PRINCESS MARGARET CANCER CENTRE
CLINICAL PRACTICE GUIDELINES

GASTROINTESTINAL

NEUROENDOCRINE GASTRO-ENTERO-PANCREATIC TUMOURS
GI Site Group – Neuroendocrine gastro-entero-pancreatic tumours

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These guidelines are evidence-based and thus subject to change. Some recommendations are currently funded in this jurisdiction, while others are in negotiation.
1. Introduction

Neuroendocrine gastroenteropancreatic tumours (GEP-NETS) constitute a heterogenous group of tumours with their origin in neuroendocrine cells of the embryological gut. Most commonly, the primary lesion is located in the gastric mucosa, the small and large intestine, the rectum and pancreas.

The 2010 World Health Organization (WHO) classification of neuroendocrine tumours arising in the digestive system (GEP-NETS) separates these tumours into two broad categories:

(1) Well differentiated neuroendocrine tumours:

Show a solid, trabecular, gyriform, or glandular pattern, with fairly uniform nuclei, salt and pepper chromatin, and fine granular cytoplasm.

These tumours have been traditionally referred to as carcinoids when arising in the tubular gastrointestinal tract, or pancreatic neuroendocrine (islet cell) tumours.

Display a spectrum of aggressiveness, generally have a better prognosis.

(2) Poorly differentiated neuroendocrine carcinomas:

High grade carcinomas that resemble small cell or large cell neuroendocrine carcinoma of the lung.

Often associated with a rapid clinical course.

Proliferative rate, as assessed by mitotic count and/or Ki67 labelling index, is of prognostic significance. The WHO classification separates well differentiated NETs into low grade (G1) and intermediate grade (G2) categories based upon proliferative rate. All poorly differentiated neuroendocrine tumours are high grade (G3) neuroendocrine carcinomas according to the classification system.
Table 1: European Neuroendocrine Tumour Society (ENETS)/WHO classification for digestive system neuroendocrine tumours

<table>
<thead>
<tr>
<th>Differentiation</th>
<th>Grade</th>
<th>Mitotic count</th>
<th>Ki 67 index</th>
<th>Traditional</th>
<th>ENETS/WHO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Well differentiated</td>
<td>Low grade (G1)</td>
<td>&lt;2 per 10 HPF</td>
<td>&lt;=2%</td>
<td>Carcinoid, islet cell, pancreatic (neuro) endocrine tumour</td>
<td>Neuroendocrine tumour Grade 1</td>
</tr>
<tr>
<td></td>
<td>Intermediate grade (G2)</td>
<td>2-20 per 10 HPF</td>
<td>3-20%</td>
<td>Carcinoid, islet cell, pancreatic (neuro) endocrine tumour</td>
<td>Neuroendocrine tumour Grade 2</td>
</tr>
<tr>
<td>Poorly differentiated</td>
<td>High grade (G3)</td>
<td>&gt;20 per 10 HPF</td>
<td>&gt;20%</td>
<td>Small cell carcinoma</td>
<td>Neuroendocrine carcinoma, Grade 3, small cell</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Large cell neuroendocrine carcinoma</td>
<td>Neuroendocrine carcinoma, Grade 3, large cell</td>
</tr>
</tbody>
</table>

Functioning NETS are defined based upon the presence of clinical symptoms due to excess hormone secretion by the tumour.

Functioning (hormone secreting) pancreatic NETS are classified according to the predominant hormone they secrete and the resulting clinical syndrome (e.g. insulinoma, gastrinoma, glucagonoma, VIPoma, somatostatinoma).

Functioning carcinoids (those associated with the carcinoid syndrome) are not classified any differently than non-functioning tumours.

Although functionality may impact prognosis (insulinomas are generally indolent tumours), the biologic behaviour of most functioning NETS is defined by the grade and stage of the tumour, just as it is in non-functioning tumours.

2. Screening and early detection

Neuroendocrine GEP tumours can appear at all ages, with the highest incidence being from the fifth decade onward. The exception is the carcinoid of the appendix, which occurs with the highest incidence at approximately 40 years of age.
Patients with multiple endocrine neoplasia type 1 (MEN-1) or von Hippel-Lindau disease (VHL), may have a clinical onset 15-20 years earlier than patients with corresponding sporadic type of neuroendocrine tumours. In addition, GEP-NETS can also be part of the familial syndromes tuberosclerosis and neurofibromatosis (NF1, 2).

3. Diagnosis

Patients with clinical symptoms suggestive of neuroendocrine GEP-NET should be referred to a centre with special interest in, and knowledge of these diseases.

Imaging may include:

- CT or MRI depending on the tumour location.
- Endoscopy (gastroscopy, endoscopic ultrasonography, colonoscopy) is often of additional value.
- Over 90% of GEP-NETS have high concentrations of somatostatin receptors, and can be imaged using a radiolabelled form of the somatostatin analog octreotide (indium-111 pentetreotide, Octreoscan). For tumours that express a significant number of somatostatin type 2 receptors, preoperative staging should, whenever possible, include somastatin receptor scintigraphy which can be replaced, if available, with $^{68}$Gallium-DOTA-TOC/-NOC/-TATE PET.
- PET scanning, if available, with specific tracers such as $^{11}$C-5HTTP, $^{18}$F-DOPA or $^{18}$F-DG can further optimize the staging of the disease.

Biochemical analysis:

- General NET marker – plasma chromogranin A (pCgA).
- Poorly differentiated G3 tumours – plasma neuro-specific enolase (NSE).
- Small intestinal NETS (carcinoids) – urine 5-hydroxy-indole-acetic acid and pCgA.
- Non functioning pancreatic endocrine tumours – pCgA and pancreatic polypeptide (PP).
- Rectal NETS – PP, somatostatin.

Histological diagnosis is mandatory in all cases and is usually obtained on surgical or endoscopic biopsies or ultrasonography guided liver biopsies.
4. Pathology

The family of neuroendocrine GEP-NETs constitutes a heterogenous group, but all share a common phenotype with immunoreactivity for the pan-neuroendocrine markers including chromogranin A and synaptophysin.

Neuron specific enolase and CD56 are often positive in GEP-NETS, but are not specific for this tumour entity.

Specific staining for hormones, such as serotonin, gastrin, insulin and glucagon, can be applied to confirm the source of a clinical symptomatology.

Immunohistochemical demonstration of a hormone alone is not proof of functionality of a NET. Immunohistochemistry for Ki-67 (MIB1) is mandatory to grade the tumour according to the WHO classification.

For TNM classification (GEP-NETS), see Oberg et al., 2012.

5. Management

5.1 Surgery

5.1.1 Local/locoregional disease

About two thirds of carcinoid tumours arise within the gastrointestinal system, with the appendix being the most common primary location. Appendectomy is inadequate if the carcinoid tumour is larger than 2cm and/or if lympho-vascular invasion or involvement of the mesoappendix is present. In these cases, right hemicolectomy is indicated as definitive oncologic surgery.

All patients with small intestinal NETs should be considered potential candidates for curative surgery and should be evaluated in a multidisciplinary setting. Curative resection of the primary tumour and locoregional lymph node metastases improves outcomes in these patients.

Surgical procedures include small intestinal resection or right hemicolecotomy depending on the localization of the primary. Curative resection also involves clearance of mesentery and retroperitoneal lymph node metastases by dissection around the mesentery, preserving intestinal vascular supply.

Resection of the primary intestinal NET and regional lymph node metastases in patients with distant metastases (liver) is generally advocated to prevent later development of mesenteric fibrosis, small-bowel obstruction or painful vascular encasement.

In patients with pancreatic NETs, indications for surgery depend on clinical symptom control, tumour size/location, extent, malignancy and metastatic spread. Small pancreatic
NETs (<2cm) may have an indolent course and radiologic observation may be indicated in some cases. Curative surgery should be considered whenever possible even in the presence of metastatic disease, including localized metastatic disease to the liver if considered potentially resectable and the patient can tolerate the surgery. The type of surgery depends on the location of the primary tumour. Adequate lymph node clearance is mandatory.

There is general agreement not to operate on G3 pancreatic NET, as these tumours are often widely metastasized at the time of diagnosis.

5.1.2 Advanced/metastatic disease

Cytoreductive surgery should be considered when metastatic disease is localized or if >90% of tumour load is thought resectable, which may decrease endocrine and local symptoms and might help to improve systemic treatment.

5.2 Carcinoid tumours

5.2.1 Carcinoid tumours – initial therapy

(i) For patients who are symptomatic from carcinoid syndrome or who have octreotide avid disease – initiate treatment with a somatostatin analog.

(ii) For patients with metastatic disease that is resectable with curative intent, in the absence of extrahepatic metastases, diffuse bilobar involvement, or compromised liver function – resection rather than medical therapy.

(iii) For patients with asymptomatic advanced unresectable carcinoid tumours and small volume disease – observation alone rather than early administration of somatostatin analog.

5.2.2 Carcinoid tumours – progressive disease

(i) For patients with octreotide-avid disease and disease progression who are not already on somatostatin analog – initiate treatment with somatostatin analog.

(ii) For symptomatic patients with hepatic-predominant unresectable disease – hepatic arterial embolization, chemoembolization, or radioembolization rather than medical therapy alone as palliative technique are options.

(iii) For patients with carcinoid tumour and progressive disease despite a somatostatin analog:

   No standard approach.
   Consider clinical trial enrolment.
   Everolimus (Pavel et al., 2011).
Benefit of cytotoxic chemotherapy under debate.
Benefit of Interferon α – no widespread acceptance.

5.3 Pancreatic neuroendocrine tumours

5.3.1 Pancreatic neuroendocrine tumours – initial therapy

(i) Patients with symptoms of hormone hypersecretion should be managed with somatostatin analogs and other agents, as appropriate to the specific syndrome.

(ii) For patients with metastatic disease that is resectable with curative intent, in the absence of extrahepatic metastases, diffuse bilobar involvement, or compromised liver function – resection rather than medical therapy.

5.3.2 Pancreatic neuroendocrine tumours – progressive disease and/or symptomatic from tumour bulk

(i) For patients with progressive advanced pancreatic NET – treat with a molecularly targeted agent – everolimus (Yao et al., 2011) or sunitinib (Raymond et al., 2011).

(ii) For patients who are highly symptomatic from tumour bulk, or who have rapidly enlarging metastases – chemotherapy with a streptozocin or temozolomide-containing regimen (Kouvaraki et al., 2004, Chan et al., 2012).

(iii) For symptomatic patients with hepatic predominant disease who are not candidates for surgical resection – hepatic arterial embolization is a reasonable alternative approach.

5.4 Poorly differentiated neuroendocrine tumours

(i) Systemic chemotherapy with a platinum-based combination regimen, analogous to that used for small cell lung cancer.

There is no established second-line therapy for poorly differentiated endocrine carcinoma but recent retrospective studies have demonstrated the efficacy of temozolomide alone or in combination with capecitabine +/- bevacizumab (Welin et al., 2011).

Data is evolving with regard to peptide receptor-targeted radiotherapy (PRRT) in the treatment of NETs with liver metastases using ⁹⁰Yttrium and ¹⁷⁷Lutetium labelled DOTATOC or DOTATATE.
5.5 Oncology Nursing

Refer to general oncology nursing practices

6. Supportive Care

6.1 Patient Education

Refer to general patient education practices

6.2 Psychosocial Care

Refer to general psychosocial oncology care guidelines

6.3 Symptom Management

Refer to general symptom management care guidelines

6.4 Clinical Nutrition

Refer to general clinical nutrition care guidelines

6.5 Palliative Care

Refer to general oncology palliative care guidelines

7. Follow-up care

Follow-up investigations should include biochemical parameters and conventional imaging.

In patients with R0/R1 resected NET G1/G2, it is recommended that imaging is performed every 3-6 months (CT or MRI).

In patients with R0/R1 resected NET G3, it is recommended that imaging is performed every 2-3 months (CT or MRI).

Somatostatin receptor imaging, either octreoscan or if available, PET/CT 68Ga-DOTA-TOC/-NOC/-TATE should be included in the follow-up and is recommended after 18-24 months if expression of somatostatin receptor 2a has been proven on the tumour cells.

In the case of rapid tumour progression or if imaging information is lacking, it may be necessary to re-biopsy liver metastases to re-assess proliferative activity. If chromogranin A is not elevated, NSE represents an alternative biomarker.
8. References


