Developments in Digestive Tract Neuroendocrine Tumours and Pheochromocytomas/Paragangliomas – A Narrative Review

Ioannis Illias1 and Karel Pacak2

1. Endocrinologist, Department of Endocrinology, E Venizelou Hospital, Athens; 2. Chief and Senior Investigator, Section on Medical Neuroendocrinology, The Eunice Kennedy Shriver National Institute of Child Health and Human Development, National Institutes of Health

Abstract
Digestive neuroendocrine tumours (carcinoids) derive from serotonin-producing enterochromaffin cells. Biochemical screening (and follow-up) is performed with measurements of 5-hydroxyindoloacetic acid in urine. Other markers are also useful. Most digestive neuroendocrine tumours are better localised with functional imaging, i.e. nuclear medicine, compared with other modalities. The treatment of choice is surgical; non-resectable tumours are treated with somatostatin analogues (unlabelled and for more advanced disease radiolabelled) or chemotherapy. Most pheochromocytomas/paragangliomas are sporadic, however, and genetically caused tumours are much more common than previously thought. Biochemical proof of disease is best carried out with measurement of plasma metadrenaline. Imaging with computed tomography or magnetic resonance imaging (MRI) should be followed by functional imaging. Chromaffin tumour-specific methods are preferred. 18F-fluoro-deoxyglucose positron emission tomography (18F-DOPA PET) should be used in patients with succinate-dehydrogenase-B-related metastatic pheochromocytoma/paraganglioma. 18F-DOPA PET may become a modality of choice for the localisation of head and neck paragangliomas. If possible, treatment is surgical. For non-operative disease, other options are available and new drugs are under investigation or in clinical trials.

Keywords
Digestive neuroendocrine tumours, pheochromocytomas, paragangliomas, metadrenaline, radionuclide imaging, succinate dehydrogenase complex

Disclosure: The authors have no conflicts of interests to declare.

Acknowledgement: The writing of this article was supported by the Intramural Research Program of The Eunice Kennedy Shriver National Institute of Child Health and Human Development at the National Institutes of Health (Bethesda, Maryland, US).

Received: 22 July 2010 Accepted: 15 September 2010 Citation: European Endocrinology, 2010;6(2):59–64 DOI:10.17925/EE.2010.06.02.59

Correspondence: Ioannis Illias, Department of Endocrinology, E Venizelou Hospital, 2 E Venizelou Sq, Athens GR-11521, Greece. E: illiasmd@yahoo.com

Digestive Neuroendocrine Tumours
Digestive neuroendocrine tumours (carcinoids) derive from serotonin-producing enterochromaffin cells. The digestive neuroendocrine tumours are classified as:

- foregut – originating from the oesophagus to the pancreas;
- midgut – ‘classic’, presenting with the carcinoid syndrome that includes flushing, diarhoea and hypotension. They originate from the jejunum to the right colon and gonads; or
- hindgut – ‘silent’, originating from the transverse colon to the rectum.

More than half of digestive neuroendocrine tumours originate in the gastrointestinal tract (with half of these in the small intestine) and the remaining from the lungs/bronchi. The overall incidence of digestive neuroendocrine tumours is estimated to be one to five per million population. Patients with midgut digestive neuroendocrine tumours may complain of vague abdominal symptoms for a long time (approximately nine years) before classic symptoms and signs, such as flushing and excess gastrointestinal motility are observed. At this time, the disease has metastasised in 90% of symptomatic patients. More than half of patients with digestive neuroendocrine tumours – via mechanisms that are not clearly understood – suffer from irreversible carcinoid heart disease. The endocardium shows fibrous thickening and the tricuspid and pulmonary valves are fixed.

Genetics
Ten per cent of individuals with multiple endocrine neoplasia (MEN) type 1 have digestive neuroendocrine tumours. MEN1 is an autosomal dominant disorder caused by deletion of the MEN1 suppressor gene on chromosome 11q13. Forty to 80% of patients with sporadic digestive neuroendocrine tumours also show loss of heterozygosity in chromosome 11 or deletion of the MEN1 gene. Pulmonary neuroendocrine tumours are associated with mutations in the p53 suppressor gene and variability in B-cell lymphoma 2 (Bcl-2) expression. Studies of polymorphisms of the nuclear factor-kappaB (NFκB) transcription factor tentatively point to differences in the genetics of digestive neuroendocrine tumours vis-à-vis pancreatic neuroendocrine tumours.

Biochemical Diagnosis
Digestive neuroendocrine tumours in the fore- and midgut metabolise tryptophan to 5-hydroxytryptophan and synthesise and secrete serotonin. The measurement of the latter’s major metabolite 5-hydroxyindoloacetic acid (5-HIAA) in urine is proposed by most experts as the biochemical screening (and follow-up) test of choice.
Neuroendocrine Tumours

Levels of 5-HIAA also correlate with tumour burden (sensitivity is 70% whereas specificity is 90–100%).

Chromogranin A is a marker with a sensitivity of 80–100% for digestive neuroendocrine tumours. Chromogranin A is not specific for these; however, it is also used as a screening test as it is elevated in most cases of metastatic fore- and midgut digestive neuroendocrine tumours.

Digestive neuroendocrine tumours in the foregut may also secrete hormones, such as corticotrophin, leading to Cushing’s syndrome. Midgut digestive neuroendocrine tumours synthesise and secrete tachykinins (neurokinin A and substance P), prostaglandins and catecholamines.

Imaging

Primary digestive neuroendocrine tumours and their metastases, particularly hepatic or in lymph nodes, are evaluated with computed tomography (CT) and magnetic resonance imaging (MRI). The sensitivity of these methods varies from 50–85%. Tumours are multiple in 40% of cases and calculations are seen in 70% of mesenteric masses. Tumours of 1–2cm are the smallest that are detected. Lesions have a low density on CT scan or low signal in unenhanced MRI views. Lesions are enhanced avidly in the early arterial phase of contrast-enhanced examinations and wash out early. Primary small intestinal tumours are better seen with barium follow-through, conventional or MRI enteroclysis.

Functional imaging is better than other modalities in localising primary digestive neuroendocrine tumours.

Digestive neuroendocrine tumours express somatostatin receptors (STR) 2 and 5. Somatostatin receptor scintigraphy (SRS) has localising sensitivity ranging from 60% (for silent) to 90% (for symptomatic) patients with carcinoid syndrome. Combined SRS/CT evaluation improves imaging compared with standalone SRS. A positive SRS result may also be predictive of response to octreotide therapy.

Positron emission tomography (PET) with 68Ga-DOTATOC (a somatostatin analogue) had 97% sensitivity and 92% specificity in a study of 56 patients with digestive neuroendocrine tumours. These results were better than SRS or CT, which had a sensitivity of 52 and 61% and specificity of 92 and 71%, respectively. In another study of patients with primary or recurrent neuroendocrine tumours, PET with another somatostatin analogue, 68Ga-DOTATATE, had 82% sensitivity. Combined 68Ga-DOTATOC-PET/CT is better than SRS alone.

Scintigraphy with 123I-metaiodobenzylguanidine (MIBG) has 60–70% sensitivity in localising digestive neuroendocrine tumours. The combination of SRS and MIBG scintigraphy results may provide even better localising sensitivity.

Digestive neuroendocrine tumours, similar to other neuroendocrine tumours, take up amine precursors such as dihydroxyphenylalanine (DOPA). PET with 18F-DOPA has 46–98% sensitivity in detecting such tumours, particularly when it is combined with CT scanning.

Management

The treatments of choice for digestive neuroendocrine tumours are:

- endoscopic resection (where possible); limited excision (for tumours <1cm); extensive surgery (for tumors >1cm) and hepatic resection (for liver involvement of <50%).

Recently standardised protocols for the pathological examination of digestive neuroendocrine tumours were presented. Extensive hepatic involvement is treated with hepatic artery embolisation, radiofrequency ablation or interferon gamma. There is symptomatic response in 80–90% and biochemical or tumour response in 50% of patients.

Patients with advanced disease (and positive SRS) are candidates for somatostatin analogue therapy. Octreotide and lanreotide can resolve carcinoid syndrome symptoms in 45–75% of patients, with biochemical response in 30–75% of them. At 10%, CT/MRI-documented tumour response is much lower.

In octreotide-resistant malignant digestive neuroendocrine tumour patients, yttrium-90-labeled octreotide administration has improved symptoms. MIBG therapy in subjects with positive MIBG scintigraphy can be also used, either alone or in combination with radiolabelled somatostatin analogues. Analogous results with octreotide in terms of biochemical response and tumour size have been observed with interferon-alpha therapy. More side effects compared with octreotide are noted though.

Chemotherapy with 5-fluorouracil, streptozocin or doxorubicin has a 20% response rate.

Prognosis

Overall five-year survival for patients with digestive neuroendocrine tumours is 47–67%, being highest at 78% for patients with localised disease and slightly lower at 72% for those with regional metastases. Contrary to this, survival of patients with distant metastases is much lower, at 40%.

For bronchial digestive neuroendocrine tumours higher survival is reported (over 82% at 15 years). In Europe significant survival disparities by country are noted. Plasma chromogranin A elevation may be the first finding of disease recurrence.

Modalities Currently being Evaluated

Video capsule endoscopy is gaining acceptance as a front-line tool in the evaluation of digestive neuroendocrine tumours. PET with 111In-labelled 5-hydroxytryptophan or 18F-labeled DOPA are very useful for the localisation of these tumours and should become more readily available to specialised medical centres. Other PET ligands, such as 64Cu-DOTANOC (with affinity for STR2 and 5) have been evaluated for neuroendocrine tumours, including digestive ones. Positron-emitting (SOM 230), a somatostatin STR1, 2, 3 and 5 ligand receptor, is currently in phase III clinical trials.

Therapies with high specific activity that hold promise for inoperable disease include ultratrace MIBG, 111In- or 90Y-radiolabelled octreotide and 177Lu-radiolabelled octreotide. There is also therapeutic potential with mammalian target of rapamycin (mTOR) inhibitors or agents that target the high vascularity of tumours, particularly vascular endothelial growth factor. These include recombinant human endostatin, thalidomide, bevacizumab and sunitinib.

Pheochromocytomas/Paragangliomas

Chromaffin cells are post-ganglionic sympathetic neurons that produce catecholamines. They are mainly located in the adrenal medulla. Nevertheless, accessory adrenal tissue comprising both cortical and medullary elements has been reported to be localised in the celiac plexus area in 16% of autopsy cases.
Digestive Tract Neuroendocrine Tumours and Pheochromocytomas/Paragangliomas

Tumours arising from extra-adrenal chromaffin cells are termed paragangliomas. They can be found along the paravertebral and para-aortic axes. Sympathetic paraganglia have a neck-to-pelvis distribution and parasympathetic paraganglia are found in the neck and skull base.

Paragangliomas that are localised in the adrenal medulla are called pheochromocytomas (or more uncommonly termed Paragangliomas that are localised in the adrenal medulla are termed paragangliomas). The term extra-adrenal pheochromocytomas is used to describe tumours of the sympathoadrenal system. There are no universally established criteria for defining malignancy in pheochromocytomas/paragangliomas. However, capsular invasion, large tumour size (>5cm) and weight (>80g) may be indicators of malignancy. The clinical course may indicate malignancy, particularly with recurrent or metastatic disease.

Pheochromocytomas (i.e. adrenal medullary paragangliomas) are rare tumours with an annual incidence of one to four per million population. Furthermore, 0.5% of subjects with hypertension and 4% of those with an incidental adrenal mass have pheochromocytoma. The caveat is that these figures are approximate; since until a few years ago 18–60% of tumours remained undiagnosed. The average lag time from the onset of hypertension to the diagnosis of pheochromocytoma is three years. Peak age for diagnosis of pheochromocytomas is between 40 and 50 years, with an almost equal female/male ratio. In most cases (downgraded from 90 to 85% or less with the advent of newer molecular genetics studies, see below for details) these tumours are adrenal, sporadic and solitary.

The symptoms of pheochromocytomas vary. The triad of tachycardia with diaphoresis and cephalalgia is encountered in 40–80% of patients and is highly sensitive and specific for a presumptive diagnosis of pheochromocytoma. Hypertension – newly diagnosed or an exacerbation of known hypertension, most often paroxysmal – is common, occurring in over 90% of patients, but is non-specific.

Most paragangliomas are intra-abdominal and adjacent to the adrenals (approximately 85%). Less than 15% are intrathoracic and 1–3% are cervical.

Chromaffin-negative neuroendocrine tumours in the head and neck that are related to the parasympathetic nervous system, such as those originating from the carotid bodies or jugular bulbs, are also termed paragangliomas.

Genetics

Familial syndromes with pheochromocytomas/paragangliomas include MEN type 2 (MEN 2); von Hippel-Lindau (VHL) syndrome; neuroectodermal dysplasias – neurofibromatosis type 1 (NF-1), tuberous sclerosis and Sturge-Weber syndrome; and other familial paragangliomas, especially those related to succinate dehydrogenase (SDH) gene mutations. In children, familial tumours are found twice as often as in adults.

Activating germline mutations in the RET proto-oncogene, usually in codons 634 or 918 (10q11.2) are implicated in the abnormal cellular proliferation of MEN 2 syndrome. Pheochromocytomas are usually adrenal and benign in MEN 2 and are bilateral in more than 50% of patients.

Missense mutations in the VHL tumour suppressor gene, usually in codon 167, 3p25–26, are commonly implicated in the pathogenesis of VHL syndrome. Twenty to 50% of subjects have mostly benign adrenal pheochromocytomas, and slightly less than 50% have bilateral disease.

The genetic background of pheochromocytomas observed in subjects with neuroectodermal dysplasias is yet to be elucidated. Mutations in the NF-1 tumour suppressor gene – associated with von Recklinghausen’s disease – have been observed (17q11.2; in 90% of cases). The risk of pheochromocytoma in patients with NF-1 is approximately 1–5%.

Familial pheochromocytomas or head/neck paragangliomas are seen in subjects with germline mutations in subunits B, C and D of the SDH gene. The risk of extra-adrenal and/or malignant disease is high for SDHb mutation carriers. SDHb mutations also predispose to head and neck paragangliomas. SDHC mutations are a rare cause of head and neck paragangliomas. SDHD mutations are associated with benign adrenal and extra-adrenal paragangliomas or multifocal head and neck paragangliomas. SDHB/SDHD mutations have been found in patients with Carney-Stratakis syndrome (they also have paragangliomas). The former are also associated with renal tumours, gastrointestinal stroma cancer and thyroid cancer. Mutations in the SDHA and SDHAF2 (SDH D) family were recently found and linked to hereditary, but not sporadic, paragangliomas.

It has been suggested that the transmembrane-encoding gene TMEM127 (chromosome 2q11) is a newly discovered pheochromocytoma susceptibility gene. Pheochromocytomas with TMEM127 mutations are transcriptionally related to tumours bearing NF1 mutations. Expression of SNAIL (a zinc-finger transcription factor) may predict the metastatic potential of pheochromocytoma.

Approximately 15% of all pheochromocytomas/paragangliomas are associated with germline SDH mutations. Immunohistochemistry is apparently the most cost-effective method of genetic testing – particularly if biochemistry is not available or considered, or results are negative. Furthermore, there is sufficient evidence to suggest that genetic testing should be carried out in all patients with pheochromocytomas/paragangliomas. If cost is a concern, then testing should at least be available to those <50 years.

Biochemical Diagnosis

Chromaffin tumours that are hormonally active may secrete catecholamines episodically, however, they metabolise catecholamines to metanephrines continuously. Free metanephrines in plasma and 24-hour urinary fractionated free metanephrines are the most accurate methods for establishing the diagnosis of pheochromocytoma. Their respective sensitivity ranges from 99–100% (plasma) and 97–100% (urine) and their specificity is 89–94% (plasma) and 69–95% (urine). Biochemistry is not only useful for establishing the diagnosis of pheochromocytoma/paraganglioma but can also guide further testing (including genetic testing). In subjects with MEN2 or NF1, there is predominantly elevation in normetadrenaline. Care must be taken to normalise metadrenaline levels for populations with normal blood pressure, match them for gender and age and avoid interference from medications.
Neuroendocrine Tumours

Dynamic testing is rarely sought. Guacagon testing is now considered to be obsolete. Suppression with clonidine and measurement of plasma-free normetadrenaline is accurate but applies only to normetadrenaline-secreting tumours.

Head and neck paragangliomas were previously rarely considered to be hormonally active. A substantial number of them (almost one-third) are, however, biochemically active. This is supported by increased excretion of the dopamine metabolite 3-methoxytyramine. Most abdominal and thoracic SDHB-paragangliomas hypersecrete either normetadrenaline or normetadrenaline and dopamine. Some only hypersecrete dopamine and are almost silent biochemically.

Imaging

CT imaging has 93–100% sensitivity for detecting intra-adrenal pheochromocytomas of approximately 0.5cm in diameter. The sensitivity of CT is slightly lower, at 90%, for localising extra-adrenal disease of approximately 1cm in size.

MRI offers slightly better sensitivity. Pheochromocytomas usually show a characteristic very high T2-weighted signal on MRI unless there is a haemorrhage or intratumoural necrosis. MRI is very good for evaluating the relationship of pheochromocytomas with blood vessels. This is of importance when surgery is planned.

CT/MRI should be used in patients with biochemically proved pheochromocytoma/paraganglioma. For most patients imaging is limited to the adrenals/abdomen, whereas evaluations of the thorax, neck and head are used when there is suspicion of malignant/metastatic disease. For head and neck paragangliomas, MRI may better explore tumour anatomy vis-à-vis this region’s blood vessels. Conventional or MRI angiography may also be very helpful.

Although positive CT/MRI studies can be diagnostic, their specificity may vary from 50–90%. Thus, negative anatomical imaging studies may not be diagnostic. Furthermore in patients with previous surgery poor quality imaging may lessen utility, particularly if recurrence is suspected. For such cases and for cases of extra-adrenal or malignant/metastatic disease, the use of functional methods is preferred.

There are two paths for functional imaging of chromaffin tumours:

- Specific methods for these tumours, since chromaffin tumours express the human noradrenaline transporter (hNAT). This permits the use of radiolabelled ligands of molecules that enter the catecholamine synthesis pathway or their analogues and specific vesicular monoamine transporters for storage in intracytoplasmic vesicles.
- Non-specific methods that make use of the high glucose metabolism of tumours or expression of STRs.

Specific functional imaging methods should be carried out first. If results are negative, non-specific modalities should be sought, particularly if recurrent, metastatic or malignant disease is suspected.

MIBG is a catecholamine precursor that is taken into pheochromocytoma cells via hNAT. Nowdays it is labelled with iodine-123 (123I-MIBG), permitting better quality imaging than 131I-MIBG. CT imaging – standalone or as single-photon emission CT (SPECT) – is also possible.

Dopamine is a catecholamine precursor. PET with 18F-dopamine is better than 131I-MIBG for imaging adrenal and/or benign pheochromocytomas or localising metastatic pheochromocytomas. DOPA is converted into dopamine and then transported into pheochromocytomas by hNAT (the large neutral amino acid transporter may also play a role in this). Standalone PET with 18F-DOPA or combined with CT has been used for localising benign adrenal pheochromocytomas and head and neck paragangliomas with good results.

PET with 18F-labelled deoxyglucose (FDG) is currently widely available and is used for localising various tumours and the staging of neoplastic disease. FDG PET is a convenient and accessible modality for localising pheochromocytomas that are negative with specific functional imaging modalities (particularly metastatic disease).

Pheochromocytomas and paragangliomas express STRs (mostly types 2, 3 and 5), although conflicting results have been presented in the past. Octreotide is an octapeptidic somatostatin analogue that is labelled with 111In for SRS. Despite intense splanchic/renal abdominal accumulation, it is a useful non-specific tool for localising malignant and/or metastatic pheochromocytomas or paragangliomas with a sensitivity approaching 90%.

18F-dopamine PET/CT is the preferred technique for localising primary pheochromocytomas and paragangliomas and to rule out metastases. 18F-DOPA PET and 123I-MIBG scintigraphy make an equally good second choice. For patients with known metastatic paraganglioma, 18F-dopamine PET is the choice for those with an unknown genotype. 18F-FDG/18F-dopamine PET should be the preferred option in SDHB mutation carriers. 18F-DOPA/18F-dopamine PET is preferable in non-SDHB patients.

Management

The definitive treatment for pheochromocytoma/paraganglioma is surgery.

For hormonally active tumours, a pre-operative blood pressure-lowering/normalisation regimen should be followed using selective alpha1 blockers (prazosin, doxazosin and others) or non-selective, non-competitive alpha blockers (phenoxybenzamine). If, despite selectivity tachycardia ensues, beta blockade is given after sufficient alpha blockade has been achieved. Pre-operative management with calcium blockers, nifedipine, angiotensin-converting enzyme (ACE) inhibitors or alpha-methyl-para tyrosine (Demser) have been also used.

Laparoscopic surgery is possible for abdominal tumors up to 9cm in diameter. Partial (cortical-sparing) adrenalectomy is used more often – particularly for small tumors. A transabdominal approach is reserved for malignant tumors, where debulking surgery and/or adrenalectomy is advised. Non-competitive alpha blockade with long-acting agents such as phenoxybenzamine is preferred for keeping blood pressure under control in patients with symptomatic malignant and/or inoperable disease. Demser is also given to block catecholamine synthesis.

Biochemical evaluation with plasma and/or urine adrenaline should be carried out two to six weeks post-surgery. Annual biochemical work-up for the first five years and once every two years thereafter is
the minimum follow-up requirement. In the case of persistence or recurrence, localisation studies should be sought.

Sixty per cent of malignant pheochromocytomas show avid 131I-MIBG uptake.108 In specialised centres such tumours can be treated with therapeutic 131I-MIBG in single or fractionated doses totalling 200–1,400mCi. Approximately 30% of tumours show an objective response to therapy (40% biochemical response) and 40% of tumours remain stable (20% biochemically).109 Radioiodine therapy may lead to serious adverse events, particularly in terms of bone marrow suppression.109-111

Less experience has been obtained with labelled somatostatin analogues.81 Overall, combination chemotherapy with dacarbazine cyclophosphamide and vincristine does not confer any significant survival benefit.110 Other regimens include etoposide plus cisplatin or etoposide plus lomustine with 5-fluorouracil.112 Radiofrequency ablation of metastatic foci can also be used.113 Another experimental modality is sunitinib, a multiple tyrosine kinase inhibitor.114

Prognosis

The life expectancy of patients with benign pheochromocytoma/paraganglioma that has been successfully excised may not be different from that of the general population. Nevertheless, half of the patients that are successfully operated on have continued hypertension114,115 and overall 16% of patients operated on for pheochromocytoma/paraganglioma have recurrent disease within 10 years.116 In a recent case series of children with pheochromocytoma/paraganglioma, all were found to harbour a predisposing mutation but were alive after follow-up of five years.117 In a large cohort of patients with pheochromocytoma, however, mortality from a second neoplasia was four-fold higher compared with that of the general population.118

Recently levels of the adrenomedullin RDC1 receptor were reported to be four times higher in malignant than in benign pheochromocytomas. Cells expressing SNAIL were frequent in metastatic pheochromocytomas compared to being absent in tumours without metastases. Despite these reports, the use of adrenomedullin RDC1 receptor and SNAIL levels as prognostic factors in pheochromocytoma/paraganglioma is not yet envisaged.71,718

Phaeochromocytoma-paraganglioma syndrome can be diagnosed reliably by immunohistochemistry.17 There are no criteria to predict survival following malignant pheochromocytoma. Surprisingly, however, 15-year survival rates of almost 50% have been reported with a combination of therapeutic modalities.119

Modalities Currently being Evaluated/Introduced into Practice

Quantification of pheochromocytoma/paraganglioma vesicular monoamine transporter content indicates whether the tumours are MIBG-avid.114,116 As PET imaging accessibility increases worldwide, more patients with pheochromocytoma/paraganglioma will be evaluated with PET studies. Ultratracer 131I-MIBG has very high specific activity and holds promise for future therapeutic applications.46 New modalities for the medical management of malignant pheochromocytomas are being assessed. Among these, the combination of temozolone and thalidomide or therapeutic modalities.119


Neuroendocrine Tumours

64 E U R O P E A N E N D O C R I N O L O G Y

42. van Tuyl SA, van Noorden JT, J Gastrointest Endosc, 2006;64: 66–72.
56. Plouin PF, Gimenez-Roqueplo AP, J Endocrinol, 2006;212:73–79.