Developments in Digestive Tract Neuroendocrine Tumors and Pheochromocytomas/Paragangliomas—A Narrative Review

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Abstract

Digestive neuroendocrine tumors (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 tumors are better localized with functional imaging, i.e. nuclear medicine, compared with other modalities. The treatment of choice is surgical; non-resectable tumors are treated with somatostatin analogs (unlabelled and for more advanced disease radiolabelled) or chemotherapy. Most pheochromocytomas/paragangliomas are sporadic, however, and genetically caused tumors 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 tumor-specific methods are preferred. ^{18}F-fluoro-deoxyglucose positron emission tomography (^{18}F-DOPA PET) should be used in patients with succinate-dehydrogenase-B-related metastatic pheochromocytoma/paraganglioma. ^{18}F-DOPA PET may become a modality of choice for the localization of head and neck paragangliomas. If possible, treatment is surgical. For non-operable disease, other options are available and new drugs are under investigation or in clinical trials.

Keywords

Digestive neuroendocrine tumors, pheochromocytomas, paragangliomas, metadrenaline, radionuclide imaging, succinate dehydrogenase complex

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Digestive Neuroendocrine Tumors

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

- foregut—originating from the esophagus to the pancreas;
- midgut—'classic'; presenting with the carcinoid syndrome that includes flushing, diarrhea 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 tumors 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 tumors is estimated to be one to five per million population.[1] Patients with midgut digestive neuroendocrine tumors 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.[2,3] At this time, the disease has metastasized in 90 % of symptomatic patients.[2,3] More than half of patients with digestive neuroendocrine tumors—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 fixated.[2,4]

Genetics

Ten per cent of individuals with multiple endocrine neoplasia (MEN) type 1 have digestive neuroendocrine tumors. 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 tumors also show loss of heterozygozity in chromosome 11 or deletion of the *MEN1* gene.[2,5] Pulmonary neuroendocrine tumors are associated with mutations in the p53 suppressor gene and variability in B-cell lymphoma 2 (Bcl-2) expression.[2] Studies of polymorphisms of the nuclear factor-kappaB (NFκB) transcription factor tentatively point to differences in the genetics of digestive neuroendocrine tumors *vis-à-vis* pancreatic neuroendocrine tumors.[6]

Biochemical Diagnosis

Digestive neuroendocrine tumors in the fore- and midgut metabolize tryptophan to 5-hydroxytryptophan and synthesize 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.[7,8] Levels of 5-HIAA also correlate with tumor burden (sensitivity is 70 % whereas specificity is 90–100 %).[2] Chromogranin A is a marker with a sensitivity of 80–100 % for digestive neuroendocrine tumors.[9] 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 tumors.[10,11] Digestive neuroendocrine tumors in the foregut may also secrete hormones, such as corticotrophin, leading to Cushing's syndrome.[12] Midgut digestive neuroendocrine tumors may synthesize and secrete tachykinins (neurokinin A and substance P), prostaglandins and atecholamines.[3,11]

Imaging

Primary digestive neuroendocrine tumors 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 %.[13] Tumors are multiple in 40 % of cases and calcifications are seen in 70 % of mesenteric masses.[13] Tumors of 1–2 cm 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.[13] Primary small intestinal tumors are better seen with barium follow-through, conventional or MRI enteroclysis.[14,15] Functional imaging is better than other modalities in localizing primary digestive neuroendocrine tumors.[7]

Digestive neuroendocrine tumors express somatostatin receptors (STR) 2 and 5. Somatostatin receptor scintigraphy (SRS) has localizing sensitivity ranging from 60 % (for silent) to 90 % (for symptomatic) patients with carcinoid syndrome.[7] Combined SRS/CT evaluation improves imaging compared with standalone SRS.[16] A positive SRS result may also be predictive of response to octreotide therapy.[17]

Positron emission tomography (PET) with ^{68}Ga-DOTATOC (a somatostatin analogue) had 97 % sensitivity and 92 % specificity in a study of 56 patients with digestive neuroendocrine tumors.[18] 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 tumors, PET with another somatostatin analog, ^{68}Ga-DOTATATE, had 82 % sensitivity.[19] Combined ^{68}Ga-DOTATOC-PET/CT is better than SRS alone.[20] Scintigraphy with ^{123}I-metaidobenzylguandine (MIBG) has 60–70 % sensitivity in localizing digestive neuroendocrine tumors.[21–23] The combination of SRS and MIBG scintigraphy results may provide even better localizing sensitivity.[17]

Digestive neuroendocrine tumors, similar to other neuroendocrine tumors, take up amine precursors such as dihydroxyphenylalanine (DOPA). PET with ^{18}F-DOPA has 46–98 % sensitivity in detecting such tumors, particularly when it is combined with CT scanning.[24,25]

Management

The treatments of choice for digestive neuroendocrine tumors are:[26] endoscopic resection (where possible); limited excision (for tumors <1 cm); extensive surgery (for tumors >1 cm) and hepatic resection (for liver involvement of <50 %). Recently standardized protocols for the pathological examination of digestive neuroendocrine tumors were presented.[27–30] Extensive hepatic involvement is treated with hepatic artery embolization, radiofrequency ablation or interferon gamma. There is symptomatic response in 80–90 % and biochemical or tumor response in 50 % of patients.[2,4,31] 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.[32] At 10%, CT/MRI-documented tumor response is much lower.[2,33] In octreotide-resistant malignant digestive neuroendocrine tumor patients, ^{90}Y-edotreotide administration has improved symptoms.[34] MIBG therapy in subjects with positive MIBG scintigraphy can be also used, either alone or in combination with radiolabelled somatostatin analogues.[35,36] Analogous results with octreotide in terms of biochemical response and tumor size have been observed with interferon-alpha therapy. More side effects compared with octreotide are noted though.[1,4,37,38] Chemotherapy with 5-flurouracil, streptozocin or doxorubicin has a 20 % response rate.[4]

Prognosis

Overall five-year survival for patients with digestive neuroendocrine tumors is 47–67 %, being highest at 78 % for patients with localized 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 %.[2] For bronchial digestive neuroendocrine tumors higher survival is reported (over 82 % at 15 years).[39] In Europe, significant disparities by country are noted.[40] Plasma chromogranin A elevation may be the first finding of disease recurrence.[41]

Modalities Currently being Evaluated

Video capsule endoscopy is gaining acceptance as a front-line tool in the evaluation of digestive neuroendocrine tumors.[42–45] PET with C^{11}-labelled 5-hydroxytryptophan or ^{18}F-labeled DOPA are very useful for the localization of these tumors and should become more readily available to specialized medical centers.[46] Other PET ligands, such as ^{68}Ga-DOTANOC (with affinity for STR2 and 5) have been evaluated for neuroendocrine tumors, including digestive ones.[47] Pasireotide (SOM 230), a somatostatin STR1, 2, 3 and 5 ligand receptor, is currently in phase III clinical trials.[1]

Therapies with high specific activity that hold promise for inoperable disease include ultratrace MIBG, ^{111}In- or ^{90}Y-radiolabelled octreotide and ^{177}Lu-radiolabelled octreotate.[48–50] There is also therapeutic potential with mammalian target of rapamycin (mTOR) inhibitors or agents that target the high vascularity of tumors, particularly vascular endothelial growth factor. These include recombinant human endostatin, thalidomide, bevacizumab and sunitinib.[4,51]

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 localized in the celiac plexus area in 16 % of autopsy cases.[52] Tumors arising from extra-adrenal chromaffin cells are termed paragangliomas. They can be found along the paravertebral and para-aortic axes.[53] Sympathetic paraganglia have a

neck-to-pelvis distribution and parasympathetic paraganglia are found in the neck and skull base.

Paragangliomas that are localized in the adrenal medulla are called pheochromocytomas (or more uncommonly termed adrenal medullary paragangliomas).[54] The term 'extra-adrenal pheochromocytomas' is used to describe tumors of the sympathoadrenal system. There are no universally established criteria for defining malignancy in pheochromocytomas/ paragangliomas. However, capsular invasion, large tumor size (>5 cm) and weight (>80 g) 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 tumors with an annual incidence of one to four per million population.[55] Furthermore, 0.5 % of subjects with hypertension and 4 % of those with an incidental adrenal mass have pheochromocytoma.[55] The caveat is that these figures are approximate, since until a few years ago 18–60 % of tumors remained undiagnosed.[54] The average lag time from the onset of hypertension to the diagnosis of pheochromocytoma is three years.[56] 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 tumors 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.[57,58] Hypertension—newly diagnosed or an exacerbation of known hypertension, most often paroxysmal—is common, occurring in over 90 % of patients, but is non-specific.[58]

Most paragangliomas are intra-abdominal and adjacent to the adrenals (approximately 85 %). Less than 15 % are intrathoracic and 1–3 % are cervical.[59] Chromaffin-negative neuroendocrine tumors 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.[60]

Genetics

Familial syndromes with pheochromocytomas/paragangliomas include[55] 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 tumors are found twice as often as in adults.[61]

Activating germline mutations in the REarranged during Transfection (*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.[55]

Missense mutations in the *VHL* tumor 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.[62]

The genetic background of pheochromocytomas observed in subjects with neuroectodermal dysplasias is yet to be elucidated. Mutations in the NF-1 tumor 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 %.[56,63]

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.[62] SDHB mutations also predispose to head and neck paragangliomas.[64] SDHC mutations are a rare cause of head and neck paragangliomas.[64] SDHD mutations are associated with benign adrenal and extra-adrenal paragangliomas or multifocal head and neck paragangliomas.[64] SDHB/SDHD mutations have been found in patients with Carney-Stratakis syndrome (they also have paragangliomas).[65] The former are also associated with renal tumors, gastrointestinal stroma cancer and thyroid cancer.[61] Mutations in the *SDHA* and *SDHAF2* (*SDH 5*) family were recently found and linked to hereditary, but not sporadic, paragangliomas.[66–69]

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 tumors bearing NF1 mutations.[70] Expression of SNAIL (a zinc-finger transcription factor) may predict the metastatic potential of pheochromocytoma.[71]

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.[61,72,73] 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.[61]

Biochemical Diagnosis

Chromaffin tumors that are hormonally active may secrete catecholamines episodically, however, they metabolize 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).[61]

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 metadrenaline, whereas in subjects with VHL there is predominantly elevation in normetadrenaline.[61] Care must be taken to normalize metadrenaline levels for populations with normal blood pressure, match them for gender and age,[74] and avoid interference from medications.[75] Dynamic testing is rarely sought.

Gucagon testing is now considered to be obsolete.[76] Suppression with clonidine and measurement of plasma-free normetadrenaline is accurate but applies only to normetadrenaline-secreting tumors.[77] 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.[78] Most abdominal and thoracic SDHB-paragangliomas hypersecrete either normetadrenaline or normetadrenaline and dopamine. Some only hypersecrete dopamine and are almost silent biochemically.[64]

Imaging

CT imaging has 93–100 % sensitivity for detecting intra-adrenal pheochromocytomas of approximately 0.5 cm in diameter.[79] The sensitivity of CT is slightly lower, at 90 %, for localizing extra-adrenal disease of approximately 1 cm in size.[79]

MRI offers slightly better sensitivity. Pheochromocytomas usually show a characteristic very high T2-weighted signal on MRI unless there is a hemorrhage or intratumoral 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 tumor anatomy *vis-à-vis* this region's blood vessels. Conventional or MRI angiography may also be very helpful.[80–82]

Although positive CT/MRI studies can be diagnostic, their specificity may vary from 50–90 %.[55] Thus, negative anatomical imaging studies may not be diagnostic.[83] Furthermore in patients with previous surgery poor quality imaging may lessen utility, particularly if recurrence is suspected.[79] 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 tumors.

- Specific methods for these tumors, since chromaffin tumors 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 tumors or expression of STRs.[84]

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. Nowadays, it is labelled with iodine-123 (^{123}I-MIBG), permitting better quality imaging than ^{131}I-MIBG. CT imaging—standalone or as single-photon emission CT (SPECT)—is also possible.[85]

Dopamine is a catecholamine precursor. PET with ^{18}F-dopamine is better than ^{131}I-MIBG for imaging adrenal and/or benign pheochromocytomas or localizing metastatic pheochromocytomas.[86–88] 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 ^{18}F-DOPA or combined with CT has been used for localizing benign adrenal pheochromocytomas and head and neck paragangliomas with good results.[89–91]

PET with ^{18}F-labelled deoxyglucose (FDG) is currently widely available and is used for localizing various tumors and the staging of neoplastic disease. FDG PET is a convenient and accessible modality for localizing 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.[92–97] Octreotide is an octapeptidic somatostatin analog that is labelled with ^{111}In for SRS. Despite intense splachnic/renal abdominal accumulation, it is a useful non-specific tool for localizing malignant and/or metastatic pheochromocytomas or paragangliomas with a sensitivity approaching 90 %.[98]

^{18}F-dopamine PET/CT is the preferred technique for localizing primary pheochromocytomas and paragangliomas and to rule out metastases. ^{18}F-DOPA PET and ^{123}I-MIBG scintigraphy make an equally good second choice. For patients with known metastatic paraganglioma, ^{18}F-dopamine PET is the choice for those with an unknown genotype. ^{18}F-FDG/^{18}F-dopamine PET should be the preferred option in SDHB mutation carriers. ^{18}F-DOPA/^{18}F-dopamine PET is preferable in non-SDHB patients.[64,99]

Management

The definitive treatment for pheochromocytoma/paraganglioma is surgery. For hormonally active tumors, 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.[56,100,101] Pre-operative management with calcium blockers, nifedipine, angiotensin-converting enzyme (ACE) inhibitors or alpha-methyl-para tyrosine (Demser) have been also used.[100,102,103]

Laparoscopic surgery is possible for abdominal tumors up to 9 cm in diameter. Partial (cortical-sparing) adrenalectomy is used more often—particularly for small tumors.[104–106] A transabdominal approach is reserved for malignant tumors,[107] where debulking surgery and/or adrenalectomy is advised.[108] Non-competitive alpha blockade with long-acting agents such as phenoybenzamine is preferred for keeping blood pressure under control in patients with symptomatic malignant and/or inoperable disease.[56] 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.[53] 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, localization studies should be sought. Sixty per cent of malignant pheochromocytoma sites show avid ^{131}I-MIBG uptake.[103] In specialized centres such tumors can be treated with therapeutic ^{131}I-BG in single or fractionated doses totaling 200–1,400 mCi. Approximately 30 % of tumors show an objective response to therapy (40 % biochemical response) and 40 % of tumors remain stable (20 % biochemically).[108] 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 analogs.[81] Overall, combination chemotherapy with dacarbazine cyclophosphamide and vincristine does not confer any significant survival benefit.[112] Other regimens include etoposide plus cisplatin or etoposide plus lomustine with 5-fluorouracil.[108] 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 hypertension[63,103] and overall 16 % of patients operated on for pheochromocytoma/paraganglioma have recurrent disease within 10 years.[115] In a recent case series of children with pheochromocytoma/paraganglioma, all were found to harbor a predisposing mutation but were alive after follow-up of five years.[116] 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.[117]

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 tumors without metastases. Despite these reports, the use of adrenomedullin RDC1 receptor and SNAIL levels as prognostic factors in pheochromocytoma/paraganglioma is not yet envisaged.[71,118] Pheochromocytoma-paraganglioma syndrome can be diagnosed reliably by immunohistochemistry.[73] 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 tumors are MIBG-avid.[95,96,120] As PET imaging accessibility increases worldwide, more patients with pheochromocytoma/paraganglioma will be evaluated with PET studies. Ultratrace ^{131}I-MIBG has very high specific activity and holds promise for future therapeutic applications.[48]

New modalities for the medical management of malignant pheochromocytomas are currently being assessed. Among these, the combination of temozoline and thalidomide or therapeutic somatostatin analogues have shown some encouraging results.[108] ■

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