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Neuroendocrine tumours

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Background

NEUROENDOCRINE cells are located throughout the body. They release hormones in response to a variety of stimuli to regulate a wide range of normal physiological functions. Neuroendocrine tumours (NETs) arise from this diverse group of cells and are most commonly found in the gastrointestinal tract and pancreas.

Although these tumours share common markers of neuroendocrine differentiation, they have different embryological origins and extremely variable biological behaviour, ranging from benign to very aggressive tumours. Some NETs secrete hormones that can cause significant morbidity and be life-threatening despite their slow growth. By contrast, some patients with very slow-growing tumours survive for many years, even in the presence of metastatic disease.

In the past decade there have been multiple advances in biochemical, histopathological and imaging techniques, resulting in improved diagnosis, classification and accuracy of prognosis. These advances are enabling a new era of personalised medicine in which a number of new targeted thera-

pies can be selected for an individual patient, leading to improved patient outcomes.

Epidemiology

Although uncommon, the incidence of NETs has risen significantly over the past few decades, and NETs now constitute the second most prevalent GI tumour after colorectal cancer. Improved awareness combined with advances and better availability of imaging, biochemistry and endoscopic techniques has almost certainly contributed to this rise. Therefore, it is difficult to discern if there has been a true increase in tumour incidence.

Most NETs are sporadic but some are observed in high frequency in inherited familial syndromes, including multiple endocrine neoplasia (MEN), von Hippel-Lindau disease and neurofibromatosis. In sporadic cases we have noted a disproportionately high number of patient referrals from non-metropolitan areas and further research is needed to elucidate potential carcinogens.

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Classification and pathology

NETs can be classified according to the site of origin and the degree of differentiation and function.

Site

Traditionally, NETs were classified by the site of origin as:

- Foregut (stomach, duodenum, pancreas, bronchus).
- Midgut (small bowel to ascending colon, including appendix).
- Hindgut (transverse colon to rectum, genitourinary).

The term gastroenteropancreatic (GEP-NETs) is now used to encompass the broad range of NETs arising from the bowel or pancreas. Pancreatic NETs (also

called islet cell tumours) arise from the cells of the islets of Langerhans of the endocrine pancreas, and are distinct from pancreatic adenocarcinomas which arise in the exocrine pancreas.

The term carcinoid ('cancer like') was introduced in 1907 to describe GI NETs that had slow growth as opposed to the malignant pattern seen with adenocarcinoma.

Degree of differentiation and function

NETs can be divided into well-differentiated or poorly differentiated categories, which charac-

terise disease biology and prognosis and enable appropriate selection of treatment (table 1). There is, however, a continuum

between the two, and moderately differentiated tumours may have characteristics of either group and much less predictable behaviour.

Well-differentiated NETs

The cells of well-differentiated NETs closely resemble the normal neuroendocrine cell from which they arose, and the tumours tend to have slow growth with an indolent natural history. The functional activity of the original cells can be preserved and amplified, resulting

in high and inappropriate levels of hormone secretion. Thus, they can be characterised as functioning (hormone producing) or non-functioning.

Serotonin (5-hydroxytryptamine) production is most commonly seen in carcinoid tumours, but production of more than 50 peptides or amines have been described. Some hormone-producing tumours can be clinically silent due to the synthesis of hormone precursors or inactive hormones.

Well-differentiated NETs have a high degree of expression of somatostatin receptors (SSTRs) on their cell surface. Somatostatin is a peptide hormone that exerts an inhibitory effect on a variety of cellular functions. For example, somatostatin normally inhibits the release of:

- TSH, growth hormone and ACTH from the anterior pituitary.
- Insulin and glucagon from the pancreas.
- Gastrin from the gastric mucosa.
- Secretin from the intestinal mucosa.

It is an important hormone for the regulation of GI function such as gastric emptying and of pancreatic hormone secretion. This common feature of high levels of SSTR expression across a range of diverse NETs provides a unique and specific target for both imaging and treatment.

Poorly differentiated NETs

The cells of poorly differentiated NETs less closely resemble normal neuroendocrine cells and behave aggressively, with rapid proliferation and clinical course.

Well-differentiated tumours can de-differentiate (or transform) over time into the poorly differentiated aggressive subtype and, as such, all NETs should be regarded as having malignant potential. Over time, tumour heterogeneity can develop, with well-differentiated and poorly differentiated phenotypes coexisting at different sites in the same patient.

Table 1: Spectrum of NETs, from well to poorly differentiated

	GRADE (ENETS)		
	Well differentiated	Poorly differentiated	
	Low (G1)	Intermediate (G2)	High (G3)
Ki-67 index	≤2	2-20	>20
Anatomical imaging		More rapid growth on serial imaging	
Functional imaging	Octreoscan SPECT or SSTR PET +ve		FDG-PET +ve
Prognosis	Indolent (slowly growing)		Aggressive
Treatment options	Surgery for localised ± resectable metastatic disease		
	Observation Somatostatin analogues Radionuclide therapy		Chemotherapy
	Everolimus, sunitinib, alpha interferon Liver metastases: radiofrequency ablation, hepatic embolisation, TACE, SIR-Spheres		

ENETS = European Neuroendocrine Tumour Society

Ki-67 = cell-cycle-dependent marker

SPECT = single photon emission computerised tomography

SSTR = somatostatin receptor

FDG = fluorodeoxyglucose

TACE = trans-arterial chemoembolisation

terise disease biology and prognosis and enable appropriate selection of treatment (table 1). There is, however, a continuum



Clinical features — symptoms and signs

SMALL NETs are usually asymptomatic and it is unusual for them to be diagnosed until there is locally advanced or metastatic disease, and even then untreated patients can remain asymptomatic or have only vague symptoms for many years. Careful history can identify symptoms related to excess hormone secretion by NETs, particularly those of carcinoid syndrome. Some early-stage NETs are discovered as incidental findings on imaging or endoscopy without clinical sequelae, or due to secretion of bioactive hormones resulting in characteristic clinical syndromes.

Carcinoid syndrome

Carcinoid syndrome is the clinical manifestation of excess serotonin production (figure 1, page 36). In patients with early-stage carcinoid tumours that secrete serotonin, systemic symptoms do not occur, as active hormone enters the portal circulation and is rapidly degraded by hepatic enzymes. Carcinoid syndrome, which occurs in about 10% of carcinoid tumours, manifests only when the tumour has metastasised to the liver or extra-peritoneal abdominal organs such as the ovary, allowing hormone to enter the systemic circulation, thereby escaping hepatic degradation.

Characteristic symptoms of carcinoid syndrome include:

- Intermittent or progressive facial flushing (figure 2, page 36).
- Secretory diarrhoea (characterised by lack of response to fasting).
- Abdominal cramps.
- Wheezing.

A carcinoid crisis (prolonged severe flushing, diarrhoea, hypotension, tachycardia, severe dyspnoea,

peripheral cyanosis and sometimes haemodynamic instability) can occur if large amounts of hormone are secreted acutely. This can be triggered by diet, alcohol, surgery or chemotherapy. In one case of which we are aware, a carcinoid crisis was precipitated by vigorous palpation by an enthusiastic group of medical students.

About 50% of patients with carcinoid syndrome have cardiac abnormalities caused by chronic exposure of the heart valves to serotonin, which causes fibrosis and thickening of the tricuspid and pulmonary valves, resulting in regurgitation or, less commonly, stenosis. Right heart failure and congestive cardiac failure can

result. Clinical signs include elevated jugular venous pressure with large *v* waves, right ventricular heave, the pansystolic murmur of tricuspid regurgitation and a large, pulsatile and tender liver. Ascites and oedema can also occur. The consequent hepatic congestion results in a decreased capacity of the liver to degrade hormones, which further exacerbates symptoms and can result in acute decompensation.

Gastrointestinal NETs

Small-bowel carcinoids are frequently asymptomatic or present with vague abdominal symptoms that can be mistaken for irritable bowel syndrome. Some patients present with intermittent or acute bowel obstruction. Production of serotonin or other bioactive amines is a typical feature of small-bowel carcinoids, and local secretion causes mesenteric fibrosis that predisposes to bowel obstruction or can compress mesen-

teric vessels, resulting in bowel ischaemia and malabsorption.

Most gastric, appendiceal and rectal carcinoids present as incidental findings. These tumours are usually non-functioning and remain asymptomatic until advanced.

Pancreatic NETs

Non-functioning pancreatic NETs may grow for a long time without causing symptoms. When large enough, obstruction of bile or pancreatic ducts may cause obstructive jaundice or symptoms due to pancreatic enzyme insufficiency, such as diarrhoea.

About half of pancreatic NETs are functional, producing a range of hormones resulting in characteristic syndromes (table 2). Tumours

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can secrete a range of hormones other than serotonin, including ACTH or corticotrophin-releasing hormone (CRH), resulting in Cushing's syndrome, or parathyroid-hormone-related peptide (PTHrP), resulting in hypercalcaemia. Co-secretion of multiple hormones is not uncommon, and some apparently non-functioning tumours can occur because of co-secretion of antagonist hormones, for example, insulin and glucagon.

Bronchial NETs

Bronchial carcinoid tumours can cause recurrent pneumonia from airway obstruction, pleurisy, haemoptysis and shortness of breath. A small proportion of these tumours produce serotonin or sim-



Table 2: Features of selected syndromes

Disease	Hormone produced	Site (most common)	Clinical features	Investigations (blood)
Carcinoid syndrome	Serotonin, others (histamine, substance P)	Small bowel	Flushing, diarrhoea, abdominal pain, carcinoid heart disease (tricuspid regurgitation, right heart failure)	CgA, urinary 5-HIAA
Insulinoma	Insulin	Pancreas	Whipple's triad: • symptoms of hypoglycaemia (eg, blurred vision, sweating, tremor, weakness, confusion, coma) • glucose <2.2mmol/L • relief of symptoms with administration of glucose	Fasting or random glucose 72-hour fast test (requires hospitalisation) Insulin, C-peptide Drug screen (to exclude factitious hypoglycaemia)
Gastrinoma (Zollinger–Ellison syndrome)	Gastrin	Duodenum Pancreas	Peptic ulcer, gastric reflux, diarrhoea	Fasting gastrin Gastroscopy/24h pH-metry Secretin test*
Glucagonoma	Glucagon	Pancreas	Rash (necrolytic migratory erythema), impaired glucose intolerance or diabetes	Glucagon
VIP-oma	Vasoactive intestinal peptide (VIP)	Pancreas	Profuse watery diarrhoea and resultant dehydration, hypokalaemia and achlorhydria (pancreatic cholera syndrome)	VIP Hypokalaemia
Somatostatinoma	Somatostatin	Pancreas	Triad of diabetes mellitus, steatorrhea and gall stones, also associated with hypochlorhydria	Somatostatin

CgA = chromogranin A

5-HIAA = 5 hydroxyindole acetic acid

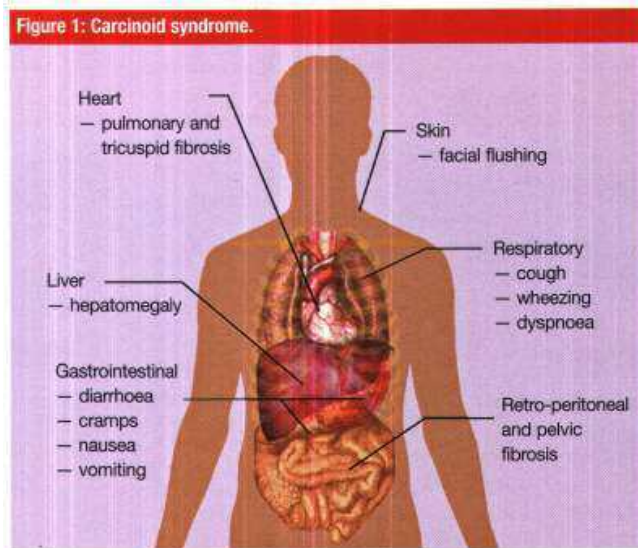
VIP = vasoactive intestinal peptide

*Secretin test: administration of exogenous secretin; test is positive if serum gastrin levels increase

ilar bioactive hormones, resulting in carcinoid syndrome, or ACTH, resulting in Cushing's syndrome.

Metastatic disease

Common sites of metastatic disease include local or distant lymph nodes, liver, bone and peritoneum. In females the ovary can be a site of metastatic disease. Some patients present with symptoms of fatigue and weight loss. Unlike other malignancies in which untreated metastatic disease is usually rapidly progressive, even widely spread metastatic NETs can be indolent, sometimes referred to as 'cancer in slow motion'. It is not uncommon for it to present initially as a cancer of unknown primary, as the burden of metastatic disease can be large, while the primary site remains small and difficult to locate.



Assessment and diagnostic techniques

INVESTIGATION should be personalised for each patient, taking into account the likely natural history and the general health of the patient.

Biochemical markers

In patients with suspicious symptoms, measurement of chromogranin-A (CgA) can be helpful, but other more complex tests are best co-ordinated by an endocrinologist, gastroenterologist or oncologist. CgA is a glycoprotein present in the secretory granules of most neuroendocrine cells. It is co-secreted along with other hormones but can be elevated in either functional or non-functional NETs. Very high levels of CgA are rarely found outside the setting of NETs. Mild or moderate elevation and consequent false-positive results may occur in patients treated with gastric acid secretory blockers, especially proton-pump inhibitors, and also in patients with impaired renal function, pregnancy, Parkinson's disease or untreated hypertension.

If there is suspicion of a specific syndrome, tests for hormone excesses are indicated (table 2).

5-Hydroxyindole acetic acid (5-HIAA) is the urinary breakdown product of serotonin and can be measured using a 24-hour urine collection in patients with features of carcinoid syndrome. Some foods, including plums, pineapples, bananas, eggplants, tomatoes, avocados and walnuts contain high levels of serotonin, which can increase urinary levels of 5-HIAA, and should be avoided three days before collection. 5-HIAA can also be increased in patients with untreated malabsorption such as in coeliac disease. A variety of medications can also increase or decrease 5-HIAA levels. CgA measurement is more sensitive and is increasingly replacing use of

urinary 5-HIAA.

Imaging

Once NET is strongly suspected on the basis of symptoms, biochemical testing, or confirmed on biopsy, systemic staging is necessary, since localisation of the primary site of disease and the presence of metastases has both prognostic and therapeutic implications.

CT of the thorax, abdomen and pelvis is generally the first test but unfortunately has relatively low

sensitivity for the primary tumour and will often significantly underestimate the extent of metastatic disease. In particular, liver metastases can be difficult to detect unless a triple-phase protocol involving pre-contrast, arterial and portal venous phase imaging is adopted.

Small hepatic metastases can be most sensitively identified using 3-Tesla MRI with a hepatocyte-specific contrast agent.

Unless a primary lesion is readily apparent, specialised imaging techniques may be necessary. These include CT enteroclysis (CT combined with intraluminal radiocontrast) for small-bowel lesions, and

MRI or endoscopic ultrasound for pancreatic lesions. These are best arranged by specialists experienced in the management of NETs, especially oncological surgeons.

By virtue of SSTR expression in most NETs, various radiolabelled somatostatin analogues have been developed for diagnostic imaging. These have three basic components — a radiometal that emits radiation detectable outside the body, linked via a chelating agent to a peptide that binds to the SSTR. The only commercially available and approved agent for SSTR-imaging is Indium-111 DTPA-octreotide (Octreoscan). The radiotracer is

injected intravenously followed by

imaging on a nuclear medicine gamma camera over the next 1-2 days. In addition to obtaining two-dimensional 'planar' imaging, it is now routine to obtain three-dimensional cross-sectional images by rotating the detectors around the patient, using a technique called single photon emission tomography (SPECT).

Although widely available, Octreoscan imaging is an expensive test and quite difficult to interpret. An inherent drawback is the absence of anatomical information, precluding lesion characterisation or precise localisation, leading to difficulty dis-

tinguishing physiological or benign uptake from pathological uptake.

These limitations can be overcome with hybrid SPECT-CT scanners, which provide both functional (SPECT) and anatomical (CT) information. Octreoscan imaging is best performed on a multi-slice SPECT-CT device and is significantly more sensitive than conventional imaging, with a large impact on patient management.

Recently, a few specialised centres have introduced SSTR-imaging on combined positron-emission tomography-CT (PET-CT) devices, using gallium-68 DOTA-octreotate (DOTATATE, GaTate) instead of indium-111 in the radiolabelled somatostatin analogues. PET provides vastly superior imaging (accurately identifying disease as small as 2-3mm [figure 3]) and speed (the scan can be completed in 60-90 minutes) compared with conventional gamma camera SPECT imaging. Patients in whom there is a strong clinical suspicion of NETs but who test negative on conventional imaging and Octreoscan, or patients who have Octreoscan findings suggesting limited disease amenable to curative resection, should be considered for this form





As well as more accurately defining the presence and extent of NETs, SSTR-imaging also characterises the biology of disease. As a marker of normal cellular differentiation, high uptake of Octreoscan or the PET analogues indicates that the disease is well differentiated and generally has an indolent natural history and therefore tends to be resistant to con-

ventional oncology treatments, such as chemotherapy.

As the disease becomes de-differentiated and aggressive, there tends to be a loss of SSTR. This is an adverse prognostic indicator but does indicate a higher likelihood of benefit from chemotherapy, as detailed below. As with most aggressive tumour types, PET-CT

imaging with fluorodeoxyglucose (FDG), a glucose analogue, is a sensitive means to detect and stage disease, as rapidly proliferating cells use glucose as a substrate for energy. In some patients, the combination of SSTR imaging and FDG PET-CT is indicated to characterise sites of well and poorly differentiated disease.
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Authors' case study 1

A MIDDLE-aged woman presented with intermittent severe epigastric pain and secretory diarrhoea. These were initially thought to be due to pancreatic duct strictures secondary to chronic pancreatitis and were treated with stenting of the proximal pancreatic duct via endoscopic retrograde cholangiopancreatography (ERCP).

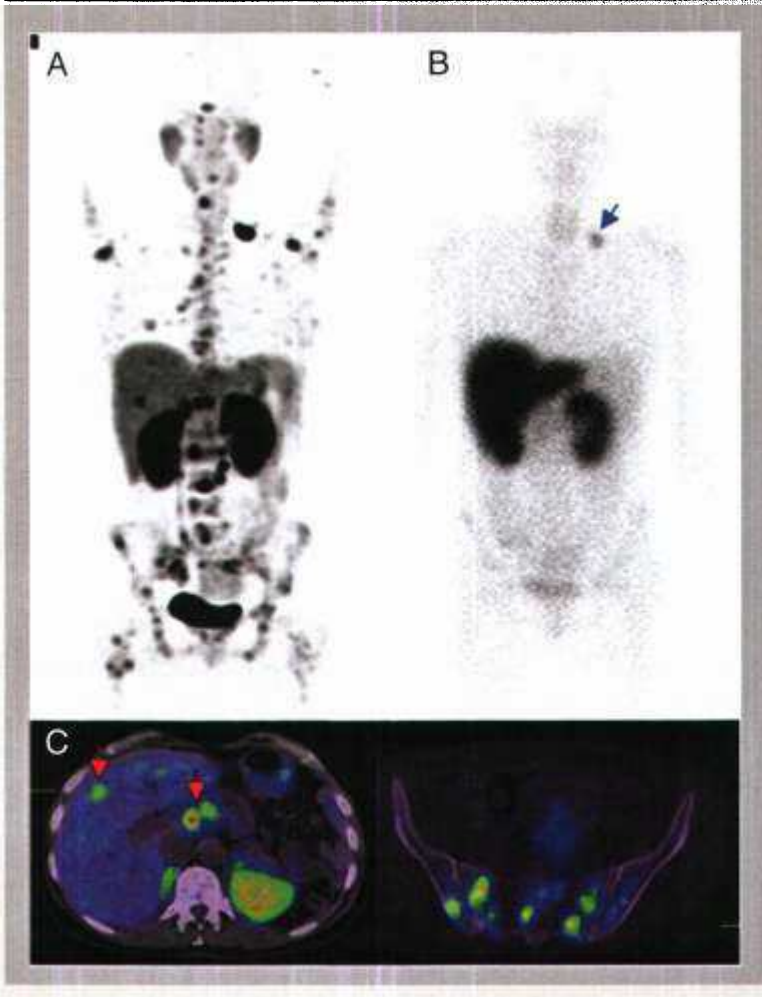
Symptoms persisted despite distal pancreatectomy and splenectomy, and a further ERCP-guided stent procedure. At re-operation two years later several sub-cm hepatic metastases were discovered, with histology demonstrating well-differentiated NET of low proliferative index (Ki-67 < 1%).

Triple-phase CT of the chest, abdomen and pelvis demonstrated no abnormality apart from multiple sclerotic bone lesions considered to be benign bony islands (osteopoikilosis) with prior 'negative' bone biopsy. 111-In-octreotide (Octreoscan) scan (figure 3B) anterior planar and SPECT-CT (not shown) demonstrated a solitary left supraclavicular nodal abnormality (blue arrow). GaTate PET-CT scan (figure 3A: anterior maximum image projection [MIP], figure 3C) demonstrated widespread small volume nodal and osseous metastatic disease, and also identified a pancreatic primary and further sub-cm liver metastases (red arrows).

Elevation of vasoactive intestinal peptide (VIP) level confirmed the diagnosis of a VIP-oma.

On the basis of the high somatostatin-receptor cell-surface expression demonstrated on this functional imaging, the patient was treated with a long-acting somatostatin analogue. Despite this there were progressive symptoms resulting in an ICU admission. The patient had a trial of alpha interferon without significant response and subsequently underwent radionuclide therapy with 111-In- and 177-lutetium-octreotate with marked reduction in symptoms.

Figure 3: Extensive metastatic disease demonstrated with GaTate PET/CT. A: GaTate PET/CT scan. B: 111-In-octreotide (Octreoscan) scan, anterior planar. C: selected axial PET/CT fusion slices.



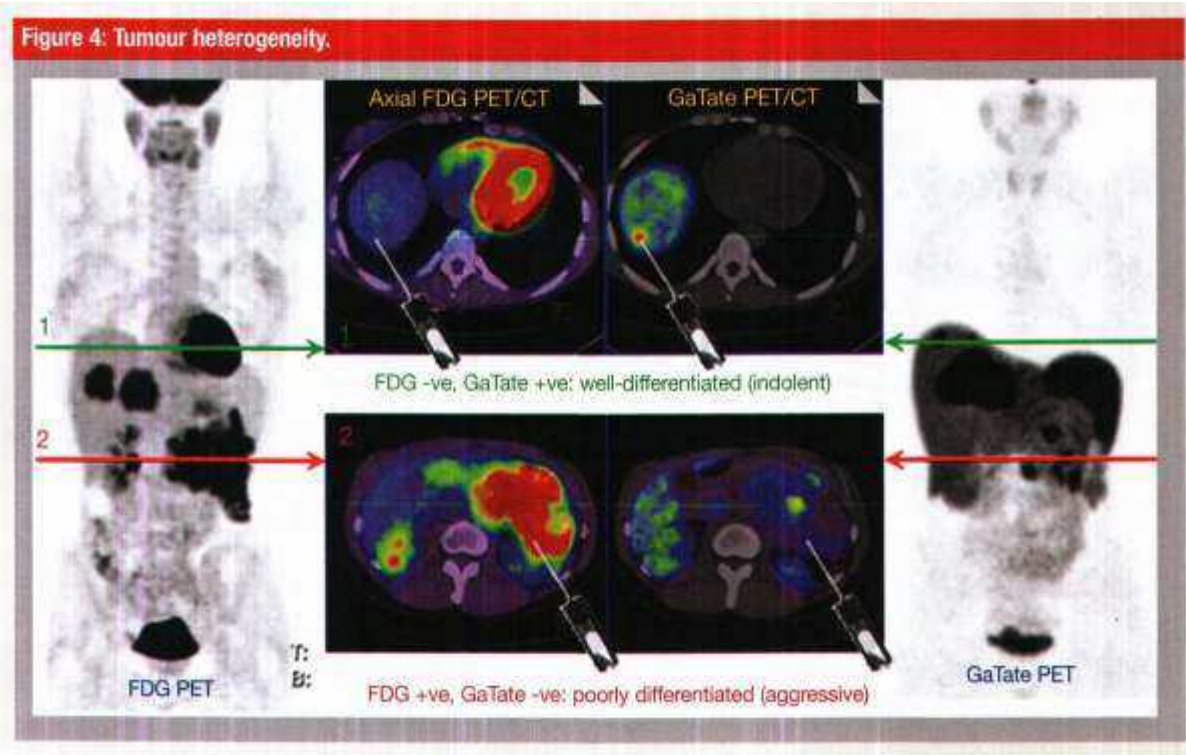
Authors' case study 2

THIS patient presented with symptoms of tremor, sweats and mild confusion associated with exercise and prevented by eating small and frequent meals. A 72-hour fast produced symptomatic hypoglycaemia with elevated insulin and C peptide levels, consistent with an insulinoma.

CT and MRI demonstrated a large left upper-quadrant mass arising from the pancreatic tail, with multiple hepatic metastases. 18F-FDG and 68Ga-Octreotate (GaTate) PET-CT demonstrated significantly different patterns of uptake, as demonstrated by the maximum intensity projection (MIP) images on the left and right in figure 4.

An axial slice through the liver (colour panel 1) demonstrates a GaTate-positive but FDG-negative hepatic metastasis, indicative of a well-differentiated lesion with high-somatostatin cell surface expression. An axial slice through the left upper-quadrant mass (colour panel 2) demonstrates a largely GaTate-negative but FDG-positive lesion, indicative of more poorly-differentiated (aggressive) phenotype.

Without the knowledge of the PET findings, core biopsy on the basis of CT or MRI could reveal either subtype, which might misinform decision-making. The PET studies demonstrate tumour heterogeneity suggesting both well- and poorly differentiated disease at different sites. (Note: Sites of physiological activity including renal/bladder activity on both studies, myocardial activity on the FDG PET, and splenic activity on the GaTate PET).



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ferentiated disease (figure 4). Neither test is currently funded and availability is limited to centres with specialist interest and expertise in these tumours. These tests are particularly valuable in selecting and monitoring the response to treatment.

Echocardiography

Carcinoid heart disease is seen in a high proportion of patients with longstanding carcinoid syndrome, and echocardiography is needed to

assess this. Specific features are thickening of valvular cusps and chordae, which results in regurgitation or stenosis (usually of the tricuspid valve) leading to right ventricular dilation and reduced function, as well as right atrial dilation.

Histopathology

Tissue from either biopsy of a primary tumour or metastases is needed to confirm the diagnosis and characterise disease biology:

- Immunostaining for neuroendocrine cell markers, including synaptophysin and chromogranin-A (CgA), is used to confirm the diagnosis.
- Aggressiveness of tumour is determined by counting the number of mitoses per high-power field or, more accurately, by immunostaining for the Ki-67 antigen, a cell-cycle-dependent marker. The Ki-67 index serves as the basis for grading tumours into grades 1-3 (see table 1).



Key points on diagnosis and staging

- Chromogranin-A (CgA) is the most practical and useful general serum tumour marker in patients with NETs.
- Elevated CgA levels occur in patients on proton-pump inhibitors, but very high levels are rarely seen outside the setting of NETs.
- Somatostatin receptor (SSTR)

imaging with Octreoscan SPECT-CT is more sensitive than conventional imaging for localisation and staging NETs.

- SSTR PET-CT imaging is available in a few specialised centres but can have a high management impact in patients with an unknown primary site of disease (by directing to curative surgery) or in patients with limited-stage disease on conventional workup

before major surgical intervention (by detecting distant metastatic disease and directing away from futile surgery).

- In patients with carcinoid syndrome, echocardiography is important to detect carcinoid heart disease.
- Tumour grading plays a key role in defining prognosis and therapeutic options.

Management

IN patients with advanced-stage disease, early referral to a centre with multidisciplinary expertise incorporating surgical oncology, medical oncology, nuclear medicine, interventional radiology, endocrinology, gastroenterology and radiation oncology is advised. Given the complexity and heterogeneity of this disease, therapy is individualised based on several factors, including:

- Disease extent.
- Rate of growth determined by temporal change on imaging and histological grade/proliferative index.
- Level of SSTR expression and FDG avidity (ie, positivity) on nuclear medicine imaging.
- Disease-related symptoms with regard to the primary lesion or metastatic deposits.
- Patient comorbidities.

Surgery

Complete surgical resection remains the only curative treatment for NETs. Unfortunately most patients present late with metastatic disease. While some pancreatic hormone-secreting tumours may be identified early due to symptoms, the more common pancreatic neuroendocrine tumours are usually silent. Metastatic disease does not, however, necessarily preclude consideration for curative or palliative surgery.

Most published data for surgical

resection of NETs reports on patients who have only had conventional CT or Octreoscan scanning preoperatively, which, as explained above, may have under-

estimated the extent of disease in those patients. The development of 3-Tesla MRI and SSTR PET-CT has significantly improved the accuracy of preoperative staging and detection of metastatic disease. Although not widely available, these should now be considered essential preoperative staging investigations when resection is being considered. Cure will only be possible in patients in whom all sites of disease can be resected.

Guidelines exist to aid in decision making about surgical treatment for the broad range of potential sites involved with tumour.¹ Gastric tumours are usually resected by partial gastrectomy, which can be performed laparoscopically. Small mucosal tumours of the stomach and duodenum can be managed with endoscopic resection. Distal pancreatectomy or pancreaticoduodenectomy are appropriate for pancreatic tumours. Small-bowel resection along with resection of the draining lymph nodes is appropriate for carcinoid tumours. Standard colorectal resections are appropriate for colonic tumours. However, small pedunculated tumours are occasionally removed endoscopically.

Surgery in the setting of metastatic or unresectable disease

Small-bowel NETs (carcinoid tumours) present particular problems related to the local effects of hormones produced by the tumour. This often leads to a sclerotic response within the mesentery of the small bowel, producing ischaemic symptoms as well as obstruction. Simple bypass of the obstruction will not resolve the ischaemic symptoms, so resection of the associated lymphadenopathy within the mesentery is required. Even in the setting of unresectable metastatic disease, palliative resection of carcinoid tumours may be warranted for control of the ischaemic and obstructive symptoms.

For patients with carcinoid syndrome secondary to hepatic metastatic disease, surgical cure is still possible if complete resection of hepatic metastatic deposits can be performed. For patients in whom not all of the liver disease is resectable, symptom control is still possible if 90% of the disease can be removed or ablated. In both surgical situations (with curative or palliative intent), resection with or without ablative techniques (eg, microwave or radiofrequency ablation) can be used.



For patients with extensive hepatic replacement by tumour, surgical resection is not possible. Hepatic transplantation has been used in this context but Australian guidelines do not recommend its use.

For locally advanced pancreatic tumours or pancreatic tumours with unresectable metastatic disease, there is little evidence to support the benefit of debulking surgery. If present, jaundice and gastric outlet obstruction can be controlled with endoscopic techniques without the need for open surgery. In contrast to pancreatic adenocarcinomas, the obstructive symptoms are less frequent and worsen more slowly.

Anaesthetic considerations

Preoperative anaesthetic preparation is an important part of surgical management. Historically the mortality following resection of carcinoid tumours has been as high as 50%. This is due to the haemodynamic consequences of hormone release, as well as the presence of carcinoid heart disease. Cardiac echocardiography is required for patients with a raised CgA or symptoms of carcinoid heart disease. Preoperative blockade with long-acting somatostatin analogues (described below) is beneficial and should be co-ordinated with anaesthetic review.

Medical

The aim of medical therapy for patients with advanced NETs is to relieve symptoms related to the tumour (due to hormone secretion or directly related to the primary tumour or its metastasis) and to slow down tumour growth. There is a broad range of medical treatments available, as outlined below.

Somatostatin analogues

Somatostatin analogues (SSAs) are indicated in patients with low- to intermediate-grade NETs whose disease is avid (strongly positive)

on SSSTR imaging and whose disease is progressing on regular radiological review, whether they have functional or non-functional tumours.

SSA therapy is associated with 40-70% biochemical response, that is, a reduction in serum CgA and urinary 5-HIAA. Up to 70%

of patients experience resolution of symptoms related to their carcinoid syndrome, including diarrhoea and flushing. There is some evidence that the response rates may increase with higher doses of the SSAs.

Apart from the inhibitory effects of SSAs on hormone secretion, these agents also have an antiproliferative effect in slowing tumour growth, stabilising them radiologically in about two-thirds of patients, and inducing tumour regression in up to 10% of patients.² The introduction of SSAs may be responsible for the increased survival of patients with NETs observed over the last two decades.

The two currently available SSAs are octreotide (Sandostatin 100-500µg [a short-acting preparation] and Sandostatin LAR 10-30mg [a long-acting repeatable depot preparation]) and lanreotide (Lanreotide Autogel 60, 90, 120mg [a depot preparation]). The short-acting preparation is given by subcutaneous injection, has a half-life of 1.5-2 hours and is used for the treatment of breakthrough secretory symptoms. The depot preparations are given once every four weeks by deep SC or IM injections and are used for long-term control.

These agents do have adverse effects, including:

- Nausea.
- Cramping.
- Diarrhoea.
- Steatorrhoea.
- Cardiac conduction abnormalities.
- Endocrine dysfunction (hypo-

thyroidism, hypo- and hyperglycaemia).

- Cholelithiasis in up to 50% of patients (although cholecystitis develops in fewer than 5%). Patients undergoing surgical resection of NETs should be considered for prophylactic cholecystectomy to facilitate later use of SSAs.

There is still debate on the utility of SSAs in patients with somatostatin-receptor-expressing but non-functional tumours whose disease is radiologically stable over a prolonged period of time. One option is continued observation; the other is to start SSA therapy for its antiproliferative effects. However, patients must be fully aware of their adverse effects and the need for prolonged therapy.

Symptomatic therapy

As stated above, SSAs are generally successful in controlling typical carcinoid syndrome symptoms such as diarrhoea and flushing. In some patients additional control can be achieved with use of over-the-counter antidiarrhoeal agents such as loperamide and or cholestyramine. The latter may be particularly helpful in patients who have undergone an ileal or extensive small-bowel resection to counteract defective bile acid reabsorption.

Histamine oversecretion in gastric and thoracic NETs can induce skin rashes that can be treated with antihistamine type-1 blockade. Bronchospasm can be treated with the usual antiasthmatic preparations.

Management of cardiac failure secondary to carcinoid cardiac disease requires input by a cardiologist and an assessment of the need of valvular surgery.

Direct treatment of islet cell hormone syndromes

Insulinomas can cause episodic and often symptomatic hypoglycaemia. Such patients can be treated with diazoxide (which decreases islet cell function), prednisolone (which



raises blood glucose by mobilising carbohydrate stores) or SSAs. Gastrinomas can be associated with Zollinger–Ellison syndrome, with severe peptic ulceration, and can be controlled with aggressive PPI therapy.

Chemotherapy

In the case of well-differentiated NETs, chemotherapy may be indicated when a patient's disease has progressed despite SSA therapy, although increasingly radionuclide therapy is used in these patients, as discussed below. In general, classic midgut carcinoids tend to be less chemosensitive than pancreatic islet cell tumours. Regimens generally are based upon streptozocin or temozolomide, with response rates in up to 30-70%, depending on the type of regimen, with higher response rates seen in tumours of intermediate grade.

In patients with poorly differentiated NETs (Ki-67 >20%), or disease that is avid on FDG PET (ie, very metabolically active), chemotherapy consisting of carboplatin plus etoposide is generally used, with response rates of 50-60%. However, the duration of response is often short-lived.

Liver-directed therapies

The liver receives its blood supply mainly from the portal vein but also the hepatic artery. Liver metastases, however, receive their blood supply principally from the hepatic artery. Trans-arterial chemoembolisation (TACE) involves injecting slow-release chemotherapy-eluting beads into the hepatic artery via a catheter placed in the groin, with the aim of maximising the dose of chemotherapy to the metastases while minimising systemic side effects.

Another form of liver-directed therapy is intra-arterial administration of SIR-Spheres, which are microspheres impregnated with yttrium-90 (Y-90), a beta-radiation-emitting isotope. These treatments can have significant mor-

bidity and should only be administered in specialist centres after careful consideration of risks vs benefits.

Biological therapies

These include the immunomodulator, alpha interferon, and the tyrosine kinase inhibitor, sunitinib (Sutent), and the m-TOR inhibitor, everolimus (Afinitor). These can be considered for the treatment of patients with low- to intermediate-grade pancreatic NETs who progress after prior therapies. All these agents can be associated with significant toxicity and so require careful monitoring by experienced oncologists. Quality-of-life considerations are important in the decision to use these agents and they are generally only indicated in patients with significant disease progression or uncontrolled symptoms.

Alpha interferon. This is a cytokine that increases the expression of the somatostatin receptors in NET cells and, therefore, has been used in combination with SSAs in patients in whom there is disease progression on SSA monotherapy. The combination is associated with a 40% biochemical and 10% radiological response rate.

Sunitinib (Sutent). This is a tyrosine kinase inhibitor that acts on several pathways involved in the growth and spread of NETs. A recent randomised study has shown that sunitinib provides greater prolongation of tumour control and radiological response compared with placebo.³

Everolimus (Afinitor). This is an oral drug that inhibits m-TOR, a protein that plays a central role in the growth of NET cells. Two recent randomised trials have demonstrated that everolimus combined with octreotide LAR (long-acting repeatable) provides greater prolongation of tumour control and radiological response compared with octreotide LAR alone.⁴

Radionuclide therapy

Radionuclide therapy relies on the specific uptake and retention of a radioactive chemical within cancer cells, then the release of radiation that induces DNA damage in that cell or nearby cells. For almost 60 years radionuclide therapy has been used in the treatment of differentiated thyroid cancer. In this situation the ability of thyroid cells to take up iodine, used in the synthesis of thyroid hormone, is leveraged to concentrate iodine-131 (I-131) within the tumour. The radioactive decay of this radioisotope leads to the emission of beta particles, which deposit all their energy within a millimetre or so, producing damage to DNA. It is particularly the formation of double-strand breaks in DNA that provides the therapeutic effect, since a relatively small number of double-strand breaks leads to cell death. Patients with quite disseminated thyroid cancer can be cured with low toxicity because of the effective targeting of radiation internal to the tumour and the relative lack of uptake in other tissues.

Recognition of the importance of the SSTR to the biology of neuroendocrine tumours and the ability to radiolabel and image SSTRs with indium-111 octreotide (Octreoscan) led to the hypothesis that this disease might be amenable to radionuclide therapy (figure 5). This treatment, called peptide receptor radionuclide therapy (PRRT), was first pioneered in the early 1990s by administering a high dose of Octreoscan. In addition to gamma radiation emission used for imaging, In-111 emits Auger (pronounced oh-zhay) electrons. This produces damage within a very short range of approximately 10 microns (a single-cell diameter). While having a low toxicity profile, the low energy of the Auger electron limits the effectiveness of this therapy, especially in patients with a large disease burden.





The use of beta particle emitters Y-90 and lutetium-177 (Lu-177) in the form of Y-90 and Lu-177 DOTATATE (LuTate) are now preferred and have demonstrated excellent objective response rates (about 70%) with low toxicity. High-energy beta particles from Y-90 can travel up to a centimetre in tissue whereas lower-energy particles from Lu-177 travel 1-2mm. Both result in 'crossfire', whereby each cell irradiates its neighbours, resulting in efficient radiation delivery to aggregations of cancer cells.

These agents are generally administered as a series of 2-5 cycles at 6-12-weekly intervals. Subsequent consolidation or maintenance therapies are feasible in responders (figure 6, page 40). There is accumulating evidence that the effectiveness of these agents is enhanced by combining them with low-dose chemotherapy, which inhibits DNA repair, thereby sensitising cells to radiation damage, without significantly increasing toxicity. Due to its lower toxicity to the kidneys, LuTate is the preferred agent in most patients and has been administered to more than 200 patients in Australia since it was

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introduced at the Peter MacCallum Cancer Centre in 2005.

The objectives of treatment are primarily to alleviate symptoms related to excess hormone secretion or due to direct mass effects of ongoing tumour growth. PRRT is highly effective in achieving these objectives with minor side effects in most patients. Tumour shrinkage tends to be most marked in patients with tumours with more rapid growth before treatment. Unlike most therapies, ongoing reduction in lesion size can occur for many months after completion of radionuclide therapy.

Prognosis

The survival rates for patients with advanced NETs are highly variable, reflecting the wide range of different tumour subtypes. Patients with primary small-bowel carcinoid tumours had a median survival of 12.5 years in one institutional series, with a shorter survival for other carcinoid tumours of 4.6 years. Patients with advanced metastatic disease, particularly those that are poorly differentiated, have a poor prognosis, with survival measured in months rather than years, although there is increasing evidence that this can be improved by care in centres providing multidisciplinary management that is personalised to the disparate biological characteristics of these tumours.

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Online resources

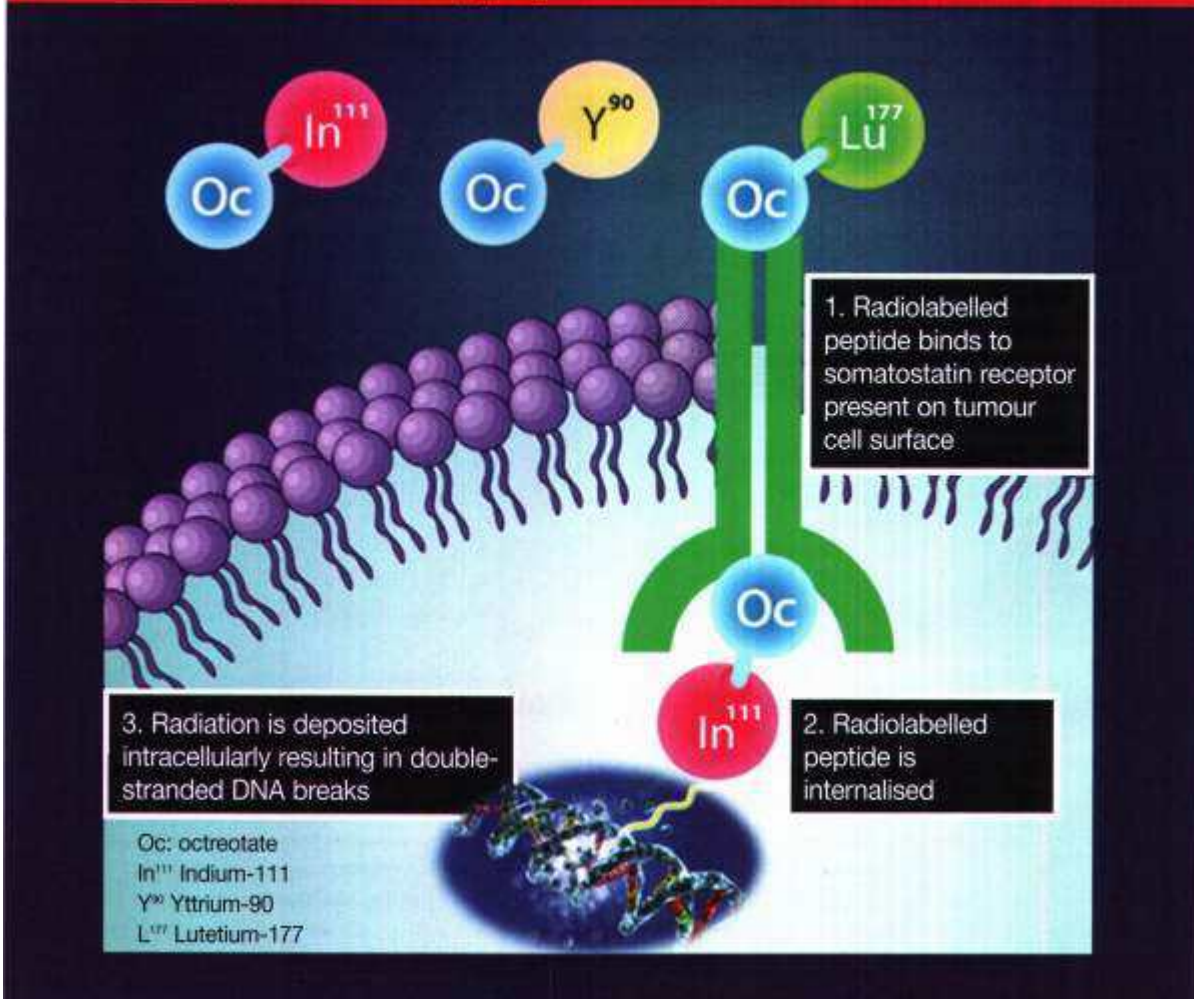
- European Neuroendocrine Tumor Society (ENETS): www.enets.org
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Key points — management and prognosis

- Symptoms and disease biology are the most important determinants of both prognosis and treatment.
- Surgery should be considered as a curative option in patients with limited disease extent and can also provide palliative benefit even when all disease cannot be resected.
- Chemotherapy is generally ineffective in patients with well-differentiated NETs but may provide benefit in poorly differentiated disease.
- New biological therapies show promise for delaying disease progression in some patients.
- Liver-directed therapies are an option in selected patients but because of significant morbidity, these need to be performed in centres with expertise in NET management.
- Peptide receptor radionuclide therapy (PRRT) is a very effective and well-tolerated treatment in selected patients but availability is currently limited.



Figure 5: Peptide receptor radionuclide therapy (PRRT).



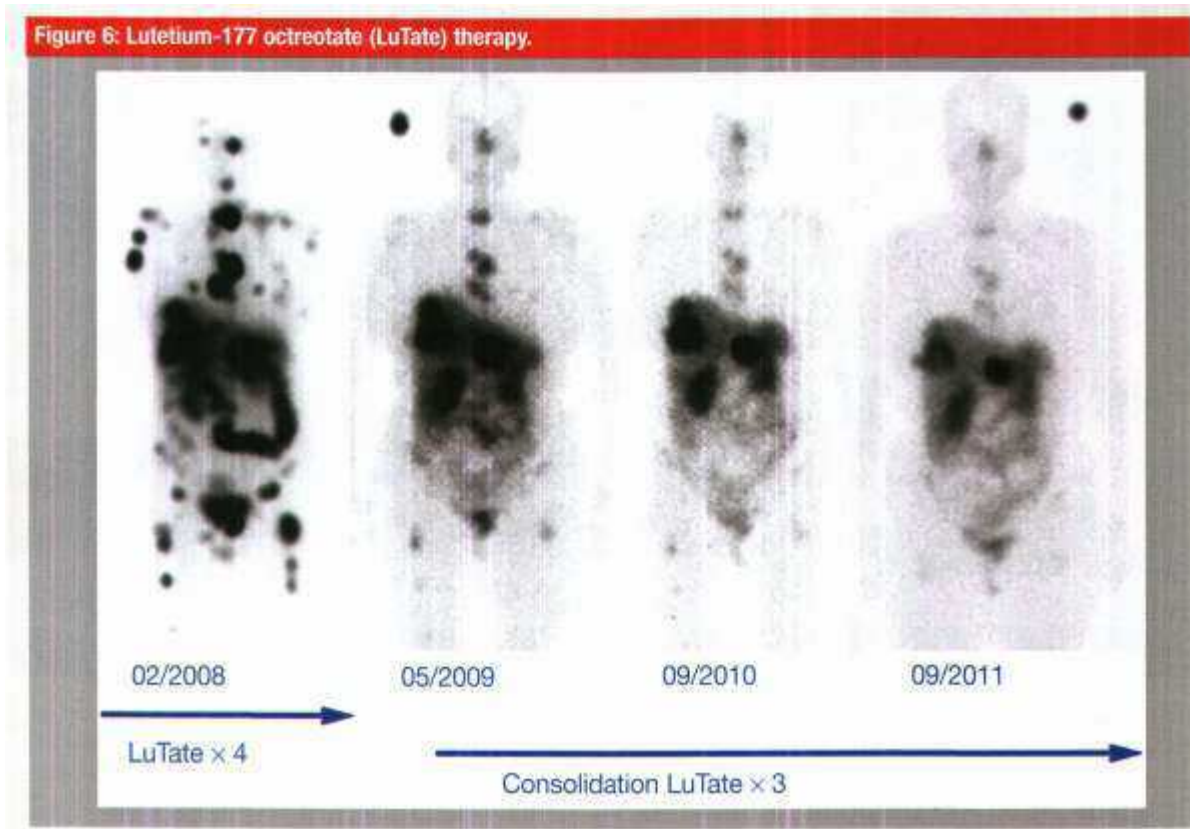
Authors' case study 3

THIS middle-aged woman initially presented with a history of sacral and sciatic pain and was found to have metastatic neuroendocrine tumour involving liver, bone and peritoneum. Her pain progressed despite palliative radiotherapy and she subsequently presented with worsening lower-limb weakness and paraesthesia.

MRI demonstrated multi-level cord compression due to widespread osseous metastases and she underwent further radiotherapy without significant improvement in mobility. She remained confined to a wheelchair with ongoing severe bone pain requiring high-dose opiate analgesia.

The patient underwent four induction cycles of lutetium-177 octreotate (LuTate) therapy with rapid improvement of bone pain. Quality of life improved and she regained normal mobility. She remains well and asymptomatic three years later, with several maintenance LuTate treatments over this time resulting in further imaging response and reduction of disease burden.





How to Treat Quiz

Neuroendocrine tumours
— 16 March 2012

INSTRUCTIONS

Complete this quiz online and fill in the GP evaluation form to earn 2 CPD or PDP points. We no longer accept quizzes by post or fax.

The mark required to obtain points is 80%. Please note that some questions have more than one correct answer.

ONLINE ONLY

www.australiandoctor.com.au/cpd/ for immediate feedback




1. Which TWO statements are correct?

- a) Neuroendocrine tumours (NETs) can occur at any gastrointestinal site from the stomach to the rectum
- b) Pancreatic NETs arise from the exocrine cells of the pancreas
- c) The term 'carcinoid' describes GI NETs that have rapid growth
- d) Well-differentiated NETs tend to have slow growth with an indolent natural history

2. Which TWO statements are correct?

- a) Well-differentiated NETs always secrete high and inappropriate levels of hormones
- b) Serotonin is the hormone most commonly produced by carcinoid tumours
- c) Well-differentiated NETs rarely express somatostatin receptors (SSTR) on their cell surface
- d) Poorly differentiated NETs behave aggressively, with rapid cell proliferation and clinical course

3. Which TWO statements are correct?

- a) Locally advanced or metastatic well-differentiated NETs are usually associated with significant symptoms
- b) NETs that secrete serotonin are usually symptomatic well before there is metastatic spread
- c) Characteristic symptoms of carcinoid syndrome include facial flushing, diarrhoea, abdominal cramps and wheezing
- d) Chronic exposure to serotonin causes fibrosis and thickening of the tricuspid and pulmonary valves

4. Which THREE statements are correct?

- a) Local secretion of serotonin can cause fibrosis leading to bowel obstruction, bowel ischaemia and malabsorption
- b) Pancreatic NETs can cause diarrhoea as a result of pancreatic enzyme deficiency
- c) Cushing's syndrome, hypercalcaemia and hypoglycaemia can all be associated with

functioning pancreatic NETs

- d) Widespread metastatic NETs are usually aggressive and fast growing

5. Which TWO statements are correct?

- a) Chromogranin-A (Cg-A) is a useful blood test for suspected NETs
- b) Cg-A is only elevated in hormone-secreting NETs
- c) Patients taking proton-pump inhibitors may have mild or moderate elevation in Cg-A levels
- d) Urinary 5-hydroxyindole acetic acid (5-HIAA) measurement is more sensitive for NETs than Cg-A


6. Which TWO statements are correct?

- a) CT is highly sensitive for detecting the primary NETs mass and the presence of metastases
- b) Radiolabelled somatostatin analogues are useful for imaging most NETs
- c) Single photon emission computerised tomography (SPECT) using Octreoscan provides 3-D cross-sectional imaging of NETs
- d) SPECT alone provides highly accurate anatomical localisation of the NET deposits

7. Which TWO statements are correct?

- a) High uptake of Octreoscan indicates that the NET is likely to have a rapid and aggressive natural history
- b) Poorly differentiated NETs are metabolically very active and are identified well by fluorodeoxyglucose-PET scanning
- c) The presence of metastatic disease means that curative or palliative surgery is not appropriate
- d) Surgery for NETs can be combined with ablating techniques such as those using microwave or radio-frequency radiation

8. Which TWO statements are correct?

- a) Preoperative use of long-acting somatostatin analogues (SSAs) decreases the risks of NETs surgery by reducing the secretory function of the tumour
 - b) SSAs are only used in patients with functioning
- 



(ie, secretory) NETs

- c) SSA therapy reduces the symptoms of carcinoid syndrome
- d) SSAs are for symptomatic treatment only and do not slow tumour growth

9. Which THREE statements are correct?

- a) SSAs may cause GI side effects, cardiac conduction abnormalities, and cholelithiasis
- b) Loperamide or cholestyramine can be used in combination with SSAs for control of diarrhoea
- c) Hypoglycaemia associated with insulinoma can be treated with diazoxide, prednisolone or SSAs
- d) Chemotherapy is usually effective in patients

with slowly growing well-differentiated NETs

10. Which THREE statements are correct?

- a) Treatment can be targeted against liver metastases by injecting chemotherapy-eluting beads into the hepatic artery
- b) Radionuclide therapy uses the specific uptake of a radioactive chemical into cancer cells, the radiation emitted then damaging DNA in those cells or in nearby cells
- c) In NETs, radionuclide therapy uses radioactive somatostatin analogues
- d) With radionuclide therapy, any reduction in lesion size is only maintained for the duration of therapy

CPD QUIZ UPDATE

The RACGP requires that a brief GP evaluation form be completed with every quiz to obtain category 2 CPD or PDP points for the 2011-13 triennium. You can complete this online along with the quiz at www.australiandoctor.com.au. Because this is a requirement, we are no longer able to accept the quiz by post or fax. However, we have included the quiz questions here for those who like to prepare the answers before completing the quiz online.

NEXT WEEK The next How to Treat looks at knee disorders in adults, ranging from traumatic and sporting injuries mostly in younger adults, to degenerative conditions in older patients. The author is **Associate Professor Peter Papantoniou**, orthopaedic and lumbar spine surgeon, St George Private Hospital, Kogarah; St Luke's Private Hospital, Elizabeth Bay; Dalcross Adventist Hospital, Killara; and associate professor, Sydney Adventist Hospital Clinical School, University of Sydney.

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Education

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