapy should be stopped 24 hours prior to scanning, and scans should be performed at least 3 weeks after a depot injection (i.e. the week before the injection is due to be repeated).

4 MIBG scanning should also be considered in all cases. This has a sensitivity of only 50% for metastatic disease, but is useful in inoperative or metastatic disease to identify those who might benefit from future MIBG isotope therapy.

5 If CT and SSRS scanning fail to demonstrate a primary lesion, or if the CT fails to demonstrate disease detected on radionuclide imaging, discuss further imaging at MDT. A triple phase CT, or MRI thorax and abdomen may be recommended. Pancreatic NETs are typically of high signal intensity on T2-weighted and T2 fat saturated images and low signal intensity on T1-weighted and T1 fat saturated images. Diffusion weighted MRI may also improve sensitivity in some cases. Barium series may also be helpful particularly in those with symptoms suggestive of subacute obstruction. Other imaging modalities such as PET CT using 68-Gallium somatostatin analogue, 18F-DOPA or 11C-5HTP are highly sensitive, but not widely available.

These may detect micrometastases unrecognized on other imaging modalities. Well differentiated NETs are not typically FDG avid, though FDG PET may be useful in the assessment of bronchial and undifferentiated or aggressive NETs.

Endoscopic ultrasound scanning, pelvic ultrasound scanning, mesenteric angiography (particularly for gastrinomas) and selective venous sampling with calcium stimulation should be considered in selected cases to aid accurate disease localization where curative surgery is being contemplated. Intra-arterial calcium with digital subtraction angiography may be particularly important for localising gastrinomas. Intra-arterial calcium stimulation combined with hepatic venous sampling for insulin gradients has been reported to achieve up to 90% success rate in localising insulinomas. Capsule endoscopy may also be used to detect occult small bowel NETs.

6 Echocardiography should be performed in all patients at baseline, and repeated if clinically indicated with progressive disease. After resection of a primary tumour, SSRS should be considered for ongoing imaging detection of recurrent or metastatic disease (grade D).

V - Treatment (grade B/C/D)

V – A) Surgery

1. Offer surgery in all cases who are fit and with limited disease (including those with local lymph nodes), as this in the only curative option.

2. **Small intestinal carcinoids** are invariably malignant, and resection of the primary and extensive resection of associated mesenteric lymph nodes should be performed. Luminal gastrointestinal tract NETs under 2cm are rarely associated with metastases. However, nodal or liver metastases are present at the presentation in 40-70% of patients. Whether liver metastases are present or not, resection of the primary and extensive resection of the mesenteric lymph nodes is appropriate, to remove tumour for cure or to delay progression that would otherwise endanger the small bowel (1).

3. Patients with **Bronchial NETs** should be offered major lung resection or wedge resection plus node dissection.

   Direct bronchial US may assist in determining resection margin. Five-year survival after such surgery is between 67-96% depending on the histology of the tumour and extent of lymph node involvement. All thoracic surgery for NETs is performed by Mr Van Leuven at the NNUH.

4. **Gastric carcinoids** are of three distinct types.

Type 1 gastric carcinoids are associated with hypergastrinaemia and chronic atrophic gastritis, and rarely invade or metastasise. Limited surgery with endoscopic polypectomy and/or antrectomy should be considered if anaemia is severe, or the patient is highly symptomatic. Otherwise, annual surveillance endoscopy is recommended.

Type 2 gastric carcinoids occur as part of Zollinger-Ellison syndrome in MEN1. Small type 1 and 2 tumours with no extension into muscle on EUS or CT can be resected endoscopically, and a combined laparoscopic and endoscopic technique may be used.

Type 3 gastric carcinoids are sporadic, are not associated with hypergastrinaemia, and have a more malignant course. These tumours have often metastasised by the time of diagnosis. Small tumours less than 1cm with no extension into muscle on EUS or CT can be resected endoscopically but most lesions will need resection and clearance of regional lymph nodes and effectively are treated as for gastric adenocarcinoma. Level of evidence 3-5 Grade of recommendation C.

5. **Appendiceal disease** may range from the tiny, clinically unimportant incidental finding to the first presentation of metastatic disease.

   Appendiceal carcinoids can be cured by an appendicectomy if the tumour is located at the tip of the appendix ***and*** the tumour diameter is <1cm. Such tumours should be logged by the MDT but do not necessarily require discussion or further investigation in the absence of suspicious features.

   Right hemicolectomy with regional lymphadenectomy and assessment for further tumours is indicated if ***any*** of following are present:

   - The tumour breaches the serosal surface, invades >3mm mesoappendix, is >2cm diameter, is located at the base of the appendix, or is resected with positive margins. Goblet cell appendix tumours always require hemicolectomy due to their aggressive natural history
   - If the tumour has signs of neural, lymphatic or vascular invasion, or has perforated, but has none of the other features, the evidence is less compelling. Close surveillance is mandatory and further surgery should be discussed. Latest guidelines also suggest consideration of bilateral oophorectomy in female patients due to the perceived risk of pelvic metastases following goblet cell tumours (Grade C, UKINETS 2010 guidelines in preparation)

6. **Colorectal disease** should be treated with standard resection with loco-regional lymphadenectomy. Clearance of metastatic lymph nodes may contribute to long-term survival. As for other luminal NETs, lesions <1 cm, with well-differentiated histology (particularly those in the rectum) may be considered adequately treated by complete endoscopic removal or transanal mucosal resection but the patient will require follow up endoscopy to ensure this has been accomplished.

7. **Pancreatic disease** requires highly specialised surgery which should be performed by an experienced hepatobiliary surgeon in a specialist centre only. The extent and suitability of surgery depends on preoperative biochemical diagnosis and localisation studies, and should be discussed at the MDT. Tumours >2cm warrant aggressive resection, though surgery may not always be indicated with small non functioning lesions in MEN1. Insulinomas can usually be resected by enucleation with no further treatment required, though gastrinomas are more frequently metastatic and require more extensive surgery.

8. **Liver metastases** may be cured by surgery in ~10% of cases, if the lesions are confined to one lobe. Surgery may also be curative in the small number of patients with an apparent primary hepatic NET, with a 5-year survival of 74% reported in one series. Debulking should also be considered if a dominant lesion is causing symptoms, although medical therapy is usually considered first. The procedure is generally well tolerated, with improved outcomes, and 5-year survival rates up to 87% (1). Level of evidence 3 Grade of recommendation B. Patients with end-stage carcinoid disease and uncontrollable symptoms that are unresponsive to any other therapy have also been considered for liver transplantation. This is not a standard treatment, and should be performed in a trial setting only, but reported outcomes are improving, and its role may increase in the future. All non emergency hepatobiliary and pancreatic surgery for NETs is performed by a dedicated hepatobiliary surgeon in a specialist centre.

9. **Extensive disease** with local or regional spread including liver metastases should always be considered for surgery at the NET MDT, since debulking is associated with delayed disease progression and prolonged survival.

10. **Cholecystectomy** should be considered at the time of *elective* surgery, in *all patients in whom* on going treatment is likely to be necessary*,* since somatostatin analogues are associated with the development of biliary sludge and stones.

11. **Emergency presentations** should be treated appropriately e.g. with limited small bowel resection for acute obstruction. However, once the diagnosis of a NET has been confirmed, the patient should be fully reassessed as above (sections I-IV), and further surgery e.g. lymphadenectomy, resection of the mesenteric reaction, or resection of synchronous tumours, performed at a later date by a specialist surgeon. Gastrointestinal luminal tumours should always be discussed at the MDT, but may not require further treatment – see appendiceal tumours above. Luminal tumours above 2cm, and appendiceal carcinoids with any sinister characteristics, generally require right hemicolectomy despite the lack of obvious malignant features.

12. The exact nature and extent of surgery in other cases should be determined on an individual case basis, and discussed at the MDT. For a thorough discussion of the types of surgery to consider, see reference 1.

V – B) Surgery and Perioperative / Periprocedure management

1. Octreotide should be administered by continuous infusion (dose 50microg/h for 24 hours pre- and continued for at least 48 hours post- surgery, radiofrequency ablation and other interventional procedures in patients with NETs. This is to reduce the possibility of carcinoid crisis and massive release of peptide hormones (see appendix 1).
2. Drugs that release histamine or activate the sympathetic nervous system should also be avoided. An experienced anaesthetist is essential, due to the possibility of such crises, and agents such as alpha and beta-adrenoreceptor blocking drugs may be required to avoid or treat these life-threatening cardiorespiratory complications.

V – C) Medical and Radionuclide therapy

1. **Somatostatin analogue therapy** should be offered to suitable patients at diagnosis. Somatostatin receptors are present in the vast majority (70-95%) of NETs but only about half of insulinomas, and less in poorly differentiated NETs and somatostatinoma. Somatostatin analogues bind principally to receptor subtypes 2 (with high affinity) and 5 (with lower affinity), and inhibit the release of various peptide hormones in the gut, pancreas and pituitary, antagonise growth factor effects on tumour cells, and at high dosage may induce apoptosis. Symptom control is achieved in the majority of patients, with a biochemical response in 30-70%. Standard treatment is with a depot preparation of somatostatin analogue (Octreotide LAR) administered IM by an NET clinical nurse specialist in the NNUH oncology day unit, every 28 days for clinically non-functioning tumours. Stabilization of radiologically-documented tumour progression has been demonstrated in 24-57% of patients, and recent data from two double-blind, placebo-controlled studies (PROMID and CLARINET) demonstrates prolonged progression-free survival in patients with metastatic NETs of midgut origin receiving octreotide LAR and Somatulin Autogel® respectively. (2). However, other studies are less clear cut and so this should be considered on an individual case basis depending on disease burden, progression and symptoms.

2. Treatment may be with Octreotide LAR (10-40mg) IM, or Lanreotide Autogel (60-120mg) by deep sc injection in symptomatic patients every 28 days. Symptoms not controlled by depot preparations may respond to the addition of regular short acting sc octreotide. Local reactions (pain and erythema) at the injection site are not uncommon. Abdominal cramps, nausea, flatulence, diarrhoea and steatorrhoea may also occur and due to the risk of cholelithiasis (10-50%), prophylactic cholecystectomy is recommended during abdominal surgery in patients due to start long-term treatment with somatostatin analogues. Rare adverse effects include bradycardia, abnormal metabolism of glucose, vitamin A, B_{12} and D malabsorption.

3. Patients unfit or unsuitable for surgery should be assessed for treatments to improve and maintain optimum quality of life (grade D). Management will depend on symptoms, disease extent, radionuclide uptake, and histological features. Patients with disease progression (as indicated by symptoms, biochemistry or imaging criteria) should be assessed and treated similarly.

4. **Radionuclide therapy** is useful in patients with progressive disease. At first disease progression (or earlier in patients unfit for surgery), refer to a tertiary referral centre (Royal Marsden Hospital, UCL or Royal Free). A tertiary referral form, with patient details, and all relevant scans must be forwarded to the chosen centre, who will contact patient for an assessment.

   Radionuclide therapy offers excellent symptom palliation following maximal medical therapy and tumour progression. Patient selection criteria include demonstration of superior radiopharmaceutical uptake at all known tumour sites on diagnostic imaging by comparison with normal tissues, reasonable bone marrow reserve and adequate renal function. MIBG therapy is the only licensed radionuclide therapy for NETs. 80% functioning tumours will take up MIBG, and 40-60% show a clinical response to therapy: symptom improvement, reduced somatostatin analogue requirement, quality of life improvement with 10-15% objective response, though complete radiological response is rare. Survival benefit appears related to symptom response and initial

administered activity, with reported actuarial survival improvement of 22% at 5 years (1).

Treatment is well tolerated and toxicity limited to temporary myelosuppression 4–6 weeks post therapy. Myelotoxicity is more severe in patients who have bone marrow infiltration by tumour at the time of treatment or who have undergone previous chemotherapy or radionuclide therapy. Myelosuppression is cumulative and may be dose limiting after repeated treatment cycles. Yttrium 90 DOTA octreotide [DOTATOC] is also considered in MIBG negative, SSR positive cases. Most patients report subjective benefit within two treatment cycles, often associated with reduction in biochemical tumour markers, with 9-33% objective response reported.

Other radiolabelled peptides show promise, but are not yet in routine use. Co-administration of amino acids, particularly D-lysine, reduces tubular peptide binding and is essential to minimise renal toxicity.

Currently funding for PRRT has been withdrawn and treatment is not available on the NHS.

5. **Other medical therapies** should be started immediately to treat symptom progression. Therapy should be tailored to clinical presentation and biochemistry (see section VII), and or with chemotherapy (grade B).

6. **Cytotoxic chemotherapy** should be recommended if symptoms are not fully controlled with medical treatments or if there is evidence of disease progression on imaging or biochemical assessment.

   Predictors of response to chemotherapy include pancreatic and other foregut sites, poorly differentiated/ anaplastic histology and SSRS positivity. Standard treatment combinations of streptozotocin, 5FU, dacarbazine and/or doxorubicin achieve response rates between 40-70%. High response rates can also be achieved with platinum-containing regimens. Various randomized controlled studies are also ongoing, and should be considered on an individual case basis, for references and further discussion see reference 1. For non-pancreatic (usually well-differentiated) endocrine carcinomas (“carcinoid tumours”) the role of chemotherapy is less certain. Studies have consistently demonstrated much lower response rates with 16-33% of patients deriving benefit, which may only last 6-8 months. All chemotherapy is administered and prescribed through the NNUH oncology day unit.

7. Patients progressing despite chemotherapy, or not fully controlled with medical treatment should proceed directly to radionuclide therapy with somatostatin or MIBG treatments.

8. **Interferon therapy** should be considered in patients unfit for chemotherapy or progressing despite this. This is prescribed through the NNUH oncology day unit, in addition to long-acting somatostatin analogues. The dose of 3-5MU 3 times per week sc. However, there is conflicting evidence as to its efficacy, and there is some evidence it may have greater effect in tumours with low mitotic rate.

9. **Targeted therapies :** Targeted therapies such as Sunitinib should be considered in patients with metastatic pancreatic NETs.

10. **Clinical Trials:** All patients should be considered for treatment under currently recruiting trials if possible.

V – D) Loco regional therapies: radiofrequency ablation, particle- and chemo-embolisation

Patients with metastatic disease should also be considered for transarterial (chemo) embolisation or radiofrequency ablation (grade C). These are considered in every case on an individual basis at the MDT, although since these treatments reduce tumour blood supply, and so reduce the efficacy of possible future radionuclide therapies, they are usually administered after radionuclide therapy. These procedures are performed by Dr Michael Crawford, consultant interventional radiologist, at NNUH.

All patients considered for loco regional therapies should ideally be of Child Pugh class A (or B), have a documented patent portal vein, and have a pre-procedure CT scan. An IV octreotide infusion and IV fluids are necessary to prevent immediate post procedure complications (for protocol, see appendix 1).

Particle embolisation of the hepatic artery in patients with liver metastases reduces tumour size and hormone output, and is primarily used for symptom palliation, achieving symptomatic improvement in 70-90% patients.

Chemoembolisation refers to the regional delivery of chemotherapy (with doxorubicin or cisplatin) in combination with hepatic artery embolisation and its possible benefits have not been fully evaluated. Serious adverse events (sepsis, hepatorenal syndrome and necrotising cholecystitis) have been reported in 7.5-23.8% patients. However, post embolisation syndrome, fever, abdominal pain and nausea, is common. Patients with >75% liver involvement and significant carcinoid heart disease are at increased risk of mortality from the procedure (and may need special precautions (appendix 1).

Radiofrequency ablation should also be considered. This has also been shown to stabilize or reduce tumour size. Randomised trials are lacking, though this appears most effective in isolated bulky disease with smaller metastases rather than disseminated disease, in combination with loco regional surgery and somatostatin analogue therapy. It should also be considered for inoperable bilobar metastases not responding to somatostatin analogue therapy. Recent case series suggest that following laparoscopic radiofrequency ablation for NET liver metastases, local recurrence is around 6% and symptomatic relief is achieved in 70-95% and five year survival of 57% with a median survival of 3.9 years post-first RFA.

V – E) Radiotherapy

Conventional radiotherapy should also be considered for the pain of bony metastases, and is administered from the department of oncology, NNUH (grade C).

V – F) Cardiac involvement

Echocardiography should be performed in all patients at diagnosis. Up to 20% of patients with carcinoid syndrome present with cardiac involvement at diagnosis. The most common pathology in carcinoid heart disease is involvement of right-sided valves (tricuspid valve affected more frequently than pulmonary). Left-sided lesions occur in ~10% of patients with carcinoid syndrome frequently with a patent foramen ovale, a broncho-pulmonary carcinoid or rarely with very severe, poorly-controlled carcinoid syndrome. Biochemical control of vasoactive peptide release is thought to reduce the incidence of cardiac involvement, though this has not been confirmed, and cytotoxic chemotherapy has been associated with an elevated risk of progressive heart disease.

When new or progressive carcinoid heart disease is suspected, patients should be referred to Dr Cairistine Grahame-Clarke at NNUH in the first instance for assessment with contrast echocardiography, consideration of cardiac MRI, and optimal medical management. They will also be assessed for suitability for cardiac valve surgery and referred to Papworth hospital when appropriate. Cardiac surgery may carry a 20% 30 day mortality and disease may recur, though marked symptomatic improvement is usual.

VI Carcinoid Crises

Patients with unrecognised NETs may develop profound flushing, bronchospasm, tachycardia and life-threatening fluctuations in blood pressure: a carcinoid crisis, during induction of anaesthesia, or during invasive therapeutic procedures. Fluid resuscitation should take immediate priority, with alpha and beta-adrenoreceptor blocking drugs to control cardiovascular complications. An IV bolus of 100-500micrograms octreotide should also be administered, and a continuous infusion should also be administered to control further vasoactive peptide release.

In confirmed or suspected cases of functioning NETs, potential carcinoid crises should be prevented by the prophylactic administration of octreotide: (appendix 1). It is also important to avoid drugs that release histamine or activate the sympathetic nervous system.

Similar prophylactic measures may be required for other functioning tumours e.g. glucose infusion for insulinoma, or oral or intravenous proton-pump inhibitor and IV octreotide for gastrinomas.

VII - Medical treatments for functioning NETs

Medical treatments can be highly effective at controlling the symptoms associated with NETs. Treatments should be tailored according to the predominant symptom, and secretory profile of the tumour.

Somatostatin analogues

Somatostatin analogues are highly effective at controlling symptoms associated with peptide secretion from a 'functional' NET. Somatostatin receptors are expressed by 70% GEP NETs, though are less commonly expressed by insulinomas and poorly differentiated tumours. Flushing and diarrhoea may be completely controlled by depot somatostatin analogue therapy administered routinely (typically 20-30mg Octreotide LAR or 60-120 mg Lanreotide Autogel® every 28 days, administered by NET specialist nurse on the oncology day unit). However, in severe clinical presentations, it is standard practise to stabilise the patient with the addition of regular sc octreotide therapy (typical starting dose octreotide 50micrograms tds, maximum daily dose 1500micrograms), for at least the first 10 days after depot injection.

Treatments for specific symptoms:

Flushing

This may be caused by most peptides (including histamine, 5-HT and VIP), and occurs in ~70% patients with functional NETs. This usually responds dramatically to somatostatin analogues. Antihistamines and 5-HT_3 antagonists may also help some patients with refractory symptoms. Long standing disease may be associated with a fixed flush which does not usually respond to treatment.

Palpitations, wheeze, lacrimation and rhinorrhoea

These may occur in association with flushing, and usually respond dramatically to treatment for the flushing. Severe episodic palpitations should always prompt investigation for possible phaeochromocytoma with urinary metanephrine estimation.

Diarrhoea

This may be associated with multiple peptide secretions: 5HIAA/5-HT, VIP, gastrin, and occurs in ~50% of patients with functioning tumours. Diarrhoea associated with most of these peptides will respond to low dose somatostatin analogues. Dose should be up titrated to control diarrhoea and aiming for normalisation of serum or urine markers. Intravenous rehydration is frequently necessary for patients with the life threatening watery diarrhoea associated with VIP secretion, which may also respond to prednisolone therapy (watery diarrhoea hypokalaemia achlorhydria – WDHA syndrome/Werner Morrison syndrome).

Diarrhoea may also be multifactorial in an individual. Codeine phosphate and loperamide may be effective where specific treatments have failed to control symptoms. Ondansetron may also help some patients. Colestyramine may also be tried to relieve refractory diarrhoea due to bile salt malabsorption. Oral antibiotics may be used for small bowel

bacterial overgrowth in patients with extensive mesenteric fibrosis. Patients may also benefit from oral vitamin B compounds to prevent clinical features of vitamin B deficiency. Pancreatic tumour mass itself, and octreotide analogue therapy may also cause malabsorption, which may respond to pancreatin treatment (Creon®).

Itch / Skin lesions

Antihistamines are very effective at treating severe itching associated with histamine release, and may help the itch associated with other peptide secretions. Ondansetron or other 5-HT_3 antagonists usually used as antiemetics, may also help some patients, though these may require approval from the Drug and Therapeutic Committee prior to use. The bile acid sequestrant colestyramine is also worth trying in patients with itching not responding to other measures. Zinc supplements may prevent the development of new skin lesions in glucagonoma. Naltrexone hydrochloride may be considered if all other measures fail.

Dyspepsia / Peptic ulcer disease

Gastrin secreting tumours typically present with severe indigestion and peptic ulcer disease. High dose proton pump inhibitors (PPI) are usually extremely effective, although these need to be stopped for biochemical screening: stop PPIs for one week prior to estimation of circulating fasting gastrin, switch to oral H_2 antagonists for the 2-3 days prior to the test, and to IV H_2 antagonist infusion until 12h prior to the gastrin estimation in high risk gastrinoma patients. Patients with gastrinoma should be advised it is dangerous to stop PPIs without supervision (replace with high dose histamine-2 antagonists).

Abdominal pain

This may occur for multiple reasons including subacute obstruction associated with small bowel NETs and mesenteric reactions, or liver engorgement due to metastatic disease. Obstruction will usually require surgery. Gall stones are also common in NET patients and should be treated conventionally. Their frequency is increased with somatostatin analogue therapy, and they are also associated with somatostatin secreting NETs.

Diabetes

Diabetes may occur with somatostatin secreting tumours, and impaired glucose tolerance is common with multiple NETs. These should be treated conventionally.

Hypoglycaemia

Insulinomas usually present with spontaneous hypoglycaemia. Surgery is the only curative option, however, hypoglycaemia will usually respond to diazoxide therapy (200-600mg in divided doses). Side effects may include fluid retention, hypertension, renal dysfunction and hypertrichosis. Prednisolone will also help many cases, and verapamil and phenytoin have also been reported to help some patients. Somatostatin analogues will also relieve hypoglycaemia in some cases, and metastatic disease has recently been reported to respond well to everolimus, though this may require approval from the Drug and Therapeutic Committee prior to use.

Thromboembolic disease

This is particularly common with glucagon secreting tumours and should be treated conventionally.

Wheeze and breathlessness

Episodic wheeze may accompany flushing and usually responds to somatostatin analogue therapy. Other respiratory symptoms should be investigated conventionally

Pellagra

Pellagra is a rare complication of carcinoid syndrome and should be treated with nicotinamide.

Anaemia

Anaemia may arise due to gastrointestinal blood loss, and should be treated conventionally.

VIII – Follow up

Gastric carcinoids

Types 1 and 2 should have annual surveillance endoscopy performed to seek disease recurrence/progression. Type 3 should be followed up as for metastatic or high risk disease.

Appendiceal and incidental GIT carcinoids <1cm

1. A proportion of NETs are identified by pathologists examining post surgical specimens removed following intervention for other indications e.g. appendicitis. These should be logged by the MDT but need not be discussed.

2. Completely resected incidental NETs which are under 1 cm in diameter, with well differentiated histology, do not require further resection, investigation or extended follow up. However, repeat endoscopy or other imaging may be required to confirm full resection eg of gastric or rectal NETs.

Gastrointestinal luminal NETs 1-2 cm

Tumours 1-2cm, invading the serosal surface, or incompletely resected should be discussed at the MDT, and consideration given to further surgery (right hemicolectomy with locoregional lymphadenectomy as above section V-A Surgery). All such patients should be followed up clinically for five years by the surgical team. No biochemical tests are required, unless the patient is symptomatic. Imaging should be as for other GI malignancies.

Tumours > 2cm / with adverse features / with confirmed metastases

Tumours above 2cm should not be considered as incidental tumours. They require full assessment (sections I-IV), and treatment. If resection is complete with no distant disease

detected, follow up may be with the surgical team, and is recommended for 10 years (1). All other cases should be followed up by the NET oncology clinic.

X – Neuroendocrine tumour Multidisciplinary team

The NET MDT currently forms part of the Upper GI cancer MDT. This is held at the NNUH every Friday 1-2pm, although a new dedicated NET MDT is planned to start shortly, after the appointment of a dedicated NET clinical nurse specialist.

MDT Members

Dr Gaurav Kapur	Consultant Oncologist
Dr Ben Simpson	Consultant l Radiologist
Dr Paddy Wilson	Consultant Radiologist
Dr Michael Crawford	Consultant Interventional Radiologist
Mr Simon Wemyss-Holden,	Consultant Hepatobiliary and Pancreatic Surgeon
Dr Simon Rushbrook	Consultant Gastroenterologist
Dr Swe Myint	Consultant Endocrinologist
Dr Daniel Holyoake	Consultant Oncologist
Alexia Tsigka	Consultant Histopathologist
Dr Wayne Kinsey	Consultant Histopathologist
Graham Dilks	NET Specialist Nurse

MDT Referrals

All patients with suspected or confirmed NETs, including those detected as incidental findings should be referred to the NET MDT at diagnosis. All cases will be rediscussed at the MDT when disease progression is detected, and where changes to management are considered, e.g. for further surgery, chemotherapy, radionuclide treatment, radiofrequency ablation, or embolisation.

Clinical audit standards

Complete biochemical staging of all NET cases referred to the MDT.
Complete radiological staging including somatostatin and MIBG scanning of all cases considered for active treatment.
All new cases discussed at MDT.

Treatment strategy adhered to in the correct order in all cases.
Treatment with somatostatin analogue therapy considered in all cases.

Summary of development and consultation process undertaken before registration and dissemination

The authors listed above drafted this guideline on behalf of the oncology and endocrinology directorates, which have agreed the final content. During its development it has been

circulated for comment to all members of the NET multidisciplinary team, as well as all endocrinology and oncology consultants, and specialist nurses. This guideline was approved by the clinical governance committees of the endocrinology and oncology directorates.
This version has been endorsed by the Clinical Guidelines Assessment Panel.

Distribution list/ dissemination method

Guidelines will be available to all via the trust intranet, and copies emailed specifically to all consultants in endocrinology and oncology.

References/ source documents

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Appendix 1

Prevention of carcinoid crises

Hepatic embolization protocol (adapted from 7)

Hepatic embolisation, other locoregional therapies and surgery may be lead to massive peptide release and carcinoid crisis, as well as more commonly malaise, hypotension and fever, and rarely tumour lysis syndrome. These complications can be prevented or minimised by appropriate pre-procedure preparation. All patients assessed as suitable for hepatic embolisation, must be Child Pugh score A or B, with a patent portal vein, and have a CT scan performed pre procedure.

Pre procedure:

- Document FBC, renal function,liver function and ensure clotting is normal
- Ensure Chest Xray, ECG and echocardiogram, chromogranin A and CT scan have been performed
- Ensure patient has good iv access
- Start IV 0.9% sodium chloride with 20mmol KCl from midnight before the procedure
- Give a single dose of prophylactic Ceftriaxone 1g IV
- Start octreotide infusion at 100micrograms/hour (800micrograms in 48 mL 0.9% sodium chloride injection) by continuous intra-venous infusion pump over 8 hours. This is usually continued for 48 hours post procedure

Post procedure:

- Continue iv fluids, and monitor fluid status closely
- Consider colloids and iv methylprednisolone if the patient becomes hypotensive
- Consider hydralazine iv if patient becomes hypertensive
- Standard post angiogram observations (temperature, pulse and BP, foot temperature, peripheral pulses)
- Daily biochemistry including U+E, GGT, CRP, and haematology for at least 3 days
- Perform blood cultures if pyrexial, though this is common for up to 10 days post procedure.
- Analgesiocs and steroids to be considered as appropriate for post procedure pain

Child PUGH Score
Define evidence levels (A/B/C/D/).