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A CLINICAL OVERVIEW OF PHEOCHROMOCYTOMAS/ PARAGANGLIOMAS AND CARCINOID TUMORS

Ioannis ILIAS[1] and **Karel PACAK**[2]

[1] Department of Endocrinology, E. Venizelou Hospital, 2, E. Venizelou Sq., Athens GR-11521, Greece; E-mail: iiliasmd@yahoo.com

[2] Section on Medical Neuroendocrinology, National Institute of Child Health and Human Development, National Institutes of Health, Building 10, CRC, Room 1E-3140, 10 Center Drive MSC-1109, Bethesda, Maryland 20892-1109, USA; E-mail: karel@mail.nih.gov

Abstract

Pheochromocytomas/paragangliomas are rare tumors, most are sporadic. Biochemical proof of disease is better with measurement of plasma metanephrines and less cumbersome than determinations in urine; its implementation is expanding. Anatomical imaging with computed tomography or magnetic resonance imaging should be followed by functional (nuclear medicine) imaging: chromaffin-tumor-specific methods are preferred. Treatment is surgical; for non-operable disease other options are available. Overall 5-year survival is 50%.

Carcinoid tumors derive from serotonin-producing enterochromaffin cells in the fore-, mid- or hindgut. Biochemical screening (and follow-up) is done with measurements of 5-hydroxyindoloacetic acid in urine. For most carcinoids functional imaging is better than other modalities in localizing primary tumors. Surgery is the treatment of choice; non-resectable tumors are treated with somatostatin analogs or chemotherapy. Overall 5-year survival for patients with carcinoids is 67%.

Keywords

Pheochromocytomas; paragangliomas; radionuclide imaging; carcinoid tumors

Pheochromocytomas/paragangliomas

Chromaffin cells are post-ganglionic sympathetic neurons that produce catecholamines [1]. When fresh tissue samples are oxidized with certain fixatives their catecholamine content is stained dark grey-brown (“pheos” in Greek). These cells are mainly located in the adrenal medulla; nevertheless, accessory adrenal tissue comprising both cortical and medullary elements has been reported to be particularly localized in the celiac plexus area in 16% of autopsy cases [2]. Tumors arising from extra-adrenal chromaffin cells are termed paragangliomas and they can be found along the paravertebral and paraaortic axes (sympathetic paraganglia have a neck-to-pelvis distribution, parasympathetic paraganglia are found in the neck and skull base) [3]. The paragangliomas that are localized in the adrenal medulla are called pheochromocytomas (or more uncommonly termed adrenal medullary paragangliomas) [4]. Lending itself to some confusion, the term *extraadrenal pheochromocytomas* is used to

Correspondence to be addressed to: Dr Karel Pacak, M.D., Ph.D., D.Sc., Professor of Medicine, Chief, Section on Medical Neuroendocrinology, National Institute of Child Health and Human Development, National Institutes of Health, Building 10, CRC, Room 1E-3140, 10 Center Drive MSC-1109, Bethesda, Maryland 20892-1109, USA; E-mail: karel@mail.nih.gov.

describe tumors of the sympathoadrenal system. There are no universally established criteria for defining malignancy in pheochromocytomas/paragangliomas. Capsular invasion and large tumor size (>5 cm in size and >80 g in weight) may be indicators of malignancy; the clinical course may indicate malignancy (particularly with recurrent or metastatic disease).

Pheochromocytomas

Pheochromocytomas are rare tumors with an annual incidence of $1–4/10^6$ population (Table 1); furthermore 0.5% of subjects with hypertension and 4% of those with an incidental adrenal mass harbor a pheochromocytoma [5]. Nevertheless, these figures are approximate, since until a few years ago 18%–60% of tumors remained undiagnosed during life [4]. The average lag time from the onset of hypertension to the diagnosis of pheochromocytoma is 3 years [6]. Peak age for diagnosis of pheochromocytomas is between 40–50 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.

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 [7,8]. Hypertension (newly diagnosed or exacerbation of known hypertension; most often paroxysmal) is very common (in over 90% of patients) but non-specific [8].

Paragangliomas

Most paragangliomas are intraabdominal and adjacent to the adrenals (approximately 85%), whereas fewer than 15% are intrathoracic and 1%–3% are cervical [9].

Interestingly, neuroendocrine tumor structures in the head and the neck regions that are chromaffin-negative and related to the parasympathetic nervous system, such as those originating from the carotid bodies or the jugular bulbs, are also termed paragangliomas [10]. These rare tumors usually do not secrete catecholamines (and if they do it is mostly not up to a clinically appreciable level) and follow an indolent no symptom course as painless neck masses.

Genetics of pheochromocytomas/paragangliomas

Familial syndromes with pheochromocytomas/paragangliomas include multiple endocrine neoplasia 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; see below) [5].

Activating germline mutations in the *RET* (***RE***arranged during ***T***ransfection) protooncogene (usually in codons 634 or 918; 10q11.2) are implicated in the abnormal cellular proliferation of the MEN 2 syndrome. Pheochromocytomas are usually adrenal and benign in MEN 2 and bilateral in more than 50% of patients [5].

Commonly missense mutations in the *VHL* tumor suppressor gene (usually in codon 167; 3p25–26) are implicated in the pathogenesis of VHL syndrome, with 25%–50% of subjects having mostly benign pheochromocytomas (and slightly less than 50% with bilateral disease)[5].

The genetic background of pheochromocytomas observed in subjects with neuroectodermal dysplasias is yet to be elucidated, although 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% [6,11].

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 extraadrenal and/or malignant disease is high for *SDHB* mutation carriers [5,12,13].

The current paradigm of pheochromocytomas being "10% tumors", i.e. 10% extraadrenal, 10% malignant or 10% hereditary is in flux, since mutations in the *SDHB, SDHD, VHL* or *RET* genes have been identified in 12%–25% of patients with apparently sporadic pheochromocytomas [14,15]. Consequently, in patients (currently mainly of age 50 or younger) with apparently sporadic pheochromocytomas and their kin, mutation screening is advised [6,16].

Biochemical diagnosis

Hormonally active chromaffin tumors may secrete catecholamines episodically but they metabolize catecholamines to metanephrines continuously (Figure 1). Free metanephrines in plasma and 24-hour urinary fractionated free metanephrines are accurate - but not infallible - methods for establishing the diagnosis of pheochromocytoma. Their respective sensitivity ranges from 96%–100% and 92%–99% and their specificity is 87%–92% and 64%–72% [17–20]. The measurement of plasma metanephrines is less cumbersome than determinations in urine and its implementation is expanding. Urine and plasma measurement of metanephrines should be considered as being complementary rather than mutually exclusive methods. Care to normalize metanephrine levels for populations with normal blood pressure, as well as for gender and age must be taken. [21]. In any biochemical evaluation for pheochromocytoma/paraganglioma care must be taken to avoid interference from medications [22].

Dynamic testing is rarely sought: glucagon testing has been insensitive in the diagnosis of familial pheochromocytomas [23]. Suppression with clonidine and measurement of plasma free normetanephrine is very accurate but applies only to norepinephrine-secreting tumors [24].

Head and neck paragangliomas are rarely hormonally active, in such cases biochemical diagnosis is not useful for assessing the patients' status.

Tumor localization

Anatomical imaging

Computed tomography (CT) has 93%–100% sensitivity for detecting intraadrenal pheochromocytomas of approximately 0.5 cm in diameter [25]. The sensitivity of CT is slightly lower at 90% for localizing extraadrenal disease of approximately 1 cm in size [25].

Magnetic resonance imaging (MRI) offers slightly better sensitivity. Pheochromocytomas usually show a characteristic very high T2-weighted signal on MRI unless there is hemorrhage or intratumoral necrosis. MRI delineates the relationship of pheochromocytomas with blood vessels; this feature is appreciated when surgery is envisaged. CT/MRI should be used in patients with biochemically-proven pheochromocytoma/paraganglioma. For most patients imaging is limited to the adrenals/abdomen, whereas evaluations in the thorax, neck and head are used when there is suspicion of malignant/metastatic disease. For head and neck paragangliomas MRI may delineate better the tumors' anatomy vis-à-vis this region's blood vessels; conventional or MR angiography are also very helpful [26–28].

With the reported high sensitivity levels, negative CT/MRI studies are diagnostic; i.e., there is a low likelihood of having pheochromocytoma. However, the specificity of CT/MRI may vary from 50%–90% [5]. Thus, positive anatomical imaging studies may not be diagnostic, i.e., there are several causes for false-positive studies. [29]. Furthermore, in patients with previous surgery poor quality imaging may lessen utility, particularly if recurrence is suspected [25]. For such cases, as well as for cases of extraadrenal or malignant/metastatic disease, the use of functional (nuclear medicine) methods is advocated.

Functional imaging

There are two facets of nuclear medicine localization methods for chromaffin tumors: specific methods for these tumors (since chromaffin tumors express the human norepinephrine transporter [hNET], thus permitting the use of radiolabeled ligands of molecules that enter the catecholamines' synthesis pathway or their analogs and specific vesicular monoamine transporters [VMATs] for storage into intracytoplasmic vesicles) and non specific methods that are not related to the synthesis, uptake or storage of catecholamines (making use of the tumors' high glucose metabolism or expression of somatostatin receptors) [30]. Specific functional imaging methods should be sought first and, if negative, nonspecific modalities should then be used, particularly if recurrent, metastatic or malignant disease is suspected.

Chromaffin-tumor-specific functional imaging

Metaiodobenzylguanidine (MIBG) is a catecholamine precursor that is taken into pheochromocytoma cells via hNET. Currently it is more commonly labeled with iodine-123 [^{123}I] than iodine-131 [^{131}I], since it lacks beta particle emission (and entails low radiation exposure), has a short half-life (13.2 h for [^{123}I] vs. 8 days for [^{131}I]) and its principal emission photon energy (159 kEv for [^{123}I] vs. 364 kEv for [^{131}I]) lies closer to the 140 kEv level (that of [^{99m}Tc]) around which gamma cameras are designed to operate. [^{123}I]MIBG permits better image quality than [^{131}I]MIBG since 10 times more counts are acquired and tomographic imaging is possible using single photon emission computed tomography(SPECT)[30].

The sensitivity of [^{123}I]MIBG is 83%–100% versus 77%–90% of [^{131}I]MIBG (sensitivity is lower for extra-adrenal and/or metastatic disease) [25,31]; their specificity is 95%–100% [32,33].

With positron emission tomography (PET), short-lived radioligands can be administered and functional imaging (including tomographic views) with higher spatial resolution than conventional scintigraphic imaging can be obtained.

Hydroxyephedrine (HED) resembles norepinephrine but is not susceptible to intracellular degradation by monoamine oxidase (MAO); it enters chromaffin cells via hNET. Labeled with the positron emitter carbon-11 [^{11}C], it enables PET imaging of pheochromocytomas. The 20 minute half-life of [^{11}C] precludes its widespread use and limits it to the few centers with an on-line cyclotron and synthesis capability [34,35]. Epinephrine is a catecholamine that resembles norepinephrine and is a substrate for catechol-O-methyltransferase (COMT) and MAO, which are catecholamine-catabolizing enzymes. PET with [^{11}C]-labeled epinephrine has been used to localize pheochromocytomas but it was not on a par with [^{123}I]MIBG [36].

Dopamine (DA) is a catecholamine precursor and PET with fluorine18-DA ([^{18}F]DA) is better than [^{131}I]MIBG for imaging adrenal and/or benign pheochromocytomas or localizing metastatic pheochromocytomas [32,37,38]. Furthermore, the 110 minute half-life of [^{18}F] permits tracers radiolabeled with this nuclide to be distributed to centers for diagnostic imaging.

Dihydroxyphenylalanine (DOPA) is converted into dopamine and then transported into pheochromocytomas by hNET (the large neutral amino acid transporter may also play a role

in this). PET with [^{18}F]DOPA has been used for localizing benign adrenal pheochromocytomas and paragangliomas [39]; results are considered to be excellent [40].

Non-chromaffin-tumor-specific functional imaging

PET with [^{18}F]-labeled 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 those pheochromocytomas that are negative with specific functional imaging modalities (particularly metastatic disease) [41,42]. In patients with *SDHB*-associated pheochromocytoma/paraganglioma (that are more prone to malignant disease) FDG PET has 97%–100% sensitivity in localizing tumor lesions (whereas the sensitivity of [^{123}I]MIBG is 65%–80% and that of [^{18}F]DA PET is 70%–88%) [43].

Both pheochromocytomas and paragangliomas express somatostatin (ST-R) receptors to some extent (mostly type 2, 3 and 5 ST-Rs), although conflicting results have been presented [44–49]. Octreotide is an octapeptidic somatostatin analog that is chelated with diethylenetriaminepentaacetate (DTPA) and labeled with indium-111 [^{111}I] for ST-R scintigraphy (SRS). Despite intense splenic and renal accumulation it is useful for localizing malignant/metastatic pheochromocytomas or paragangliomas with sensitivity approaching 90% [25,28,50–54].

Management

Definitive treatment for pheochromocytoma/paraganglioma is surgical. For hormonally active tumors a preoperative blood pressure lowering/normalization regimen should be followed. Selective alpha-1 blockers (prazosin, doxazosin and others) or nonselective noncompetitive alpha blockers (phenoxybenzamine) are the mainstay of treatment. If, despite selectivity of the alpha blockers tachycardia ensues, beta blockade is then given [6,55,56]. Preoperative management with calcium blockers is reported to have good results but is not widely used [57]. Nifedipine, angiotensin-converting enzyme inhibitors or alpha-methyl-para tyrosine (Demser) are also effective [55,58]. Laparoscopic surgery is possible for abdominal tumors up to 9 cm in diameter and cortical-sparing adrenalectomy can be done for patients with hereditary tumors [59]. A transabdominal approach is reserved for malignant tumors [60], where debulking surgery and/or adrenalectomy is advised [61]. Noncompetitive alpha blockade with long-acting agents like phenoybenzamine is preferred for keeping blood pressure under control in patients with symptomatic malignant and/or inoperable disease [6]. Demser is also given to block catecholamine synthesis.

Biochemical evaluation with plasma and/or urine metanephrines should be done 2–6 weeks post surgery [3]. Annual biochemical work-up for the first five years and once every two years thereafter is the minimum required for follow-up. In case of persistence or recurrence of disease localization studies should be sought.

Sixty percent of malignant pheochromocytoma sites show avid [^{131}I]MIBG uptake [58]. In specialized centers such tumors can be treated with therapeutic [^{131}I]MIBG in single or fractionated doses totaling 200–1400 mCi; approximately 30% of tumors show objective response to therapy (40% biochemical response) and 40% of tumors remain stable (20% biochemically) [61]. This treatment is almost as onerous as chemotherapy, particularly regarding bone marrow suppression [62–64]. Less experience has been obtained with labeled somatostatin analogs [27]. Chemotherapy is chosen in case of rapidly progressive metastatic pheochromocytoma or in those patients where functional imaging with MIBG is negative [65]. Combination chemotherapy with cyclophosphamide, vincristine and dacarbazine shows transient partial remission in one third of patients [61]; other regimens include etoposide and cisplatin or etoposide and lomustine with 5-fluorouracil [61].

Prognosis

Life expectancy in patients with benign pheochromocytoma/paraganglioma that has been successfully excised was considered not to be compromised; nevertheless, 50% of patients that are successfully operated remain with hypertension [11,58] and overall 16% of patients operated for pheochromocytoma/paraganglioma have recurrence within 10 years post-surgery [66]. Furthermore, in a large cohort of patients with pheochromocytoma mortality from a second neoplasia was fourfold higher compared to the general population [67]. There are no criteria to predict survival of malignant pheochromocytoma, since, albeit surprisingly, 5-year survival rates of 55% have been reported even with a combination of therapeutic modalities [68].

Perspectives

Quantification of pheochromocytoma/paraganglioma VMAT content may indicate whether the tumors are MIBG-avid [47,48]. As PET imaging accessibility increases worldwide, more patients with pheochromocytoma/paraganglioma will be evaluated with PET studies. New modalities for the medical management of malignant pheochromocytomas are assessed; among these, the combination of temozoline and thalidomide or therapeutic somatostatin analogs have shown some encouraging results [61].

Carcinoid tumors

Carcinoid tumors derive from serotonin-producing enterochromaffin cells. According to their embryonic origins these are classified into 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 the gonads) and hindgut (“silent”; originating from the transverse colon to the rectum) carcinoids (Table 1). More than 60% of carcinoids originate in the gastrointestinal tract (with half of these in the small intestine) and the remaining from the lungs/bronchi. Analysis of relatively more surgical pathology specimens of the appendix compared to other tumors may have biased upwards the high percentage (up to 35%) of appendiceal carcinoids. The broad spectrum of these tumors and their multifaceted presentation lends to some confusion and even the term “carcinoid” is considered to be obsolete; “neuroendocrine tumor” may be more appropriate, particularly for gastrointestinal tumors [69–71]. The overall incidence of carcinoids is estimated at 1–2/10^6 population, although from autopsy data even a 1% incidence may be a realistic figure [72]. Diagnosis may elude the clinician: patients with midgut carcinoids may complain of vague abdominal symptoms for a long time (approximately 9 years) before classic symptoms and signs such as flushing and excess gastrointestinal motility are observed (for 90% of symptomatic patients at that time the disease has metastasized) [72,73]. Sixty percent of patients with carcinoids, 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 [70,72]. Interestingly these valvular lesions are identical to those observed in patients that were exposed to fenfluramine/dexfenfluramine [72].

Genetics of carcinoids

Mainly gastric carcinoids are found in 10% of individuals with Multiple Endocrine Neoplasia (MEN) type 1, which is an autosomal dominant disorder caused by deletion of the *MEN1* suppressor gene on chromosome 11q13. Forty to eighty percent of patients with sporadic carcinoids also harbor loss of heterozygozity in chromosome 11 or deletion of the *MEN1* gene [71,72]. Pulmonary carcinoids are associated with mutations in the p53 suppressor gene and variability in *bcl-2* expression [72].

Biochemical diagnosis

Foregut and midgut carcinoids metabolize tryptophan to 5-hydroxytryptophan (5-HTP), and synthesize and secrete serotonin (Figure 1); 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 [74,75]. Levels of 5-HIAA also correlate with tumor burden; sensitivity is 70% whereas specificity is 90%–100% [72]. Chromogranin A is a tumor marker of neuroendocrine tumors with a sensitivity of 80%–100% for carcinoids [76]; although it is not specific for carcinoids it is also used as a screening test, as it is elevated in most cases of metastatic foregut and midgut carcinoids [77]. Foregut carcinoids may also secrete hormones such as corticotrophin, leading to Cushing's syndrome [78]. Midgut carcinoids may also synthesize and secrete tachykinins (neurokinin A and substance P), prostaglandins and catecholamines [73].

Tumor localization

Anatomical imaging

CT/MRI is used to evaluate primary carcinoid tumors and their metastases (particularly in the liver and lymph nodes: sensitivity varies from 50%–85%) [79]. Tumors are multiple in 40% of cases and calcifications are seen in 70% of mesenteric masses [79]. The lower limit of detection ranges from 1 cm to 2 cm; lesions have low density (on CT) or low signal (on MRI) in unenhanced views, enhance avidly in the early arterial phase of contrast-enhanced examinations and wash out early [79]. Primary small intestine tumors are better seen with barium follow-through or better with enteroclysis. For most carcinoids functional imaging is better than other modalities in localizing primary tumors [74].

Functional imaging

Carcinoids, like other neuroendocrine tumors, take up amine precursors like DOPA. PET with [^{18}F]DOPA has 46%–98% sensitivity in detecting carcinoids (particularly when it is combined with CT) [80,81]

Carcinoids express ST-R-2 and -5 and SRS has sensitivity ranging from 60% (for silent) to 90% (for symptomatic patients with the carcinoid syndrome) in localizing these tumors [74]. A positive SRS result may also be predictive of response to octreotide therapy (see below) [82]. In a recently published study of 84 patients with neuroendocrine tumors (56 of whom had carcinoid tumors) PET was done using Gallium68-labeled 1,4,7,10-tetraazacyclododecane-*N*,*N*′,*N*″,*N*‴-tetraacetic acid-D-Phe(1)-Tyr(3)-octreotide ([^{68}Ga]DOTATOC; a novel ST analog) and compared to SRS and CT. Results were excellent, with 97% sensitivity and 92% specificity, better than SRS or CT (with sensitivity 52% and 61% and specificity 92% and 71%, respectively) [83]. In another study of patients with primary or recurrent neuroendocrine tumors, PET with [^{68}Ga]DOTA-Tyr(3)-Thr(8)-octreotate (another ST analog; [^{68}Ga] DOTATATE) had 82% sensitivity [84].

Scintigraphy with [^{131}I]MIBG has 55%–85% sensitivity and 95% specificity in localizing carcinoids [72] and the combination of SRS and MIBG scintigraphy results may provide even better localizing sensitivity [82].

Management

Endoscopic resection (where possible), limited excision surgery (for tumors < 1 cm), extensive surgery (for tumors > 1 cm) and hepatic resection (for liver involvement of <50%) are the treatments of choice for carcinoids [85]. 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 [70,72,86]. Patients with advanced disease (and positive SRS) are candidates for somatostatin analog therapy. In particular, octreotide can resolve carcinoid syndrome symptoms in 75% of patients, with biochemical response in 25%–75% of these; CT/MRI-documented tumor response is much lower at 10% [72]. Analogous results regarding biochemical response and tumor size have been observed with interferon alpha therapy [70,87]. Chemotherapy with 5-flurouracil, streptozocin or doxorubicin has a 20% response rate [70]. [^{131}I]MIBG has been used to treat MIBG-avid carcinoid tumors with some success [88,89].

Prognosis

Overall 5-year survival for patients with carcinoids is 67%, being highest at 78% for patients with localized disease and slightly lower at 72% for those with regional metastases. On the contrary, survival of patients with distant metastases is lower at 40% [72].

Perspectives

Multidetector CT may enable better anatomical imaging for the evaluation of carcinoids [90]. Video capsule endoscopy is currently being evaluated as an alternative to “classic” endoscopy [82]. PET with [^{11}C]-labeled 5-HTP or [^{18}F]-labeled DOPA are very useful for the localization of carcinoids and should become more available to specialized medical centers [91]. Other PET ligands, such as [^{68}Ga]DOTANOC (with affinity for ST-R-2 and -5) are being evaluated for neuroendocrine tumors, including carcinoids [92]. Therapy with Indium111- or Yttrium90-radiolabeled octreotide and Lutetium177-radiolabeled octreotate holds promise for inoperable disease [93,94]. There is also therapeutic potential with agents that target tumors’ high vascularity and in particular vascular endothelial growth factor (VEGF); these include recombinant human endostatin, thalidomide, bevacizumab and sunitinib [70].

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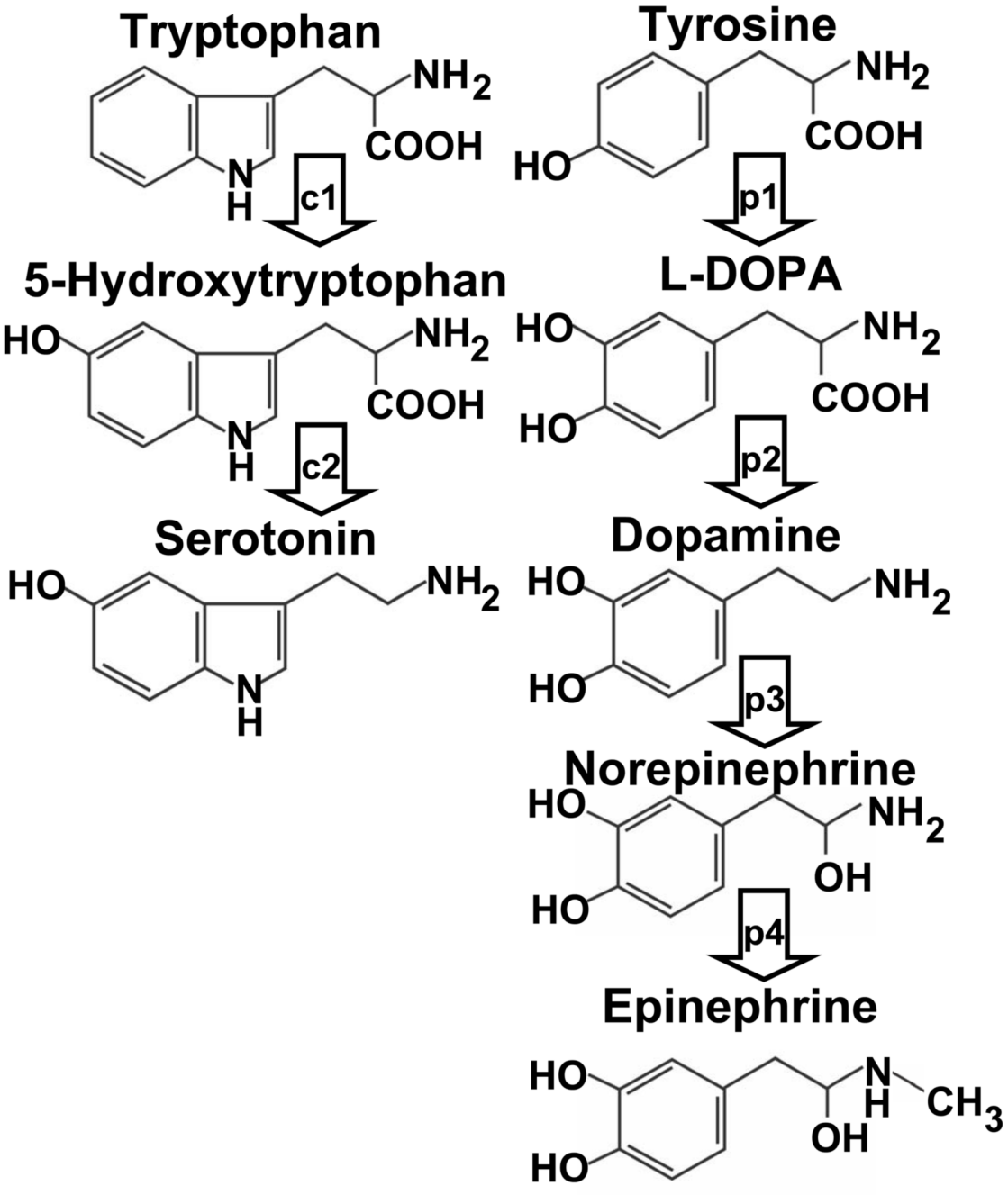

Figure 1.
Biosynthetic pathways in pheochromocytomas/paragangliomas and carcinoids; *c1: tryptophan hydroxylase; c2: hydroxytryptophan decarboxylase; p1: tyrosine hydroxylase; p2: DOPA decarboxylase; p3: dopamine-beta-hydroxylase; p4: phenylethanolamine-N-methyltransferase*

Table 1

An overview clinical characteristics of pheochromocytomas/paragangliomas and carcinoids

	Pheochromocytomas/paragangliomas	Carcinoids
Epidemiology	1–4/10^6	1–2/10^6
Localization	Adrenal and extra-adrenal (mainly torso)	Fore-, mid- and hindgut
Genetics	Mostly sporadic; however an increasing number of patients (>20%) are currently found to have mutations in *RET, VHL, NF-1, SDHx*	Mostly sporadic; mutations in *MEN1, bcl2*
Products	Catecholamines	Serotonin
Signs	Tachycardia, diaphoresis, hypertension (paroxysmal); pallor	Excess gastrointestinal motility
Symptoms	Cephalalgia, Palpitations	Flushing
Anatomical imaging	CT, MRI	CT, MRI
Functional imaging	[^{18}F]DA, [^{18}F]DOPA, [^{123}I]MIBG, SRS	[^{18}F]DOPA, [^{11}C]5-HTP, SRS
Median survival	50%	67%

Please see text for abbreviations