REVIEW

Neuroendocrine tumours

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Abstract

Neuroendocrine tumours are a heterogeneous group including, for example, carcinoid, gastroenteropancreatic neuroendocrine tumours, pituitary tumours, medullary carcinoma of the thyroid and phaeochromocytomas. They have attracted much attention in recent years, both because they are relatively easy to palliate and because they have indicated the chronic effect of the particular hormone elevated. As neuroendocrine phenotypes became better understood, the definition of neuroendocrine cells changed and is now accepted as referring to cells with neurotransmitter, neuromodulator or neuropeptide hormone production, dense-core secretory granules, and the absence of axons and synapses. Neuroendocrine markers, particularly chromogranin A, are invaluable diagnostically. Study of several neuroendocrine tumours has revealed a genetic etiology, and techniques such as genetic screening have allowed risk stratification and prevention of morbidity in patients carrying the particular mutation. Pharmacological therapy for these often slow-growing tumours, e.g. with somatostatin analogues, has dramatically improved symptom control, and radiolabelled somatostatin analogues offer targeted therapy for metastatic or inoperable disease. In this review, the diagnosis and management of patients with carcinoid, gut neuroendocrine tumours, multiple endocrine neoplasia types 1 and 2, and isolated phaeochromocytoma are evaluated.

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Introduction and definition

The definition of a neuroendocrine cell has changed over the last few years as our understanding and experimental techniques have advanced. In 1969, Pearse proposed the APUD (amine precursor uptake and decarboxylation) classification to describe cells producing polypeptide hormones and biogenic amines identical to those found in neurons (Pearse 1968, 1969). These cells would make up the tightly coordinated diffuse neuroendocrine system, present either in endocrine organs or dispersed throughout the body (Polak & Bloom 1979). The gastroenteropancreatic system alone provides the richest source of regulatory peptides outside the brain (Polak & Bloom 1986a). Indicating a unified origin to these cells, it was originally thought that they all derived from neuroectoderm, but increasingly this was found not to be the case for all neuroendocrine cells (Le Douarin 1988). The following criteria are now generally accepted as defining neuroendocrine cells (Langley 1994): the production of a neurotransmitter, neuromodulator or neuropeptide hormone; the presence of dense-core secretory granules from which the hormones are released by exocytosis in response

to an external stimulus; and the absence of axons and synapses. In practical terms, molecular markers are invaluable in defining neuroendocrine cells, and in particular chromogranin A (Winkler & Fischer-Colbrie 1992, Taupenot *et al.* 2003). More recently, the subtilase proprotein convertases (SPC), particularly SPC2 and SPC3, have been added to the list of useful markers (Bergeron *et al.* 2000). With the discovery of neuroendocrine phenotypes developing in cells such as immunocytes and certain neoplastic cells such as small cell carcinomas, it has recently been proposed that activation of specific genetic switches leading to neuroendocrine phenotypes should also be included in the definition (Day & Salzet 2002).

Neuroendocrine tumours are therefore a very heterogeneous group arising from these neuroendocrine cells, and include carcinoid, non-carcinoid gastroenteropancreatic tumours (such as insulinoma, gastrinoma and VIPoma (VIP, vasoactive intestinal polypeptide)), catecholamine-secreting tumours (phaeochromocytomas, paragangliomas, ganglioneuromas, ganglioneuroblastomas, sympathoblastoma, neuroblastoma), medullary carcinoma of the thyroid, chromophobe pituitary tumours,

small cell lung cancer and Merkel cell tumours. The World Health Organization's definition of neuroendocrine tumours is 'morphofunctional' and is primarily based on microscopic characteristics, but incorporates immunohistological data (with such markers as the chromogranins, synaptophysin and non-specific enolase), special stains (e.g. silver), in addition to immunohistochemical stains for specific hormones which result in endocrine hyperfunction syndromes (Solcia *et al.* 2000). For the purposes of this review, the following topics are covered in the vast field of neuroendocrine tumours: etiology, general markers and the specific syndromes related to a limited subset of neuroendocrine tumours, namely carcinoid and other gastroenteropancreatic neuroendocrine tumours, multiple endocrine neoplasia types 1 and 2, and phaeochromocytoma.

Etiology

The genetic predisposition to certain neuroendocrine tumours has generated much interest, particularly with advanced techniques facilitating the identification of mutated genes. Similarly, with analysis of gene expression microarray profiles and multivariate analysis of complex traits (Phillips & Belknap 2002), important information can be used to prognosticate and risk stratify patients. A plethora of genes are known to be involved in neuroendocrine tumorigenesis, including *MEN1*, *RET*, *VHL*, *TSC1* and *TSC2* (Calender 2000), with mutations in *MEN1* remaining the most common form of genetic predisposition to neuroendocrine tumours. Despite the lack of direct evidence, it is likely that neuroendocrine tumorigenesis is similar to that of the well-studied colorectal carcinoma model of a series of multiple genetic alterations leading to activation of oncogenes and/or inactivation of tumour suppressor genes and failure of apoptosis (Fearon & Vogelstein 1990, Shannon & Iacopetta 2001). Intriguingly, the exact sequence of events is crucial for determining the phenotype, as demonstrated by the effect of early loss of *Lkb1* in protection against transformation in Peutz-Jeghers syndrome (Bardeesy *et al.* 2002).

In multiple endocrine neoplasia type 1 (MEN1), germline inactivating mutations in the tumour suppressor *MEN1* gene (chromosome 11q13; Larsson *et al.* 1988) are found in 95% of patients. Somatic mutations of *MEN1* are also found in sporadic cases: 21% of parathyroid adenomas, 33% of gastrinomas, 17% of insulinoma, 36% of bronchial carcinoid, and 50–70% of sporadic thymic and duodenal carcinoid (Jakobovitz *et al.* 1996, Lubensky *et al.* 1996, Emmert-Buck *et al.* 1997, Marx *et al.* 1998, 1999). The absence of detectable mutations in *MEN1* may reflect deficiencies of current technology, or that the inactivation process is via non-mutation mechanisms such

as methylation in the CpG-rich 5′-region of *MEN1*. Indeed, such hypermethylation is found in the *VHL* promoter in von Hippel Lindau (Herman *et al.* 1994, Prowse *et al.* 1997).

In keeping with Knudson's model (Knudson 1971, Pannett & Thakker 2001), a two-hit process is required for *MEN1* tumorigenesis (Larsson *et al.* 1988, Thakker *et al.* 1989, Bystrom *et al.* 1990). Familial and somatic *MEN1* mutations differ in terms of the former usually presenting with tumour expression at an earlier age, multiple organs affected, and multiple tumours in one organ (Marx *et al.* 1999). Although many mutations have been found in *MEN1*, there seems to be poor genotype–phenotype correlation (Kouvaraki *et al.* 2002). The majority of patients with familial MEN1 will develop non-functioning pancreatic tumours, while 40% will develop gastrinoma, 10% insulinoma and 2% other functioning pancreatic tumours, such as glucagonoma, VIPoma and somatostatinoma (Marx *et al.* 1999).

Based on Fearon and Vogelstein's (1990) genetic model for colorectal tumorigenesis, Fig. 1 illustrates the possible pathways from induction to metastases for neuroendocrine tumours (Calender 2000), including MEN1, MEN2 and phaeochromocytoma.

General markers for neuroendocrine tumours

The group of neuroendocrine tumours can be characterized both by general and specific markers, the most strikingly consistent general markers being the chromogranins. Other general staining markers include pancreatic polypeptide, neuron-specific enolase (NSE), peptide histidine-methionine and human chorionic gonadotrophin subunits (Tapia *et al.* 1981, Hamid *et al.* 1986, Yiangou *et al.* 1987). Chromogranin A (CgA), a secretory granule, is located alongside specific hormones in large dense-core vesicles of neuronal and neuroendocrine cells. Chromogranin B (CgB) is also widely distributed in neuroendocrine cells, although CgA seems to be more widespread (Winkler & Fischer-Colbrie 1992). Staining for the chromogranins in different neuroendocrine tumours is summarized in Table 1 (adapted from Taupenot *et al.* 2003), where CgA seems ubiquitous with the exception of the CgB-staining pituitary lactotrophs and some pancreatic beta-cell tumours.

In one study, plasma CgA was elevated in 94% of endocrine pancreatic tumours, and pancreatic polypeptide in 74% (Eriksson *et al.* 1990). Elevated CgA levels were even more frequent (99%) in malignant carcinoid and gastroenteropancreatic tumours (99%) (Stridsberg *et al.* 1995), with the highest levels seen in metastatic carcinoid (particularly midgut). Plasma CgB (and its 74-amino-acid
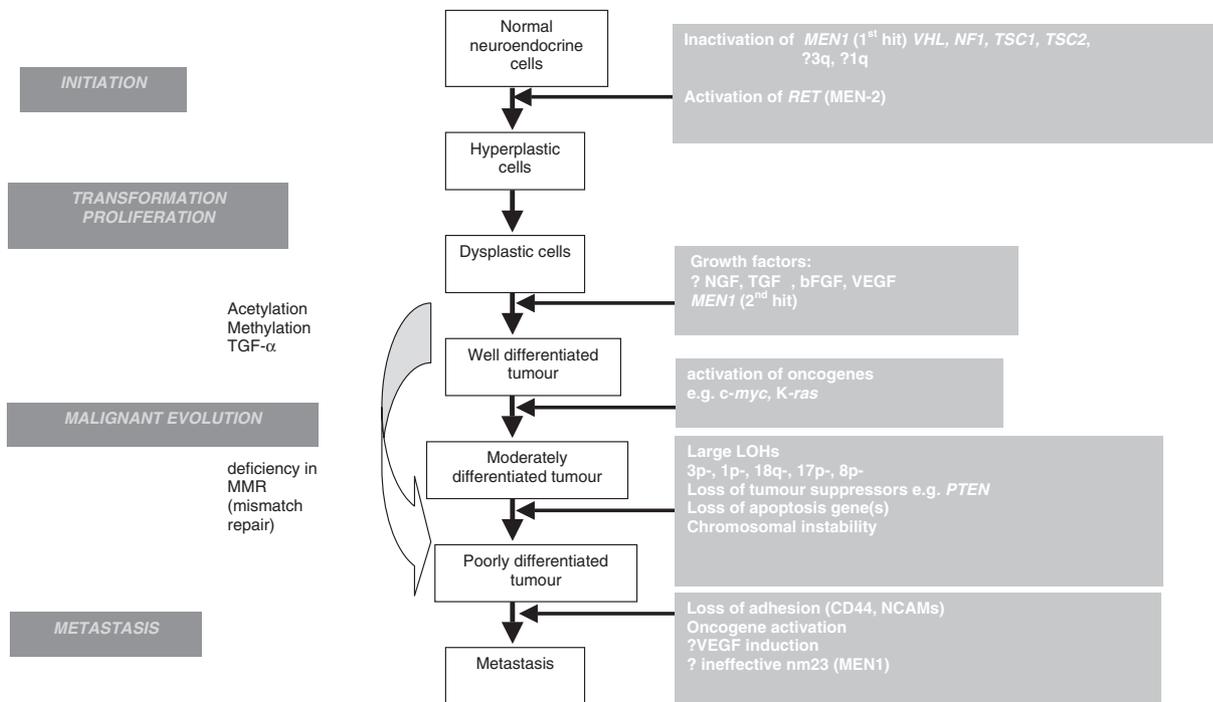
Figure 1 Process of tumorigenesis from initiation to metastatic cancer in neuroendocrine tumours. Based on Calender (2000) and Fearon and Vogelstein (1990). Genes: *MEN1*, multiple endocrine neoplasia type 1; *VHL*, von Hippel Lindau; *NF1*, neurofibromatosis type 1; *TSC1* and *TSC2*, tuberous sclerosis genes 1 and 2; *PTEN*, tumour suppressor gene *PTEN* ('phosphatase and tensin homolog, deleted on chromosome 10'). NGF, nerve growth factor; TGF, transforming growth factor; bFGF, basic fibroblast growth factor; VEGF, vasculoendothelial growth factor; NCAM, neural cell adhesion molecule; nm23, tumour metastasis suppressor nm23 (in *MEN1*); LOH, loss of heterozygosity.

fragment termed GAWK) is usually a better marker for benign insulin-producing tumours (Sekiya *et al*. 1989, Yasuda *et al*. 1993). Finally, multiple hormones may be secreted by some tumours (Wood *et al*. 1983), and up to 62% have elevated gastrin despite only 30% presenting with peptic ulcer disease.

Specific syndromes

Carcinoid and other gut neuroendocrine tumours

Over the last few years, a new classification of neuroendocrine gastroenteropancreatic tumours (GEPs) has been developed based on clinicopathologic features (Capella *et al*. 1994, Kloppel & Heitz 1994, Rindi *et al*. 1998). Tumours are termed functioning neuroendocrine tumours according to their leading clinical and endocrine profile, while those without plasma hormone elevation and lacking endocrine symptoms are labelled non-functioning neuroendocrine tumours (Taheri & Meeran 2002). In excess of 50% of neuroendocrine tumours are of the 'carcinoid' type, with the remainder being mostly pancreatic and including insulinomas, gastrinomas, VIPomas and glucagonomas.

Although these two categories differ in specific histology and location, there are many diagnostic and therapeutic similarities between them, and these will be covered in the sections below. In general, neuroendocrine tumours are slow-growing. The classification into benign and malignant depends on various features summarized in Table 2 (Rindi *et al*. 1998).

Carcinoid

Mostly derived from serotonin-producing enterochromaffin (EC, or Kulchitsky's) cells, these tumours termed 'carcinoid' have a wide clinical spectrum of presentation and symptomatology (McStay & Caplin 2002). Indeed, it is felt by some that the term should be made archaic because of this wide spectrum (Gilligan *et al*. 1995). Fewer than 10% of patients with carcinoid suffer from the classical carcinoid syndrome of flushing, hypotension, diarrhoea, wheezing and heart disease. These symptoms seem to be related directly to serotonin levels (elevated in 93–94% of 600 patients with carcinoid syndrome), although serotonin can still be elevated in asymptomatic individuals (elevated in 25–30% of 7000 asymptomatic patients) (Vinik 2001). High serotonin levels seem to predict the development of carcinoid heart disease (Moller

Table 1 Detection of granins in neuroendocrine tumours. Adapted from Taupenot *et al.* (2003).

	Chromogranin A	Chromogranin B	Secretogranin III
Carcinoid	+	+	+
Gastrinoma	+	+	ND
Glucagonoma	+	+	+
Insulinoma	+	+	+
PPoma	+	ND	ND
Somatostatinoma	+	ND	ND
VIPoma	+	ND	ND
Non-functioning islet cell carcinoma	+	ND	ND
Corticotrophinoma	+	+	+
Gonadotrophinoma	+	+	+
Somatotrophinoma	+	+	+
Thyrotrophinoma	+	+	+
Prolactinoma	−	+	+
Non-functioning pituitary adenoma	+	+	+
Phaeochromocytoma	+	+	+
Parathyroid adenoma	+	+	+
Ganglioneuroblastoma	+	ND	ND
Ganglioneuroma	+	ND	+
Neuroblastoma	+	+	+
Medulloblastoma	+	ND	ND
Paraganglioma	+	+	+
Medullary thyroid carcinoma	+	+	+
Prostate tumour with neuroendocrine differentiation	+	+	+
Breast tumour with neuroendocrine differentiation	+	+	+

ND, not detected.

et al. 2003). Other carcinoid tumours deriving from the gastric histamine-secreting enterochromaffin-like (ECL) cells produce an 'atypical' carcinoid syndrome. These tumours, which have low serotonin levels, frequently secrete the serotonin precursor 5-hydroxytryptophan (5-HTP). This produces the 'atypical' symptoms seen in foregut carcinoids with more intense and protracted purplish flushing; the limbs as well as the upper trunk are often affected and frequently result in telangiectasia (Snow *et al.* 1955, Sandler & Snow 1958, Vinik 2001).

From the most recent and largest US epidemiology series (using the 1992–1999 cohort), the age-adjusted incidence of carcinoid tumours varies between 2.47 and 4.48 per 100 000 population, with the rates being highest

in black males, then black females, then white Americans (Modlin *et al.* 2003). In this series, the population-corrected male-to-female ratio for all carcinoid sites was 0.86, and the average age at diagnosis for all carcinoids was 61.4 years (compared with 63.9 years for non-carcinoid tumours). Table 3 summarizes the frequency of carcinoid at different sites (most occurring in the gut at 67.5%, then the lung at 25.3%), with the associated 5-year survivals. Predisposition to metastatic spread depends on location and size (Lauffer *et al.* 1999, Modlin *et al.* 2003).

In addition to the general markers mentioned above, the specific markers for carcinoid include urinary 5HIAA, neuropeptide K, substance P and other tachykinins. Urinary 5-hydroxyindole acetic acid (5HIAA) and neuropeptide K show high sensitivity in midgut carcinoid, with less diagnostic usefulness in foregut and hindgut carcinoid (Janson *et al.* 1997). If a diagnosis of carcinoid is suspected with normal baseline urinary testing, the pentagastrin test with measurements of plasma tachykinins is helpful (Norheim *et al.* 1986).

Table 2 The proposed classification into benign, uncertain and malignant gastroenteropancreatic tumours (Rindi *et al.* 1998).

Tumour characteristic	Benign	Uncertain	Malignant
Size of tumour (cm)	≤2	> 2	> 2
Local spread	No	Yes	Yes
Vascular invasion	No	Yes	Yes
Nuclear atypia	No	Yes	Yes
Gross invasion	No	No	Yes
Metastases	No	No	Yes

Non-carcinoid gastroenteropancreatic neuroendocrine tumours

Most of the non-carcinoid gastroenteropancreatic neuro-endocrine tumours arise in the pancreas. Making up less

Table 3 Carcinoid tumours – relation between site, metastatic potential and 5-year survival. Data from the 1992–1999 cohort (Modlin *et al.* 2003).

Site	% of all carcinoids	Regional metastases (%)	Distant metastases (%)	5-year survival with no metastases (%)	5-year survival with regional metastases (%)	5-year survival with distant metastases (%)
Lung	25.3	5.2	0.5	81.1	76.7	25.6
Small intestine	28.2	35.9	22.4	59.9	72.8	50
Appendix	2.4	28.9	9.9	80.8	88.1	9.6
Colon	7.6	25.8	29.5	76	71.6	30
Rectum	18.5	2.2	1.7	90.8	48.9	32.3
Stomach	5.9	3.1	6.5	69.1	N/A	21.2
Ovary	1.4	5.2	0.5	90.9	N/A	28.3

N/A, not available.

than half of all neuroendocrine tumours and only 1–2% of all pancreatic tumours, pancreatic neuroendocrine tumours (PET) form an important group with a better prognosis than non-neuroendocrine tumours. Deriving from the diffuse neuroendocrine system of the gut (Polak & Bloom 1986a), PETs were formerly classified as APUDomas (tumours of the amine precursor uptake and decarboxylation system), and can secrete a vast number of hormones depending on the cell of origin. Physiologically, these hormones are involved in an intricate network of autocrine, paracrine, endocrine and neurotransmitter communication.

Although the annual incidence of PETs is approximately 3.5 to 4 per million population, post-mortem data suggests a much higher incidence. Indeed they have been detected in 0.3% to 1.6% of unselected autopsies in which only a few sections of pancreas were examined, and in up to 10% of autopsies in which the whole pancreas was systematically inspected (Kimura *et al.* 1991).

Depending on whether secreted hormone is detectable and associated symptoms are present, gastroenteropancreatic neuroendocrine tumours (GEPs) can be divided into 'functioning' and 'non-functioning' tumours. The 'functioning' tumours may secrete several peptides, only some of which may produce symptoms. Similarly, a tumour which originally secreted one peptide may dedifferentiate to co-secrete other peptides. Typically, these tumours are slow-growing, and often morbidity is from the secreted hormone (or hormones) rather than tumour bulk. The presence of a specific endocrine hyperfunction syndrome seems to be as important as purely pathological features for predicting tumour behaviour (Kloppel & Heitz 1988, Solcia *et al.* 1990) (see Table 4 taken from data from Aldridge & Williamson 1993, Arnold *et al.* 2000, Schindl *et al.* 2000, Jensen 2001, Taheri *et al.* 2001). In the case of 'non-functioning tumours', it is accepted that there may be secreted, but as yet undetectable, peptides. These non-functioning tumours tend to be more

aggressive and often present after metastasizing with symptoms of tumour bulk (Legaspi & Brennan 1988).

The following are specific markers for functioning non-carcinoid GEPs: fasting hormones such as gastrin, glucagon, pancreatic polypeptide, somatostatin, neurotensin, and vasoactive intestinal polypeptide (VIP), and random parathyroid hormone-related peptide levels (PTHrP) (with simultaneous calcium and parathyroid hormone (PTH) measurements). In the case of gastrin, the patient has to be off proton pump inhibitors for at least two weeks and off H2-blockers for at least three days. Caution, however, is required if the clinical likelihood of gastrinoma is high, since there is a high risk of peptic ulcer perforation when medical therapy is stopped for the gastrin test. Even on proton pump inhibitors, very high gastrin levels (> 500 pg/ml or > 250 pmol/l) are indicative of gastrinoma, and repeat testing off therapy should not be recommended (Ashrafian *et al.* 2002). Differential diagnoses, which include atrophic gastritis, hypercalcaemia and renal impairment, may be excluded by measuring basal acid output: spontaneous basal acid outputs of 20 to 25 mmol/h are almost diagnostic and > 10 mmol/h suggestive. If the test results are equivocal, the secretin test is helpful: a rise of gastrin (instead of the normal fall) in response to intravenous secretin of greater than 200 pg/ml (100 pmol/l) has a sensitivity of 80–85% for gastrinoma (McGuigan & Wolfe 1980, Frucht *et al.* 1989).

The dynamic test for the diagnosis of an insulinoma is a three-day fast, allowing unlimited non-caloric fluids (Service 1995, Service & Natt 2000). Elevated plasma insulin and C-peptide levels are diagnostic in the presence of hypoglycaemia (glucose below 2.2 mmol/l (40 mg/dl)), and this is achieved by 48 h of the fast in > 95% of insulinomas (Friesen 1987). If no hypoglycaemia is achieved by the end of the fast, the sensitivity can be further increased by exercising the patient for 15 min. The fast is terminated after the exercise period, or prior to this if hypoglycaemia is achieved, with simultaneous plasma

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Table 4 Tumour syndromes of gastrointestinal neuroendocrine tumours (NET). Adapted from Aldridge & Williamson (1993), Arnold *et al.* (2000), Jensen (2001), Schindl *et al.* (2000) and Taheri *et al.* (2001). The percentage with MEN1 of each tumour is independent of family history.

Tumour	Frequency of pancreatic neuroendocrine tumours (%)	Tumour location	% with MEN1	Malignancy (%)	Clinical syndrome
Insulinoma	70–75	Pancreas > 99%	4–5	<10	Hypoglycaemia Weight gain
Gastrinoma	20–25	Duodenum 70% Pancreas 25%	20–25	> 50	Abdominal pain Diarrhoea Peptic ulceration
VIPoma	3–5	Pancreas 90%	6	> 50	Secretory diarrhoea Hypokalaemia Achlorhydria Metabolic acidosis Flushing
Glucagonoma	1–2	Pancreas 100%	1–20	> 70	Necrolytic migratory erythema Diabetes Cachexia Thromboembolic disease
PPoma	<1	Pancreas 100%	18–44	> 60	Pain Weight loss Diarrhoea
Somatostatinoma	<1	Pancreas 55% Duodenum + jejunum 44%	45	> 50	Steatorrhoea Diabetes Gallstones Weight loss
Carcinoid	<1 mostly extrapancreatic	Midgut 75–87% Foregut 2–33% Hindgut 1–8% Unknown 2–15%	Rare	90	Classical carcinoid Flushing Diarrhoea Wheeze Cardiac fibrosis Pellagra dermatosis
Corticotrophinoma CRFoma	<1	Pancreas 4–14% (of all ectopic ACTH)	Rare	> 99	Cushing's syndrome Pigmentation
PTHrPoma	<1	Pancreas	Rare	> 99	Hypercalcaemia Nephrolithiasis Nephrocalcinosis Osteoporosis
Calcitoninoma		Pancreas	16	> 80	Diarrhoea, flushing
Somatotrophinoma	<1	Pancreas 30% Lung 54% Jejunum 7%	16	50	Acromegaly
"Non-functioning"	<1	Pancreas + gastrointestinal tract	18–44	> 80	Symtoms of tumour bulk Weight loss

PPoma, pancreatic polypeptide secreting tumour; CRF, corticotrophin releasing factor.

Table 5 Imaging modalities for gastroenteropancreatic neuroendocrine tumours.

Somatostatin- receptor- scintigraphy	Sensitivity 90% (excluding insulinoma) Specificity 80% (excluding insulinoma) Sensitivity 10–50% for insulinoma
CT	Useful preoperatively for localizing tumours, but difficulty detecting tumours <1 cm Sensitivity of 29% in one study for detecting pancreatic insulinoma compared with endoscopic ultrasound
Endoscopic ultrasound of pancreatic neuroendocrine tumours	Sensitivity 80–90% Most sensitive for detecting insulinomas (94%) Smallest lesion detectable 5 mm in pancreatic head Lower sensitivities for extrapancreatic tumours (50%)
Visceral angiography	Helpful for subcentimetre tumours, where a tumour blush is seen Futhermore, can be combined with calcium stimulation in individual pancreatic arteries with venous sampling from the hepatic vein (see text for details)
MRI	In general no more helpful than CT
Positron emission tomography with 11C-serotonin precursor 5-HTP instead of 18F-deoxyglucose	Selective uptake in carcinoid with high resolution allowing liver and lymph node lesion detection
Intraoperative ultrasound for pancreatic tumours	Additional invaluable information for the surgeon operating on the delicate pancreas
Intraoperative gamma probes with somatostatin analogue (111InDTPA-D-Phe1)-pentetreotide tracer	Recently introduced, allows detection of lesions <5 mm and identified 57% more lesions than the "palpating finger"
MIBG for gastroenteropancreatic neuroendocrine tumours	Very few gastroenteropancreatic tumours take up MIBG, since they derive from endoderm and not neuroectoderm

and urine samples for sulphonylurea analysis, which must be shown to be negative for the diagnosis of insulinoma (Todd & Bloom 2002). Finally, the reader needs to be aware of the various insulin assays: the competitive and increasingly used two-site noncompetitive immunoassays. The main problems relate to the variable specificity, with some detecting proinsulin, the interference from insulin-degrading enzymes in haemolysed samples and the presence of anti-insulin antibodies (Sapin 2003)

Radiological localization of carcinoid and other gut neuroendocrine tumours

The Delphi consensus has recently been published for standardizing the diagnostic imaging of neuroendocrine tumours (Ricke *et al.* 2001). Somatostatin receptor scintigraphy (SRS) forms the mainstay of imaging techniques, with a sensitivity of up to 90% and specificity of 80% (Krenning *et al.* 1993, Lebtahi *et al.* 1997, Termanini *et al.* 1997, Kwekkeboom & Krenning 2002), although only 10 to 50% of insulinomas are SRS-positive (Modlin & Tang 1997, Warner & O'dorisio 2002). Table 5 summarizes the different modalities and their usefulness, including computed tomography (CT), endoscopic ultra-sonography (EUS) (Lightdale *et al.* 1991, Glover *et al.* 1992, Palazzo *et al.* 1992, Rosch *et al.* 1992, de Kerviler *et al.* 1994, Thompson *et al.* 1994, Ruszniewski *et al.* 1995, Zimmer *et al.* 2000), positron emission tomography

(Eriksson *et al.* 2000, 2002, Warner & O'dorisio 2002), intraoperative ultrasound and intraoperative gamma probes with the tracer (111)In DTPA-D-Phe1-pentetreotide (Adams & Baum 2000). Given that GEPs derive from endoderm and not catecholamine-producing neuroectoderm, there is little place for ^{131}I-metaiodobenzyl-guanidine (MIBG) in GEP imaging (European Neuroendocrine Tumour Network (ENET) 2000).

With pancreatic tumours, the surgeon requires as much information regarding location as possible. Selective angiography with secretagogue injection into the main pancreatic arteries allows biochemical in addition to angiographic localization. In this procedure, the main pancreatic arteries (gastroduodenal, superior mesenteric, inferior pancreaticoduodenal and splenic) are cannulated separately and examined for a tumour blush. A secretagogue (calcium has taken the place of secretin; Turner *et al.* 2002) is injected into each of these arteries individually, and venous samples are collected from the hepatic vein for biochemical analysis of the suspected hypersecreted hormone (e.g. gastrin or insulin). In the presence of a tumour, the hormone levels double after 30 s, whereas the normal effect is a reduction in levels (Doppman *et al.* 1990, 1991, Fedorak *et al.* 1993, Goldstone *et al.* 1996, O'Shea *et al.* 1996). The tremendous advantage of this technique is that it allows biochemical localization of the tumour (e.g. a very small insulinoma) even if the radiology appears

Table 6 The specific medical treatments for some neuroendocrine tumour syndromes.

Hypersecretion syndrome	Medical therapy
Carcinoid	Somatostatin analogue for SRS positive carcinoid Interferon-α for SRS negative carcinoid Histamine antagonists (H1 and H2) Cyproheptadine, nicotinamide
Insulinoma	Frequent slow-release complex carbohydrate intake Guar gum Diazoxide Intravenous dextrose if period of fasting Somatostatin analogue if SRS positive (usually malignant)
Gastrinoma	High dose proton pump inhibitor (life-long in patients with MEN1, since high recurrence rate with surgery)
Glucagonoma	High dose somatostatin analogue Anticoagulation since associated with thrombophilia Insulin for diabetes mellitus
VIPoma	High dose somatostatin analogue Aggressive intravenous rehydration in acute attack of diarrhoea Potassium + bicarbonate in acute attacks
Somatostatinoma	Pancreatic enzyme supplementation Insulin for diabetes mellitus
PTHrPoma	High dose somatostatin analogue Intravenous rehydration Bisphosphonates for often life-threatening hypercalcaemia Somatostatin analogue
Non-functioning	Somatostatin analogue if SRS scan positive and progressive disease

normal. Furthermore, with MEN1, different tumours may co-exist, and this technique will help to distinguish them biochemically. Finally, and perhaps the procedure's greatest advantage is that it allows the detection of liver metastases, since the hepatic artery is always cannulated at the end of the procedure and a rise in hormone levels detectable in the hepatic vein after calcium injection into the hepatic artery is diagnostic of liver metastases.

Medical treatment

Until curative surgical treatment is performed, or if surgery is not indicated, medical treatment has to be initiated for symptom control. Table 6 summarizes the medical treatments for the various hypersecretion syndromes. The greatest impact for control of symptoms has been afforded by the somatostatin analogues in SRS-scan positive tumours, and it is known that somatostatin immunoreactivity is often found in neuroendocrine tumours (Polak & Bloom 1986*b*). There are five somatostatin receptors (sstr1–5), but the longer-acting analogues, lanreotide and octreotide, bind preferentially to sstr2 and to a lesser extent to sstr5 (Patel & Srikant 1994, Reisine & Bell 1995, de Herder & Lamberts 2002). The effectiveness of these analogues at reducing hormone production and tumour stabilization (Arnold *et al.* 1996, di Bartolomeo *et al.* 1996, Eriksson

et al. 1997, Faiss *et al.* 1999) has been attributed to the sstr2 receptor (Patel & Srikant 1994, Buscail *et al.* 1995, Reisine & Bell 1995, Wulbrand *et al.* 1998). Given the low sensitivity of SRS imaging for insulinomas, it is not surprising that only 50% of insulinomas express sstr2 (Wulbrand *et al.* 1998), and it therefore follows that long-acting somatostatin analogues benefit only those with sstr2-positive tumours. In 'non-functioning' tumours, somatostatin analogues are beneficial where the SRS scan is positive and there is evidence of tumour progression or high mitotic rate (European Neuroendocrine Tumour Network (ENET) 2000). An exciting prospect in this field is the development of new somatostatin analogues that have differing specificities to the various somatostatin receptors, improving their therapeutic effectiveness in tumours that lack, for instance, sstr2. Until these are available, for progressive SRS-negative (i.e. sstr2/5 negative) carcinoid tumours, interferon-alpha should be the treatment of choice.

Interferon-alpha and chemotherapy for gut neuroendocrine tumours

Interferon-alpha has been used in the treatment of carcinoid for some time (Oberg *et al.* 1983) to control hormone secretion, symptoms and tumour growth. Many trials looking at its effectiveness in malignant and mostly

Table 7 Non-medical treatment options for gastroenteropancreatic neuroendocrine tumours.

Non-medical treatment	Effectiveness
Curative surgery	Best option if feasible
Resection of primary	Often pancreatic insulinomas can be enucleated easily
Resection of resectable liver metastases	70–80% 4–5 year survival with curative surgery
Liver transplantation	In highly selected cases can improve survival
Hepatic arterial embolization	Most effective for liver metastases from functioning neuroendocrine tumours producing symptoms. Significant reduction in symptoms (40–90%)
Chemotherapy with hepatic arterial occlusion	Difficult to compare with other treatments owing to lack of randomized trials and different patient groups
Hepatic chemoembolization	Hepatic arterial occlusion with local cytotoxic chemotherapy. Only palliative but has good symptomatic responses (63%)
Hepatic radioembolization	Hepatic artery occlusion with radio-isotope microspheres (brachyradiotherapy). Limited experience with this as yet
Hepatic cryosurgery	Placement of cryoprobes into each metastasis. Useful for palliation, but only when <40% of liver is infiltrated
Palliative surgery	Shown to provide an average of 6 months symptom relief but only when >90% tumour resected (63% 5-year survival)
Radio-labelled somatostatin analogues	Most exciting development in the field of neuroendocrine tumours. Large multi-centre trials are currently running, with encouraging initial reports of tumour regression (10%) as well as symptom relief

carcinoid neuroendocrine tumours have been published (Oberg 2000). In the largest studies, interferon-alpha showed a 42% biochemical and 14% tumour response in carcinoid, and a 51% biochemical and 12% tumour response in neuroendocrine pancreatic tumours (Oberg & Eriksson 1991, Eriksson & Oberg 1993). Side-effects, however, are not insignificant and include flu-like symptoms in 89%, weight loss in 59%, fatigue in 51% and depression in 50%. There is also a risk of hepatotoxicity, autoimmune disorders and the development of neutralizing antibodies. It is useful to note that in a recent prospective randomized trial using interferon-alpha alone, somatostatin analogue alone, or the combination showed no additional benefit of the combination over the monotherapies (Faiss *et al*. 2003).

In slow growing, well-differentiated neuroendocrine tumours (NETs), where tumour growth <25% in 1 year, chemotherapy has limited benefit, and other treatment modalities should be given priority in a multidisciplinary approach. Chemotherapy should be considered for the faster-growing metastatic tumours, and has response rates of 20 to 69% (Rougier & Mitry 2000). Indeed, in undifferentiated NETs, the chemosensitivity is similar to that of small cell carcinoma of the lung. Various combinations of chemotherapy have been used, including streptozotocin and adriamycin in well-differentiated pancreatic NETs (Moertel *et al*. 1992), lomustine (CCNU) and 5-fluorouracil (5FU) in advanced NETs (Kaltsas *et al*. 2002), etoposide (VP16) and cisplatin (CDDP) (Moertel *et al*. 1991, Fjallskog *et al*. 2001) in poorly-differentiated, aggressive NETs giving response rates of 50 to 56% and

benefitting pancreatic NETs and foregut carcinoids most. However, toxicity rates were high.

Surgical treatment of carcinoid and other gut neuroendocrine tumours

In general, curative surgical resections of the primary should be attempted if surgically feasible, even if the tumour size is small and slow-growing, since the secreted hormones may cause significant morbidity and potential mortality (e.g. small insulinoma). Increasingly now, surgeons are even attempting curative surgery of metastases when confined to the liver and where there is sufficient hepatic reserve (Que *et al*. 1995, Chen *et al*. 1998, Chamberlain *et al*. 2000, Jaeck *et al*. 2001, Yao *et al*. 2001), with 4–5 year survival between 70–85%. Outcomes were best with previous resections of the primary tumour and with fewer than 5 liver lesions (Yao *et al*. 2001). In selected patients with numerous liver metastases, liver transplantation has been performed, with survival of 52% after 1 year (Bechstein & Neuhaus 1994).

Surgery also has a place in palliation, where tumour bulk is too extensive for curative resections. In one study, the estimated 5-year survival was 63% with palliative resections (Chamberlain *et al*. 2000). Cryosurgery, where a cryoprobe is inserted surgically into each metastasis causing tumour necrosis, has been used in palliation of liver metastases where less than 40% of the liver is affected. In a small series, symptoms were relieved for a median time of 12 months (Bilchik *et al*. 1997). A rigorous comparison with other treatment modalities is required to assess the overall benefit of cryosurgery, particularly on survival.

Treatment with interventional radiology

Numerous non-medical treatment modalities for gastro-intestinal NETs are available (summarized in Table 7). For symptomatic control, hepatic arterial embolization with polyvinyl alcohol microspheres (150–500 μm diameter) is very effective in metastatic pancreatic NETs and carcinoid with benefit in 40 to 90% of patients for a median duration of 10 to 15 months (Carrasco *et al.* 1983, Ajani *et al.* 1988, Eriksson *et al.* 1998). This procedure, however, needs operator expertise and stringent adherence to formal hospital pretreatment protocols of intravenous methylprednisolone, meticulous fluid balance, intravenous octreotide, aprotinin, broad-spectrum antibiotics and oral allopurinol. In addition, oral cyproheptadine and nicotinamide are required for carcinoid, and dextrose infusions for insulinomas. These precautions are to minimize the high complication rate, where hepatic abscess, renal failure, intestinal and cholecystic necrosis can occur in up to 10% of patients with a mortality of 3 to 7%. When beneficial in individual patients, the procedure can be repeated several times as symptoms recur. Some centres have combined hepatic embolization with systemic chemotherapy using 5FU–streptozotocin alternating with adriamycin–dacarbazin to some additional benefit (Moertel *et al.* 1994), although the patient groups were different, making direct comparisons difficult.

Chemoembolization is where the hepatic arterial injection is with local cytotoxic chemotherapy, which has given response rates of 63% for symptoms and mean survival of 2 years (Stokes *et al.* 1993, Wallace *et al.* 1996, Ruszniewski & Malka 2000). When compared with curative hepatic resections, it provided a median survival from treatment of 32 months and an actuarial 5-year survival of 40% (Yao *et al.* 2001). Finally, the procedure of radioembolization has been attempted for hepatic metastases of NETs, where microspheres labelled with radio-isotope (for example yttrium 90) are used to occlude the hepatic arterial branches supplying the metastases. This form of brachyradiotherapy remains experimental, and further experience is awaited (Andrews *et al.* 1994).

Targeted therapy with radio-labelled somatostatin analogues

Perhaps the most exciting development in the therapeutic armamentarium against metastatic or inoperable NETs has been the introduction of targeted therapy with radio-labelled somatostatin analogues for SRS-scan positive tumours. Various trials are currently underway to assess efficacy, but initial results are very encouraging. Compounds such as (111)In-DTPA-D-Phe1-octreotide (Tiensuu *et al.* 1999), 90-yttrium-DOTA-D-Phe1-Tyr3-octreotide (de Jong *et al.* 1997), (177)Lu-DOTA(0), Tyr3-octreotate (Kwekkeboom *et al.* 2003) and 90-yttrium-DOTA-lanreotide (Leimer *et al.* 1998, Virgolini *et al.* 2002) have been used. In the phase IIa MAURITIUS study (Virgolini *et al.* 2002), 90-yttrium-DOTA-lanreotide in 70 patients with SRS-scan positive tumours resulted in stable disease in 35% and regression in 10%. This field is currently attracting much attention as further results are made available.

Multiple endocrine neoplasia type 1 (MEN1)

A consensus statement giving guidelines for the diagnosis of MEN has recently been published (Brandi *et al.* 2001). It was agreed that no simple definition for MEN1 existed, but a practical definition was the presence of two of the three main MEN1-related tumours (parathyroid adenomas, enteropancreatic endocrine tumours and pituitary tumours). Familial MEN1 was defined as at least one MEN1 case with one first degree relative with one of the three MEN1-related tumours. Table 8 lists the features of MEN1.

The genetic test for the *MEN1* (menin) gene mutation (11q13) is indicated in index cases and asymptomatic relatives. However, no mutation is found in 10 to 20% of index cases for familial MEN1, probably reflecting mutations in untested parts of the *MEN1* gene or deficiencies in PCR amplification methods. Screening for tumour expression in a patient with or suspected of having the *MEN1* mutation should take place from the age of 5 years for anterior pituitary tumours (prolactin, insulin-like growth factor-I, MRI) and insulinomas (fasting glucose, insulin and three-day fast), age of 8 years for parathyroid adenomas (calcium, PTH), and age of 20 for enteropancreatic tumours (chromogranin A, fasting gut hormones, octreotide scan, CT) and foregut carcinoid (endoscopy, CT). Some centres advocate the standardized meal stimulatory test with measurements of pancreatic polypeptide and gastrin (Oberg & Skogseid 1998). The response is abnormal in pancreatic endocrine tumours with a 75% sensitivity in individuals whose mean age was 25 years. Furthermore, the test was useful in differentiating between the high gastrin seen in achlorhydria and gastrinoma.

As tumours arise in patients with MEN1, morbidity results primarily from hormone secretion (e.g. PTH, insulin, gastrin, growth hormone) and also from tumour bulk (e.g. pituitary tumours compressing the optic chiasm, non-functioning pancreatic tumours with liver metastases). The consensus statement regarding the management of these tumours (Brandi *et al.* 2001) is as follows: subtotal parathyroidectomy for hyperparathyroidism, surgical resection of pancreatic neuroendocrine tumours where surgically feasible except for gastrinoma where recurrence is high post surgery in MEN1 and where some advocate non-surgical therapy, and management of

Table 8 Tumours associated with MEN1, with estimated penetrance at age 40. Adapted from Brandi *et al.* (2001).

MEN1 tumours	Penetrance at age 40 (%)	Speculated frequency of germline *MEN1* mutations presumed to be sporadic from family study (%)
Parathyroid adenoma	90	1
Enteropancreatic tumour		
Gastrinoma	40	5
Insulinoma	10	
PPoma	20	
Glucagonoma, VIPoma, somatostatinoma	2	
Non-functioning (often incidental finding)	nearly 100	
Anterior pituitary		
Prolactinoma	20	1
Somatotrophinoma + prolactinoma	5	
Somatotrophinoma	5	
Non-functioning	5	
Corticotrophinoma	2	
Thyrotrophinoma	rare	
Foregut carcinoid		1
Thymic carcinoid	2	
Bronchial carcinoid	2	
Gastric carcinoid	10	
Adrenal cortex (non-functioning) tumour	25	
Lipomas	30	0.1
Facial angiofibromas	85	1
Collagenomas	70	
Ependymoma	1	
Phaeochromocytoma	<1	

pituitary tumours in a similar way to sporadic cases. There has been a comprehensive recent review of the latter (Arafah & Nasrallah 2001).

Multiple endocrine neoplasia type 2 (MEN2)

MEN2 and all its variants (including familial medullary carcinoma of the thyroid, FMTC) are autosomal dominant syndromes resulting from germline mutations in the *RET* gene (10cen-10q11.2). In all variants, there is a high penetrance (90%) of medullary carcinoma of the thyroid (MTC); the likelihood of *RET* germline mutations in a patient with apparently sporadic MTC is 1 to 7% (Eng *et al.* 1995). The clinical features are summarized in Table 9. The criteria for *RET* mutation testing (Brandi *et al.* 2001) should be as for *MEN1* (noted above) and is mandatory in all children at 50% risk, to facilitate prophylactic thyroidectomy in positive cases. In MEN2, there is the added advantage that 98% of MEN2 index cases have an identified *RET* mutation, and only a limited number of mutations exist, involving exons 10, 22, 13, 14, 15 and 16. If testing these exons yields no mutation, then the remaining 15 exons should be sequenced (currently available in research laboratories). Tumour tissue testing

for somatic *RET* mutations in sporadic MTC or sporadic phaeochromocytoma is generally not indicated.

The screening for tumour expression in MEN2 in practical terms refers primarily to the screening for phaeochromocytoma (annual 24-h urinary catecholamines, CT, MIBG scanning) in MEN2A and 2B, and hyperparathyroidism (annual calcium, PTH – seen most with codon 634 mutations) in MEN2A. As regards the thyroid gland, all *RET* mutation carriers should undergo prophylactic total thyroidectomy to prevent the almost certain development of MTC. Thyroidectomy should be performed before the age of 6 months in MEN2B and before the age of 5 years in MEN2A, with MEN2B having a more aggressive course than MEN2A or FMTC. Table 10 lists the three categories of MTC risk based on RET mutation stratification. Following thyroidectomy, MTC surveillance can be achieved with fasting calcitonin values and, if elevated, a pentagastrin stimulation test. MRI scanning and where available pentavalent 99m Tc-dimercaptosuccinic acid (DMSA) nuclear medicine imaging (Warner & O'dorisio 2002) help localize disease recurrence. More than 90% of MTC cells express cholecystokinin B (CCK-B) receptors, and radio-labelled

Table 9 MEN2 syndromes and penetrance. Adapted from Brandt *et al.* (2001).

MEN2 and variant syndomes	Features	Penetrance in adult carriers (%)
MEN2A (> 75% of all MEN2)	MTC	90%
	Phaeochromocytoma	50%
	Parathyroid adenomas	20–30%
	(variant also with cutaneous lichen amyloidosis or Hirschsprung's disease)	
FMTC	MTC (variant also with Hirschsprung's disease)	90%
MEN2B	MTC	90%
	Phaeochromocytoma	
	Intestinal and mucosal ganglioneuromatosis	
	(with intestinal autonomic dysfunction leading to megacolon)	
	Mafanoid habitus	
	Decreased upper/lower body ratio	
	Medullated corneal fibres	

CCK-B ligands have also been used diagnostically (Behr & Behe 2002).

The management for tumour development in MEN2 has again been summarized in the consensus statement (Brandi *et al.* 2001). MTC conveys the main morbidity (when diagnosis is made after the opportunity for prophylactic thyroidectomy). Local spread is common and reoperation in the neck is indicated, particularly when there is no evidence of distant spread and for tumour-debulking to relieve calcitonin-induced symptoms such as diarrhoea. Unfortunately, MTC tends not to be responsive to either chemotherapy or radiotherapy. For MIBG-positive MTC, the option of targeted therapy (with radioactive MIBG) is an encouraging development, and more recently 90-yttrium-labelled CCK-B ligands have been shown to have therapeutic uses in MTC (Behr & Behe 2002), although limited by nephrotoxicity. The preferred therapy for unilateral adrenal phaeochromocytoma is laparoscopic resection, following adequate pre-operative alpha- (with or without beta-) adrenergic blockade. Bilateral adrenal and extra-adrenal phaeochromocytoma require open resection. Hyperparathyroidism is milder than in MEN1, but often more than one parathyroid gland is enlarged. The exact parathyroid procedure performed (e.g. subtotal, only enlarged glands) should be the same as in other disorders with multiple parathyroid tumours.

Phaeochromocytoma

Phaeochromocytoma has already been briefly mentioned in the section on MEN2. Catecholamine-secreting tumours derive from neuroectoderm and arise from the adrenal medulla (phaeochromocytoma) or from extra-adrenal neural crest. The cells of origin include chromaffin cells (phaeochromocytoma and paraganglioma), ganglion cells (ganglioneuroma and ganglioneuroblastoma), sympathogone (sympathoblastoma) and sympathoblast (neuroblastoma) (Bouloux 2002). The annual incidence of catecholamine-secreting tumours is 2 to 8 per million population, although post-mortem studies indicate a higher incidence (up to 0.1%). Multiple and extra-adrenal tumours are seen in 35% of children compared with only 8% of adults, and criteria for malignancy are based more on size of tumour and metastatic spread than on histology; features suggestive of malignancy are seen 3 to 15 times more in paragangliomas than in phaeochromocytoma (Bouloux 2002).

These tumours have attracted much interest in the literature recently, with the finding that 24% of nonsyndromic phaeochromocytoma without a family history of the disease had a germline mutation in one of the familial conditions known to be associated with phaeochromocytoma (Neumann *et al.* 2002) (see Table 11). The authors concluded that routine analysis for mutations of *RET*, *VHL*, *SDHD* and *SDHB* (the latter two genes encode the

Table 10 Risk stratification of MEN2 mutations and MTC. Adapted from Brandi *et al.* (2001).

MTC risk category in MEN2	Mutated *RET* codon	Recommended age for thyroidectomy
Highest risk (level 3)	883, 918, 922	Within first 6 months of life (preferably within 1st month)
High risk (level 2)	611, 618, 620, 634	<age 5 years
Least risk (level 1)	609, 768, 790, 804, 891	<age 5 years/<age 10 years (little consensus in this group)

Table 11 Familial syndromes associated with phaeochromocytoma.

Familial syndromes associated with phaeochromocytoma	Gene	Chromosome
MEN2	*RET*	10q11.2
von Hippel Lindau	*VHL*	3p26-p25
Neurofibromatosis type 1	*NF1*	17q11.2
Ataxia telangiectasia	*ATM*	11q22.3
Tuberose sclerosis	*TSC1, TSC2*	9q34, 16p13.3
Sturge–Weber	?	
Familial paragangliomas of the neck	*SDHD, SDHB*	11q23, 1p36.1-p35

mitochondrial complex II enzymes succinate dehydrogenase subunits D and B) should be performed in patients presenting with apparently sporadic phaeochromocytoma.

Conclusion

Neuroendocrine tumours form a diverse group of conditions with a large spectrum of clinical syndromes depending on the presence of secreted hormones. Their management is challenging, since morbidity is quite often related to the hypersecretion syndrome rather than tumour bulk. The advent of genetic screening has had a significant effect on patient management and counselling, and it is hoped that new technologies will allow for more precise patient risk stratification. The frequent expression of somatostatin receptors by these tumours allows for the highly beneficial use of somatostatin analogues, and most recently the introduction of targeted therapy. This is a very exciting development in the field, and further results are currently awaited.

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