Neuroendocrine tumour management: a team approach

A Banfield, S Green, JK Ramage

This article gives an overview of neuroendocrine tumours of the gut, liver and pancreas and will make the case for a multidisciplinary approach to management.

Neuroendocrine tumours (NETs) are relatively rare, but with an estimated incidence of 25 per million population per year (Modlin et al, 2003) and a long life expectancy (median 5 years even in those with metastases), the prevalence represents a significant burden of disease. Previously individual patients have been managed by individual clinicians with wide-ranging backgrounds, and the type of investigation and treatment has often depended on the training of the clinician rather than the requirements of the patient. In the new patient-focussed environment and with the advent of greater information about their diseases, patients will benefit from opinions from various experts who can each contribute to the global management of these complex tumours. This is facilitated by a multidisciplinary or multispecialty clinic, which is described at the end of this article.

DEFINITION AND CLASSIFICATION

NETs originate from neuroendocrine cells within the gastrointestinal (GI) tract, the pancreatic islets, the respiratory epithelium, the adrenal medulla, the gonads or the parafollicular cells of the thyroid gland. Tumours originating from the lung (which technically include small cell lung cancer) and from the thyroid (medullary carcinoma) are managed by other specialist teams and will not be further considered here.

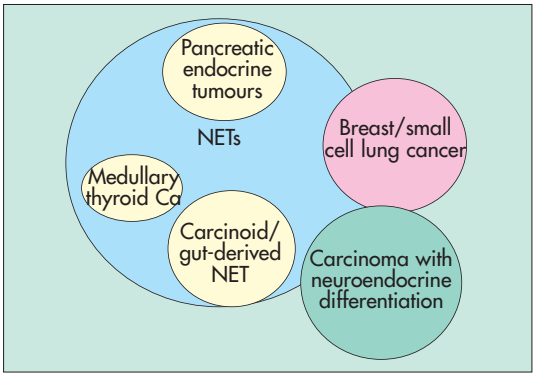
The term 'carcinoid' is still commonly used and generally refers to tumours secreting 5-hydroxytryptamine (5-HT) and originating in the gut, although the exact definition is unclear. Many NETs secrete hormones which cause a variety of clinical syndromes (see below) and this has led to one form of classification of these tumours, i.e. insulinomas, gastrinomas, glucagonomas. A further classification system is the embryological site of the primary, i.e. foregut (bronchi, stomach, pancreas, gallbladder and duodenum), midgut (jejunum, ileum, appendix and right colon), or hindgut (left colon and rectum). Another more widely accepted and useful classification is that determined by the histopathology, which has been categorized by a World Health Organization (WHO) (Kloppel et al, 2000; Solcia et al, 2000) system as discussed later (*Figure 1*).

AETIOLOGY AND EPIDEMIOLOGY

The incidence of NETs is rising. This is probably at least partly a result of an increase in incidental diagnosis as scans become more accurate. Most recent estimates are in the region of 3 per 100 000 with a consistent slight female predominance (Levi et al, 2000; Hemminki and Li 2001a,b; Modlin et al, 2003).

Most NETs are thought to be sporadic and non-familial. There is, however, an estimated four times increased risk for those with an affected first degree relative and an estimated twelve times risk for those with two affected first degree relatives (Hemminki and Li, 2001b). NET patients have an increased risk of developing other cancers, particularly in the GI tract. Modlin et al (2003) found that of 13 000 patients with NETs, 20% developed other cancers.

Figure 1. Classification of neuroendocrine tumours (NETs). Ca = carcinoma.



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One important association is with the multiple endocrine neoplasia syndrome type 1 (MEN-1) (Gibril et al, 2004). For pancreatic tumours, particularly gastrinomas, somatostatinomas and insulinomas, careful clinical examination and detailed family history are essential to try and exclude MEN-1 syndrome. In about 75% there will be at least one other family member affected because of the dominant inheritance. Patients thought to be at high risk are generally referred to a geneticist for genetic testing of the MEN-1 (menin) gene located on chromosome 11 (Brandi et al, 2001).

CLINICAL SYNDROMES

Symptoms of GI-related NETs are often missed, partly because of the rarity of the tumours but partly also because of the protean nature of the symptoms. Non-secreting tumours are often diagnosed at a late stage when liver metastases are picked up by liver function tests or ultrasound abnormalities. Patients with hormone syndromes often do not present with the classical textbook symptoms and can easily be missed. Common problems are: flushing in the postmenopausal woman with carcinoid in whom the symptoms are put down to oestrogen deficiency, gastric ulceration as a result of gastrinoma in a patient with long-standing dyspepsia who is maintained on a proton pump inhibitor (PPI) with no further investigation, or fits in an insulinoma patient in whom the symptoms are thought to be caused by idiopathic epilepsy.

Foregut NETs

Lung NETs: These arise from the Kulchitsky cells of the respiratory epithelium and up to 30% are asymptomatic. Symptoms of bronchial obstruction can be the only presenting feature. The clinical syndrome is only apparent when liver metastases are present and constitutes episodic diarrhoea, alcohol-related flushing, cough, wheeze, haemoptysis, lacrimation, rhinorrhoea and facial oedema (Beasley et al, 2000; Filosso et al, 2002).

Gastric NETs: These are often an incidental finding at upper GI endoscopy and the type 1 tumours (associated with atrophic gastritis) rarely produce a clinical syndrome. Type 2 tumours are associated with high gastrin levels as a result of gastrinomas (with or without MEN1) and are of intermediate malignancy while the more aggressive type 3 (sporadic) form of tumour usually metastasizes and has a shorter survival (Rindi et al, 1996; Granberg et al, 1998; Modlin et al, 2004).

Islet cell NETs: These tumours are responsible for a wide range of clinical syndromes. Although most are caused by pancreatic islet hormone secretion, some tumours may be found elsewhere, e.g. gastrinomas in the duodenum. Some tumours may secrete more than one hormone, either at the same time or at different time intervals (Faiss et al, 1996; Tomassetti et al, 2001) (*Table 1*).

TABLE 1.
Islet cell neuroendocrine tumours

Tumour	Symptoms	Malignancy
Insulinoma	Confusion, sweating, dizziness, weakness, unconsciousness, relief with eating	10% of patients develop metastases
Gastrinoma	Zollinger–Ellison syndrome of severe peptic ulceration and diarrhoea	Metastases develop in 60% of patients; likelihood correlated with size of primary
Glucagonoma	Necrolytic migratory erythema, weight loss, diabetes mellitus, stomatitis, diarrhoea	Metastases develop in 60% or more patients
Vipoma	Werner–Morrison syndrome of profuse watery diarrhoea with marked hypokalaemia	Metastases develop in up to 70% of patients; majority found at presentation
Somatostatinoma	Cholelithiasis; weight loss; diarrhoea and steatorrhoea. Diabetes	Metastases likely in about 50% of patients
Non-syndromic pancreatic neuroendocrine tumour	Symptoms from pancreatic mass and/or liver metastases	Metastases develop in up to 50% of patients

Midgut NETs

Midgut NETs (which are still often described as carcinoid tumours) often secrete 5-HT which, along with other vasoactive compounds, gives rise to the classical carcinoid syndrome of episodic diarrhoea, abdominal pain and flushing (which can be alcohol related). Signs include facial telangiectasia, right heart failure as a result of tricuspid regurgitation (pulmonary valve lesions also occur) and skin lesions caused by pellagra. Pellagra occurs as a result of deficiency of nicotinamide in the body after excessive diversion of tryptophan into the pathway for production of 5-HT (Bax et al, 1996). The clinical syndrome in carcinoid generally occurs only after hepatic metastases have developed, allowing the vasoactive compounds to be released directly into the systemic circulation (occasionally it can be caused by large volume extrahepatic disease, especially when porto-systemic shunting is present)(*Figure 2*).

The primary tumours are often misdiagnosed as other more common conditions such as irritable bowel syndrome. Consequently midgut tumours are often found incidentally at routine scanning or laparotomy, or very late in the disease. Post-mortem studies reveal a much higher incidence than expected compared with those

diagnosed during life, indicating that many are never correctly diagnosed (Modlin et al, 2003).

Hindgut NETs

These hardly ever present with hormonal symptoms but some will have histological staining for glucagon, somatostatin or pancreatic polypeptide (O'Briain et al, 1982). They are often octreotide-receptor negative on somatostatin receptor scintigraphy (SSRS) imaging (Octreoscan, Mallinckrodt Medical Inc., St. Louis, Missouri, USA).

DIAGNOSIS

Diagnosis is based on clinical symptoms, hormone concentration, radiological and nuclear medicine imaging, and histological confirmation. The gold standard in diagnosis is detailed histology and this should be obtained whenever possible.

The biochemical diagnosis

The initial diagnosis is often biochemical. Baseline tests may include full blood count, urea and electrolytes, thyroid-stimulating hormone, calcium, chromogranin A (CgA) and urine 5-hydroxyindoleacetic acid (5-HIAA). CgA is the main screening marker as it is found in almost all NET cells, and it can also be a valuable indicator of tumour activity. Depending on which syndrome is suspected by the clinician, more specific markers and stimulation tests can then be requested (e.g. secretin stimulation for gastrin secretion).

Imaging

Endoscopy may allow visualization and biopsy of gastric, duodenal, colonic and lung NETs. Tumours of the small bowel, pancreas, thyroid, adrenals and gonads often prove more elusive. Often several different imaging modalities will be needed in order to localize the primary. Opinion remains divided on whether finding and removing the primary is of clinical benefit after metastases have already occurred. Commonly used imaging modalities include:

- SSRS in which radio-labelled somatostatin analogues are bound to the somatostatin receptors present on NET tumours, a technique which has sensitivity of up to 90% (Krenning et al, 1994) (*Figure 3*)
- Ultrasound
- Endoscopic ultrasound for pancreatic NETs (Anderson et al, 2000)
- Magnetic resonance imaging (MRI)
- Triple phase multislice computed tomography
- Venous sampling for insulin gradients in insulinomas and other islet cell tumours (used in only a few centres) (Brandle et al, 2001).

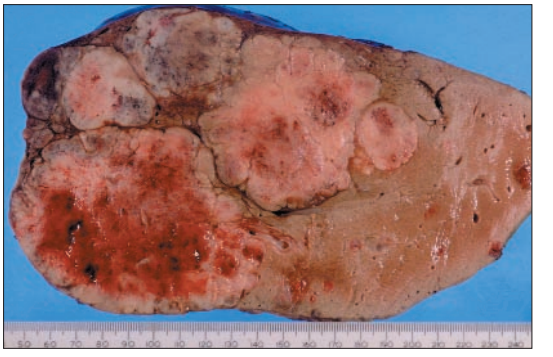

Figure 2. Liver explant specimen from a patient with massive liver metastases from a hindgut neuroendocrine tumour.

SSRS offers the additional benefit of predicting response to somatostatin therapy.

Histopathology

The World Health Organization (Kloppel et al, 2000; Solcia et al, 2000) categorizes NETs into the following four types:

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.

This classification is based on the size of the primary, the level of invasion and microscopic features including immunohistochemistry. Immunostaining is an increasingly important tool: the percentage of cells staining positive for the proliferation marker Ki-67 is an aid to assessing prognosis (Gentil et al, 1998).

QUALITY OF LIFE ISSUES

In the past, the outcome of treatment, whether it be medical or surgical, has been assessed in terms of survival. With regard to NET tumours, appropriate treatments have rarely shown a conclusive increase in survival. The assessment of quality of life before and after treatment is the next important parameter to measure (Ramage and Davies, 2003). At present the European Organisation for Research and Treatment of Cancer (EORTC) generic questionnaire, the QLQ-C30 (Aaronson et al, 1993), is the most extensively used tool for

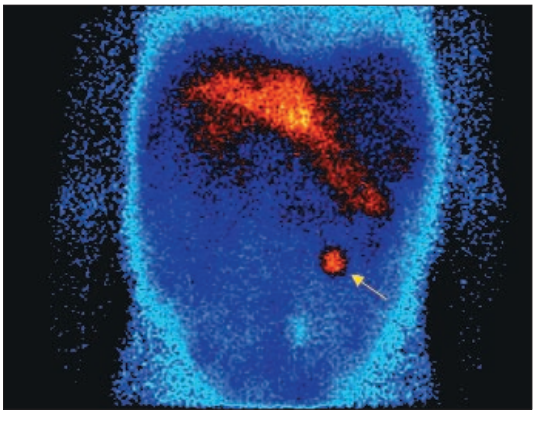

Figure 3. Somatostatin receptor scintigraphy (Octreoscan, Mallinckrodt Medical Inc., St. Louis, Missouri, USA) using indium-111 which has demonstrated a primary gut neuroendocrine tumour (arrow).

measuring quality of life in cancers and a module to add to this is under evaluation.

TREATMENT OPTIONS

It is essential that therapy be tailored to the individual patient. The treatment selection is guided by the histology (with Ki-67 staining), site of primary, extent of disease, SSRS (*Figure 4*) and iodine-123-meta-iodobenzylguanidine (MIBG) scan appearances. The main aim is to extend life but also to improve quality of life.

Patients often maintain a good quality of life for many years despite having metastases.

Surgery

This is the only curative treatment for NETs. Those tumours more amenable to curative surgery include appendiceal, lung and rectum. Despite perioperative support, intraoperative handling of functional tumours can lead to life-threatening cardiorespiratory complications and senior anaesthetic cover is essential. Often NETs are an incidental finding of surgery and this is particularly common following appendicectomy. Criteria for which patients should have right hemicolectomy and long-term follow up are not well-defined and have been reviewed (Goede et al, 2003).

In the presence of liver metastases, if the lesions are within one lobe only, resection is curative in about 10% of cases. More extensive disease may be suitable for a debulking procedure, which can ease the endocrine manifestations. Transplantation has been considered for patients with uncontrollable symptoms who are unresponsive to any intervention.

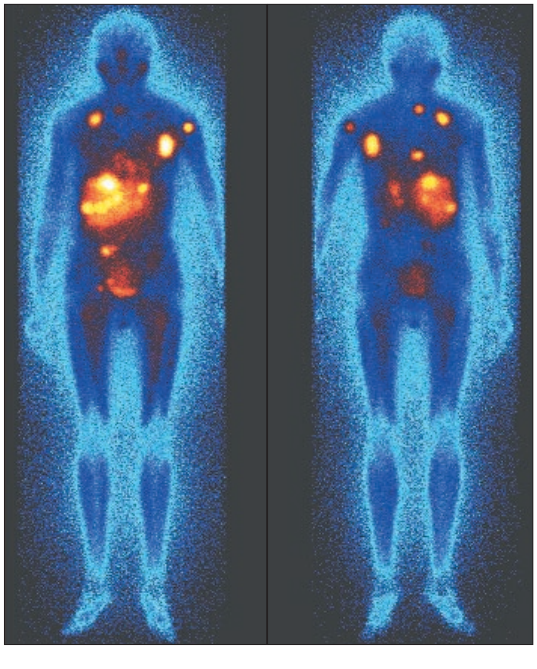

Figure 4. Somatostatin receptor scintigraphy (Octreoscan, Mallinckrodt Medical Inc., St. Louis, Missouri, USA) showing widespread metastases.

Embolization of the hepatic arterial supply to the tumours

This can reduce tumour size and hormone output. Arterial embolization induces ischaemia of the tumour cells thereby reducing their hormone output. There is significant morbidity and occasional mortality, but embolization is effective and can be repeated. Ischaemia of the tumour cells also increase their sensitivity to chemotherapeutic substances, hence the development of particle embolization and chemoembolization. Particles used include polyvinyl alcohol (PVA) and gel foam powder (Chamberlain et al, 2000).

Radiofrequency ablation

This has been used with some effect in stabilizing or reducing tumour size but randomized trials are lacking. It may be indicated in patients with inoperable bilobar metastases in whom hepatic artery embolization has failed. It can be performed percutaneously or laparoscopically.

Radiotherapy

External beam radiotherapy may give excellent relief from pain caused by secondary bone metastases.

NET-specific therapies

Somatostatin is a natural brain gut peptide that inhibits both exocrine and endocrine functions. Somatostatin receptors are present in the vast majority (70–95%) of NETs but only in about half of insulinomas, and less in poorly differentiated NETs and somatostatinomas. The synthesis of analogues (octreotide) has resulted in considerable advances in the management of NET tumours. Octreotide can improve symptoms in up to 70% of patients and provide biochemical control in around 60% (Oberg et al, 2004).

Analogues with sustained release from depot injections have been developed. Sandostatin LAR (monthly, Novartis UK Ltd, Frimley), Somatuline LA (fortnightly, Ipsen UK Ltd, Slough) and Somatuline Autogel (monthly, Ipsen UK Ltd, Slough) have shown significant improvement in the quality of life of patients and have as good or better efficacy compared to octreotide.

Vasoactive intestinal peptide-producing NETs (VIPomas): Patients frequently respond dramatically to small doses of somatostatin analogues with cessation of diarrhoea.

Glucagonomas: Improvement by somatostatin analogues has been reported in these patients, although it is unlikely that circulating glucagon levels can be normalized. Anticoagulation and zinc therapy for the characteristic rash are commonly used (Wermers et al, 1996).

Gastrinomas: The syndrome is adequately controlled with high-dose PPI drugs and H2 receptor antagonists. In some cases somatostatin is used in addition.

Insulinomas: Only 50% of insulinomas have somatostatin receptors. For this reason somatostatin analogues have variable effects on the blood-glucose levels but some patients can be stabilized using these. Diazoxide has been shown to be effective in controlling hypoglycaemic symptoms. Glucose infusion and intramuscular glucagon are used in an emergency.

Interferon-alpha

This is used on its own (Faiss et al, 2003) or added to long-acting somatostatin analogues if the patient is not responding to maximum dosage of somatostatin analogues. However, there is conflicting evidence as to its efficacy.

Chemotherapy

The role of chemotherapy for NETs is controversial. It is essential to consider the tumour types individually in view of their varying response to chemotherapy and the indications for its use. The highest response rates with chemotherapy are seen in the poorly differentiated NETs. These responses may be relatively short, lasting only 8–10 months (Moertel et al, 1991).

For the less aggressive midgut carcinoid tumours, 80% response rates have been seen by combining embolization of the hepatic artery with intra-arterial chemotherapy (Ruszniewski et al, 1993).

Targeted radionuclide therapy

This is an increasingly used palliative option for symptomatic patients with inoperable or metastatic tumours. The principle of treatment is to give radionuclide therapy when there is abnormally increased uptake of the corresponding imaging agent. ^{131}I-MIBG is the only licensed therapy and only 30–70% of tumours will take up enough isotope on imaging to warrant therapy. Responses may be slightly higher in midgut than pancreatic tumours.

Yttrium-90-Octreotide (Yttrium DOTATOC) has been used in trials and rarely on a named-patient basis but availability is severely limited. Some objective responses have been seen but this is in less than 50% of cases (*Figure 5*).

PROGNOSIS

This depends on the tumour and the syndrome involved. In many cases survival rates are longer than for other cancers. The overall 5-year survival rate ranges from 30–70% in those presenting with metastases, to 83% in those where the primary was removed with surgery. Some patients have a rapidly progressing disease while others show a much more indolent course. The reasons for the differing prognoses are unclear.

ISSUES CONCERNING MULTISPECIALTY CARE

Since this is an uncommon tumour, when metastatic disease is identified, most patients will need their case discussed with a NET centre. The patient does not necessarily have to travel to the centre. Upon referral, all centres should provide a multidisciplinary approach with specialists in hepatobiliary and GI surgery, GI oncology, endocrinology, pathology, genetics, radiology, cardiology, gastroenterology, hepatology and specialist nursing. Not all of these specialists will be present in all centres but routes of communication to all these specialists should be clear and available in view of the complex nature of many of these tumours. Data collection should be prospective so that cases can be audited and outcomes compared between centres. The advantages of the multispeciality team include:

- Accurate diagnosis and staging
- Evaluation of performance status and quality of life
- Obtain consensus agreement on treatment plan
- Delivery of information on treatment modalities to patients
- Delivery of support, and information on prognosis to patients
- Continuous reassessment, discussion and peer review of the individualized treatment plan.

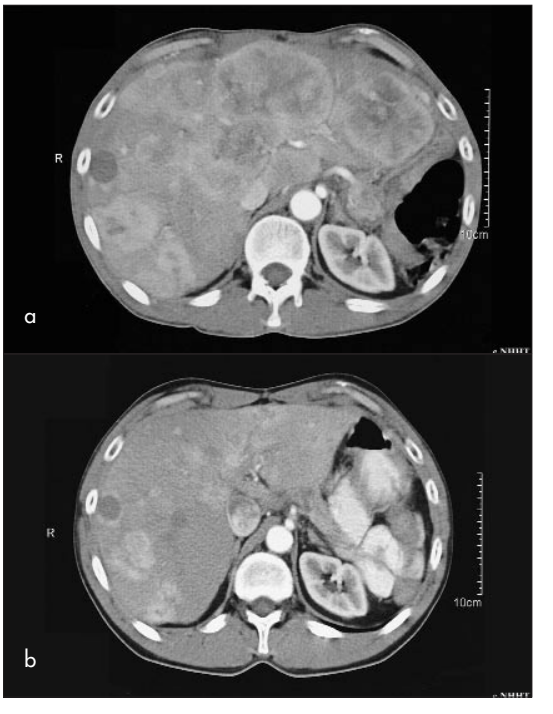

Figure 5. Post-arterial phase computed tomography films (a) pre and (b) post two courses of yttrium-90-octreotide.

It is essential that clinicians have a forum in the UK where they can discuss the organization of patients' care and the availability of NET centres. UK NETwork is a national group set up for this purpose, in addition to compiling a controlled trial database and treatment register. Three national meetings have been organized and a fourth planned. A committee meets regularly and guidelines for hospital-based care have been drawn up and are about to be published (Davies and Ramage, 2005). Information for GPs, entitled 'A best practice approach to the care of neuroendocrine tumour patients: a guide for primary care teams', has been produced through UK NETwork and will soon be available on the forum website www.uk-network.org.uk.

Patient support is essential, either through direct contact with members of the multidisciplinary team or through patient support groups. Living With Carcinoid (www.livingwithcarcinoid.org.uk – under construction) is a national patient support group. The contact is livingwithcarcinoid@lineone.net. **HM**

Figures 3 *and* 4 *are reproduced courtesy of Dr V Lewington.*
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KEY POINTS

- Neuroendocrine tumours are relatively rare but the incidence is increasing.
- Treatment should be conducted at or guided by a multidisciplinary team.
- Medical treatment should be tailored to the symptoms, stage of disease, degree of uptake of radionuclide and the histological features of the tumour.
- Treatment should focus on prolonging survival, controlling symptoms and improving quality of life.

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