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Surgical approaches and results of treatment for hereditary paragangliomas

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Paragangliomas (PGL) are rare neuroendocrine tumours; parasympathetic PGL are predominantly non-secreting and located at the skull base and neck, while sympathetic PGL are typically catecholamine-secreting and located at abdomino-pelvic level. Approximately 40% of PGL may be caused by germline mutations; hereditary variants should be suspected especially in case of positive family history, early onset, multifocal, or recurrent PGL. Significant genotype–phenotype correlation has been recognized, including syndromic presentation, location, multifocality and risk of malignancy. Surgical resection remains the only curative strategy, but the outcomes may be unsatisfactory because of surgical morbidity and recurrence rate. However, due to the rarity of the disease, most data derive from case-report or limited series. This paper was aimed to review the available literature on the epidemiology, diagnosis, clinical features, treatment of PGL in order to discuss the surgical approach and the results of treatment in hereditary PGL.

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Introduction

Paragangliomas (PGL) are neuroendocrine neoplasms deriving from paraganglia, specialized neural crest-derived groups of chromaffine cells able to synthesize and secrete various amines.

Parasympathetic paraganglia are localized almost exclusively in head and neck region along the branches of the cranial nerves, acting as chemoreceptors [1]. The sympathetic paraganglia are symmetrically distributed along the paravertebral axis from the superior cervical ganglion to the pelvis and predominantly located in the abdomen where the largest ones are the adrenal medullas.

Because of the widespread distribution of paraganglia, PGL can occur at virtually all locations in the body except the brain and bone. Parasympathetic-derived PGL arise from parasympathetic ganglia located along the cranial nerves in the neck and at the base of the skull (head and neck paraganglioma, HNPGL); sympathetic-derived PGL arise from adrenal medulla (pheochromocytoma, PHEO) or extra-adrenal sympathetic ganglia of thorax, abdomen, and pelvis (Table 1) (Figs. 1 and 2) [2].

Usually, sympathetic PGL tend to be functional and symptomatic, while HNPGL are non-functional and may present with mass effect [1–3].

About 40% of PGL are caused by specific germline mutations and are hereditary, even if penetrance and clinical expressivity may be incomplete. In this setting PGL may be also associated to other tumors (syndromic PGL) [3]. During the last two decades more than 20 germline mutations causing PHEO/PGL have been identified; they can be grouped into two major clusters: mutations involved with the pseudo-hypoxic pathway and reduced oxidative response (including *VHL*, *EGLN1*, *SDH*, *IDH*, *HIF2A*, and *FH* genes), and mutations associated with abnormal activation of kinase signaling pathways (*RET*, *NF1*, *KIF1Bbeta*, *MAX* and *TMEM127* gene mutations) [4]. The phenotype of syndromic PHEO/PGL, including secretotype, age at onset, tumor aggressiveness, clinical presentation and associated diseases/neoplasia, is influenced by genotype as well as anatomic site of origin (Table 2). Thus, all individuals with PHEO/PGL should be referred for clinical genetic testing. Hereditary PHEO/PGL should be suspected in any individual with a PGL or PHEO, particularly those with family history of PHEO/PGL or sudden unexplained death of cardiovascular origin, or with multiple, bilateral, early onset (<45 years), extra-adrenal and metastatic disease. In fact, compared to sporadic variants, syndromic and hereditary PGL may occur at earlier age; they may occur at multiple sites (even if asynchronously), and as a malignant or recurrent disease (Fig. 3). However, familial history may be absent because of variable penetrance of putative genes and the phenomenon of parental imprinting (as in case of *SDHD* mutations), simulating an apparently sporadic variant [5].

PGL are usually benign tumors, but malignancy varies between 10 and 40%; formally it cannot be predicted only by histology but should be definitively confirmed in presence of regional lymph-nodal or distant metastases to non-endocrine tissue. However, rapidly enlarging painful mass, younger onset age and specific genetic background (*SDHB*, *FH* and *MDH2* mutations) are risk factors for malignancy [6] (Table 2).

Surgery represents the only curative treatment in hereditary PGL but it should be tailored according to the age of patient, genotype, hormonal secretion, biologic behaviors/aggressiveness, number and location of PGL, and the presence of associated tumors, as occur in MEN2, VHL and *SDHx*-related PGL [7]. The timing, the extent and the approach of surgery (minimally invasive or open) should take into account the variable behaviors of these tumors, the multiple locations (neck, thorax, abdomen) in the

Table 1
Sympathetic and parasympathetic paragangliomas.

	Sympathetic Paraganglioma	Parasympathetic Paraganglioma
Location	Thoracic-Abdominal	Head and Neck
	Adrenal 85%	Carotid body 60%
	Extra-adrenal 15%	Jugulo-tympanic 30%
	Thoracic <2%	Vagal 5%
	Genitourinary 1%	Other sites <5%
Secretive status	Frequent	Uncommon
Familial history	Variable	Common
Malignancy	14–50%[a]	1–13%[a]

[a] Varies according to site of origin of the paraganglioma.

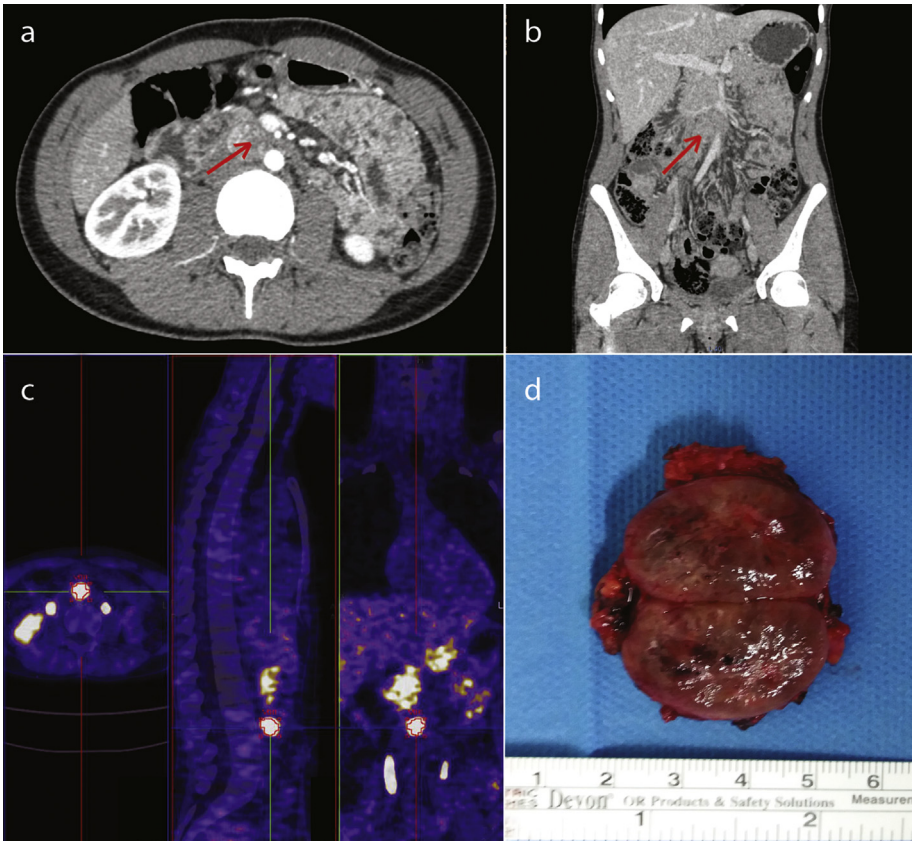

Fig. 1. Hereditary interaortocaval paraganglioma (red arrow) in a 25 years old woman: a, b: Axial and coronal Computed Tomography reconstructions showing a 30 mm mass located between aorta and inferior vena cava, below the renal vessels; c: DOPA-PET uptake of the mass; d. Surgical specimen (sectioned).

same patient, and the tendency to recur metachronously (with variable disease-free interval) and the surgical morbidity. Thus, alternative strategy to surgery and a prolonged, long-life follow-up may be required in patients with hereditary PGL.

The aim of this paper is to develop a surgical concept for the most frequent hereditary PGL based on type of mutation, risk of malignancy, and risk factors for potential surgical complications.

Head and neck paraganglioma

HNPGL are neural crest-derived neuroendocrine neoplasms arising from parasympathetic head and neck paraganglia along the branches of the glossopharyngeal and vagus nerves, and account for 7–16% of all chromaffine tumors [8,9].

Although most HNPGL are sporadic, nearly 40% presenting with a single mass and 90% with multifocal and/or bilateral disease are hereditary. Hereditary HNPGL are most frequently associated with PGL syndromes due to germline mutations in *SDH* subunits (Table 2): *SDHD* mutations have been found in up to 51% of cases, *SDHB* in up to 34%, *SDHC* in up to 14%, while *SDHA* and *SDHAF2* were less frequent. *VHL* and *TMEM127* mutations have been rarely found in HNPGL [10]; in *RET*, *NF1*, and *MAX* mutations only individual cases have been reported. Hereditary PGL syndromes should be suspected in any individual with a HNPGL, particularly young patients with multiple and/or bilateral tumors. HNPGL may arise in carotid body (60%), middle ear (30%), vagal (10%), and larynx (very rarely).

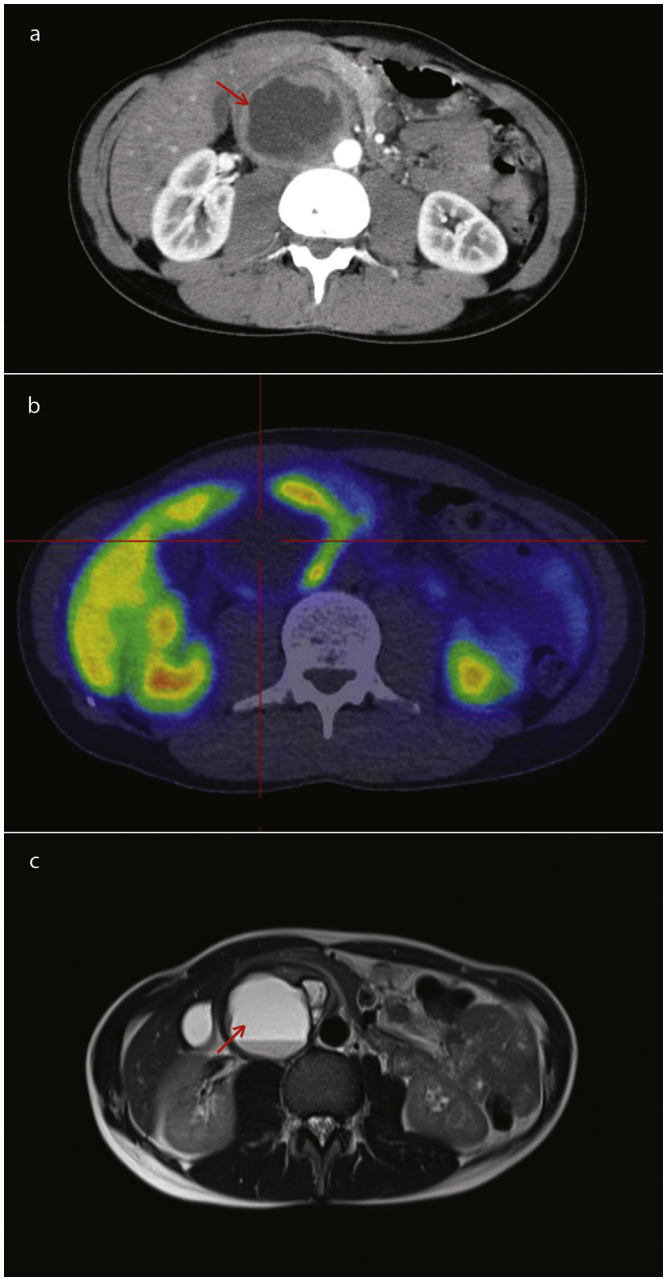

Fig. 2. Paraortic paraganglioma: a: Abdominal CT scan showing an heterogeneous 7 cm mass; b: 68-Ga-DOTATOC uptake; c: Magnetic Resonance Imaging.

Diagnostic work-up and radiological imaging

The majority of HNPGL, both sporadic and hereditary, are non-secreting tumors, with low expression of tyrosine hydroxylase, the rate-limiting enzyme for catecholamine synthesis, and lack of

Table 2
Genotype-phenotype correlation in hereditary paragangliomas.

Gene, Chromosome Location	Syndrome	Location	Biochemistry	Rate of metastatic disease (%)	Multifocality (%)	Recurrence rate (%)	Bilateral adrenal involvement (%)	Associated tumors or clinical features
NF1, *17q11.2*	NF1	PHEO >> AT-PGL	A	3–5	0	11	0	Optic glioma, breast cancer MPNST, cafè-au-lait spots, freckels, Lisch nodules, PHEO
VHL, *3p25.3*	VHL	PHEO >> AT-PGL > HNPGL	NA	5–6	0	6	64	Hemangioblastoma, RCC, testicular tumors, pancreatic NET, retinal abnormalities
RET, *10q11.21*	MEN2	PHEO	A	17	0	17	68	MTC, primary hyperparathyroidism
SDHA, *5p15.33*	PGL5	HNPGL > PHEO + AT-PGL	NA	12	9	unknown	4	GIST, pituitary tumors
SDHAF2, *11q12.2*	PGL2	HNPGL	A	10	39	unknown	37	
SDHB, *1p36.13*	PGL4	AT-PGL > PHEO > HNPGL	NA, D, Ø	37	11	unknown	0	RCC, GIST, pituitary tumors
SDHC, *1q23.3*	PGL3	HNPGL > PHEO + AT-PGL	NA, D, Ø	8–28	0–14	0	0	RCC,GIST
SDHD, *11q23.1*	PGL1	HNPGL > PHEO > AT-PGL	NA, D	6–31	25	58	0	GIST, pituitary tumors
TMEM127, *2q11.2*	TMEM127-related Familial PGL	PHEO >> HNPGL	A, NA	5–10	39	unknown	37–50	RCC, meningiomas
MAX, *14q23.3*	MAX-related Familial PGL	PHEO	NA, A	9	82	unknown	73	RCC
EPAS1/HIF2A, *2p21*	ECYT4	PHEO + AT-PGL	NA	29	100	100	possible	Polycythemia, somatostatinoma, retinal abnormalities, organ cysts (Pacak-Zhuang syndrome)
FH, *1q42*	HLRCC	PHEO and/or AT-PGL > HNPGL	NA, Ø	3–5	3–5	unknown	1–5	RCC, leiomioma

MEN 2: Multiple Endocrine Neoplasia type 2; *NF1*: Neurofibromatosis type 1; *VHL*: Von Hippel Lindau syndrome; *PGL1-5*: Hereditary Paraganglioma syndrome type 1–5; *ECYT4*: Familiar Erythrocytosis type4; *HLRCC*: Hereditary Leiomyomatosis and Renal Cell Carcinoma; *PHEO*: Adrenal Pheochromocytoma; *AT-PGL*: abdomino-thoracic paraganglioma; *HNPGL*: Head Neck Paraganglioma; *A*: Adrenergic; *NA*: Noradrenergic; Ø: biochemically silent; *MTC*: medullary thyroid cancer; *MPNST*: malignant peripheral nerve sheat tumor; *RCC*: renal cell carcinoma; *NET*: neuroendocrine tumors; GIST: Gastrointestinal Stromal Tumor.

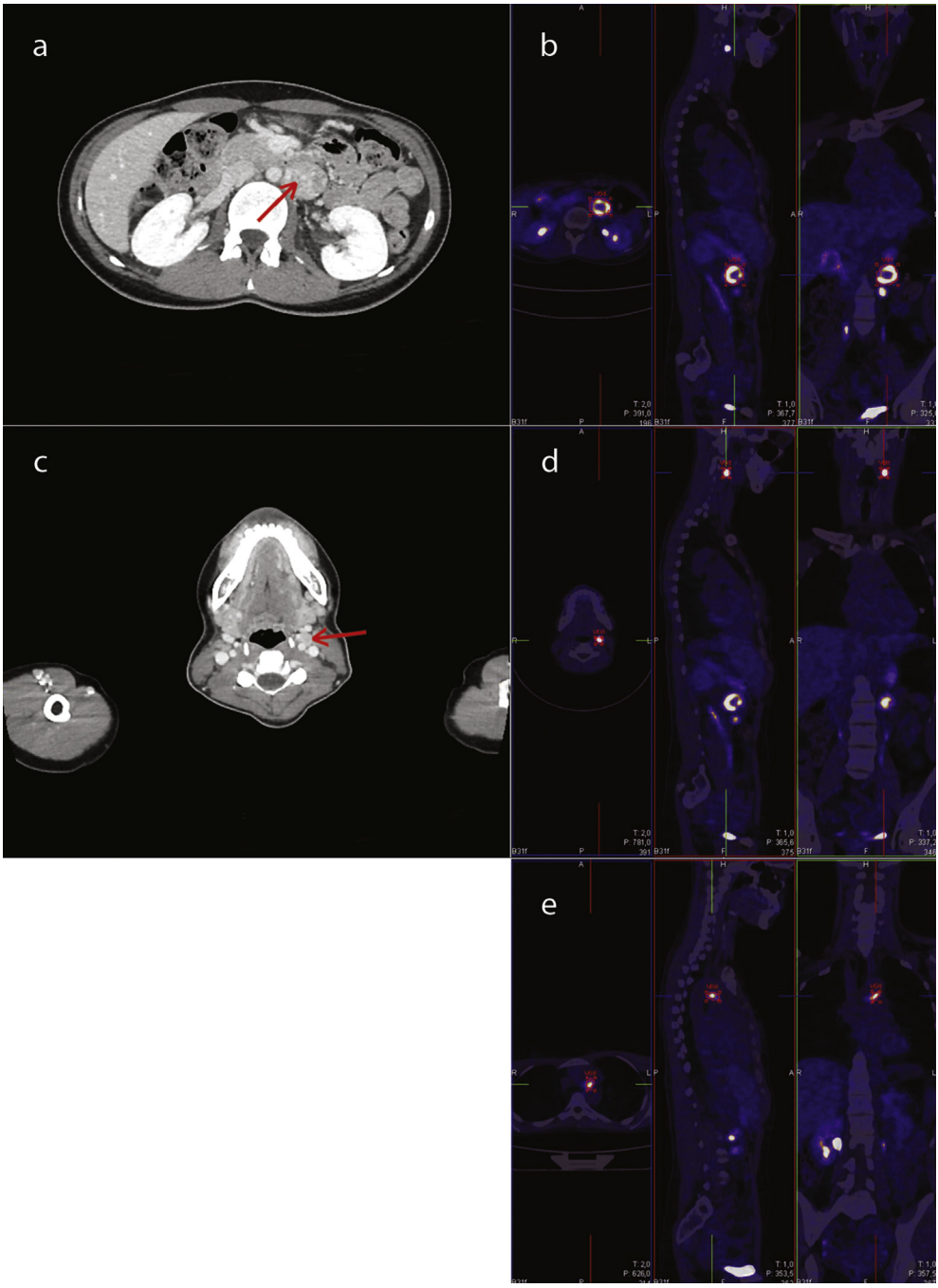

Fig. 3. Hereditary multiple paragangliomas in a 26 years old woman: Left paraortic paraganglioma (a: computed tomography scan; b: DOPA-PET scan uptake); Left cervical Paraganglioma (c: computed tomography scan; d: DOPA-PET scan uptake); Mediastinal paraganglioma (e: DOPA-PET scan uptake).

phenylethanolamine N-methyltransferase, with subsequent absence of epinephrine. Accordingly, HNPGL often occur as asymptomatic and incidentally detected cervical neck mass, with mass-effect symptoms due to involvement of adjacent cranial nerves (pulsatile tinnitus, hearing loss, aural fullness, dyspnea, hoarseness, and stridor) [11]. However, they can occasionally secrete dopamine. Recent data have demonstrated that 50% of HNPGL secrete catecholamine metabolites and up to 32% of HNPGL are dopaminergic, as determined by the elevated 3-methoxytyramine levels. Moreover, symptoms such as palpitations, diaphoresis and hypertension have been observed. Thus, initial biochemical testing should include measurements of plasma free or urinary fractionated metanephrines and 3-methoxytyramine [6,11].

Computed tomography (CT) and magnetic resonance (MR) are considered gold standards for HNPGL imaging; ultrasonography has a role limited to the evaluation and follow-up of carotid body PGL. Angiography can be performed for pre-operative endovascular embolization in order to minimize intraoperative blood loss.

HNPGL localization is often easily done by radiological imaging, but these techniques often lack specificity because sometimes they cannot distinguish HNPGL from peripheral nerve sheath tumors, nodal metastases, other rare primary tumors. Moreover, they could miss multifocal systemic PGL in hereditary syndromes. Therefore, radionuclide imaging techniques are crucial and unavoidable to fully evaluate the extent of the disease and multifocality.

Somatostatin receptor scintigraphy using 111In-DTPA-pentetreotide (Octreoscan) has been used to localize PGL, since they overexpress somatostatin receptors with a sensitivity of 75–100%, even if small sized lesions are not detectable even by the best available cameras. More recently, position emission tomography (PET) scanning techniques, including fluorodopa (18F-F-DOPA)-PET, and 68Ga-labeled somatostatin analogs PET-CT [12] have been introduced as an alternative to Octreoscan, with a sensitivity and specificity closed to 100% (Figs. 1 and 2).

Surgical approaches and results of treatment

The management and treatment of HNPGL depend on their location, multifocality and genotype. Surgery is the treatment of choice, aiming to achieve and prevent local destruction of adjacent cranial nerves. To date, mortality due to vascular complications is near 0% compared to 30–40% of historical series [13,14]. However, surgical morbidity due to cranial nerve involvement remains significant, mainly in case of bilateral/multiple lesions. Thus, even if surgery remains the only curative treatment, alternative strategy (active surveillance, radiotherapy) have been proposed.

Carotid body PGL

Carotid body PGL (also named carotid body tumor, glomus tumor, chemodectomas, or non-chromaffin tumor) are rare tumors, representing less than 0.5% of all head and neck tumors, arising from carotid body paraganglia, paired and bilateral aggregates (3–7 mm) of specialized neuroendocrine tissue at the bifurcation of the common carotid artery. Carotid body paraganglia act as chemoreceptors sensitive to changes in oxygen tension and determine sympathetic stimulation to hypoxia.

Carotid body PGL are limited to the carotid adventitia; the growth is essentially upward in the space between the internal and external carotid body branches. The tumor progressively surrounds the artery wall and reaches the cranial nerves.

Despite being rare, carotid body PGL represent 60% of HNPGL cases, with a female predominance, especially at high altitudes in presence of chronic hypoxia. Since they are non-functional, patients are generally asymptomatic; the most frequent clinical manifestation is a painless palpable neck mass deep to the anterior border of the sternocleidomastoid muscle, mobile in the lateral plane with limited mobility vertically. The tumor mass may transmit the carotid pulse or demonstrate a bruit or thrill. Dysphagia, odynophagia, hoarseness may occur in case of involvement of cranial nerves. Horner's syndrome, caused by cervical sympathetic chain involvement, and syncope, due to carotid sinus or internal carotid artery compression, may occur.

Up to 25% of carotid body PGL are bilateral and/or multifocal (even if sometimes asynchronously) with predominant *SDHD* mutations; they are mostly benign tumors, with malignant forms in 5% [15].

Surgical resection is the only curative treatment for resectable carotid body PGL. Internal and external carotid arteries should be preserved; if a major arterial sacrifice is required for local infiltration, an artery bypass grafting must be performed with the monitoring of cerebral activity during the entire procedure to detect early ischemic signs. Resection remains a surgical challenge and it is associated in more than 15% with cranial nerve (vagal, superior laryngeal, hypoglossal and accessory), sympathetic trunk palsies and vascular complications (injuries of the posterior face of the carotid bifurcation) [16]. Moreover, in case of bilateral carotid body PGL, a bilateral simultaneous excision carries the risk of bilateral Hering nerves palsy and consequently postoperative baroreflex dysfunction, causing headache, anxiety, or emotional lability, blood pressure variability with tachycardia, orthostasis, and episodes of hypotension.

The vascular complication risk can be partially predicted by the Shamblin classification based on tumor size and carotid artery involvement, to better categorize and stratify the vascular outcomes. Shamblin Class I PGL are small and easily resectable (localized type); Class II PGL are adherent, partially surrounding the carotid vessels, and resection is technically more difficult (partially wrapped type); Class III PGL are large (usually >5 cm), completely encasing the carotid vessels; resection is very difficult, and interrupting the cerebral circulation is almost always inevitable (wrapped type).

Makeieff [17] reported that the rate of serious complications (permanent nerve palsy and vascular complications) was 2.3% for Shamblin Class I/II and 35.7% for Shamblin Class III PGL ($p < 0.001$).

A meta-analysis of Jansen and coauthors [18], aiming to evaluate the surgical risks associated with different types of surgery for carotid body PGL confirmed that in Shamblin Class I-II, associated with symptoms and/or progressive growth, surgery seems to provide proper local control and relatively low risk of cranial nerve damage or adverse events, particularly when carotid artery manipulation is minimized. Conversely, in Shamblin class III, vascular and nervous morbidity is considerable, particularly in case of manipulation/reconstruction of internal carotid artery.

Radiotherapeutic options have been suggested as an alternative and results are promising, with reduced iatrogenic morbidity. The long-term results of advanced radiotherapeutic options (fractionated stereotactic techniques), however, remain unknown; complications, such as xerostomia, sensorineural hearing loss, vascular stenosis with consecutive cerebrovascular accidents, and irradiation-induced malignancies have been described.

Thus, given their frequent benignity and slow growth, a more conservative approach through a wait and scan period as initial management has been suggested, aiming to prevent iatrogenic morbidity particularly in case of multiple/bilateral variants [19].

The preoperative transarterial embolization of carotid body PGL has been advocated in order to decrease intraoperative blood loss by occluding the tumor's feeding vessels. Embolization should be performed less than 48 h before surgery to avoid revascularization edema and vascular rupture due to hypoxia-induced inflammation and congestion of the vasa vasorum. However, its routinely use is debatable, since embolization has been associated with increased cranial nerve injuries, no significant difference in blood loss or transfusion requirements, increase in cost of care and risk of cerebral embolization [20].

Jugulo-tympanic PGL

Small paraganglia similar to the carotid bodies have been described in the ear, in relation to the jugular bulb; a minority are found under the mucosa of the middle ear in the region of the medial promontory wall. The tumors arising from these paraganglia form the more frequent jugular PGL (glomus jugulare) and the less frequent tympanic PGL (glomus tympanicum).

Middle ear PGL represent approximately 30% of HNPGL, in patients that are usually middle aged. They are generally non-functioning, slow growing, benign but locally destructive tumors, even if distant metastasis may occur in more than 5% in hereditary cases. Hereditary associations result in earlier presentation, multiple and/or bilateral PGL including concurrent carotid body PGL.

The most common symptoms are pulsatile tinnitus, conductive deafness, hypoacusia, headache, vertigo, and multiple cranial nerve palsy with possible involvement of V to XII cranial nerves, with hoarseness and dysphagia. The presence of jugular foramen syndrome (paresis of cranial nerves IX–XI)

is pathognomonic for this tumor. Less commonly, glomus tumors produce facial nerve palsy, hypoglossal nerve palsy, Horner syndrome, ataxia.

Due to their rarity and potentially debilitating clinical presentation, the management of these tumors remains a matter of debate. Treatment strategies include microsurgery, preoperative embolization followed by surgical resection, fractionated external beam radiotherapy, and gamma knife radiosurgery.

A recent systematic review [21] evaluating the local control and complication rates for the different treatment modalities stratified by the broadly accepted Fisch classification (Table 3), has demonstrated that, although surgical procedures varied, surgery seems to be a suitable treatment option for class A and B tumors. For class C and D tumors, an initial wait and scan period should be considered. In the case of tumor growth (confirmed by imaging) or clinical progression of the tumor (result of early cranial nerves palsy), radiotherapy might be the better option due to lower complication rates and similar or better local control rates when compared to the surgical groups.

Endovascular treatment seems to be technically difficult in achieving complete occlusion of the lesions.

Vagal PGL

Vagal paraganglia consist of 6–7 small, dispersed aggregates of paraganglionic tissue within or adjacent to the vagus nerve, usually at the level of the nodal ganglion.

Vagal PGL (5% of all HNPGL) are highly vascularized tumors that usually originate in the nodal ganglion, and hence are located in the retrostyloid compartment of the parapharyngeal space, behind the internal carotid artery. These tumors usually present as a slow-growing neck mass that may protrude the oro-pharyngeal tissues and also reach the skull base and extend intracranially. Consequently, tumor growth can lead to voice changes, foreign body sensation or dysphagia, symptoms of IX, X, XI and XII cranial nerve palsies and sympathetic deficits.

Many factors should be considered in the treatment of vagal PGL: the age and general condition of the patient, the biological behavior of the tumor, tumor size, genetic results, bilaterality, multicentricity, lower cranial nerve function, and the potential morbidity of the surgical treatment itself. Wait and scan strategy is considered a valid option in asymptomatic patients over 60. Surgery has been suggested when the tumor erodes the skull base or extends intracranially, or to avoid additional damage to the lower cranial nerves. Surgery is the treatment of choice in young patients. Radiotherapy can also be a good option in patients with growing tumors in which the surgical risk is greater than the morbidity of an unresected tumor [22].

Laryngeal PGL

Laryngeal PGL are rare slow-growing and non-functional tumors and must be differentiated from neuroendocrine carcinomas, which are clinically aggressive, and may secrete catecholamines. Laryngeal PGL are present in both the supraglottic and infraglottic larynx. Presenting symptoms vary from stridor, to hoarseness and dyspnea. Their rarity limits available correlative data for mutation frequency; however, overall metastatic rate is low (2%).

Table 3
The Fisch classification of jugulo-tympanic paraganglioma.

Tumor class	Location and extension of tumor
A	Tumors that arise along the tympanic plexus on promontory
B	Tumors with invasion of hypotympanum; cortical boneover jugular bulb intact
C1	Tumors with erosion of carotid foramen
C2	Tumors with destruction of carotid canal
C3	Tumors with invasion of carotid canal; foramen lacerum intact
C4	Tumors with invasion of foramen lacerum and cavernous sinus
De	Tumors with intracranial but extradural extension
Di	Tumors with intracranial and intradural extension

Surgical resection is the treatment of choice, including endoscopic removal, microlaryngoscopy with laser excision, and open resection via a transcervical, lateral thyrotomy, or laryngofissure approach. Endoscopic techniques are successful with smaller lesions but have been associated with higher rates of recurrence. Since these tumors are highly vascular and often adhere to vital structures, some authors advocate preoperative radiotherapy or embolization to reduce the vascularity. However, these tumors are generally diagnosed after surgical removal [23].

PHEO and extra-adrenal thoracic-abdominal sympathetic PGL

Sympathetic PGL may arise from the adrenal medulla (PHEO, 80–85%) or from extra-adrenal ganglia of the sympathetic chain in thorax, abdomen, and pelvis (15%–20%). In more than one third of patients they are linked to germline mutations [3,6]. The rarity of PGL calls for a multidisciplinary approach to each patient involving endocrinologists, surgeons, medical oncologists, and genetic counselors to optimize patient outcome. Hereditary thoraco-abdominal PGL are predominantly related to underlying *SDHx* mutations causing PGL syndromes. Amar found *SDHB* and *SDHD* mutations in 24% and 13% of patients with sympathetic PGL, respectively [24]. Synchronous multiple thoraco-abdominal PGL have been associated with *SDHB* germline mutations in 50% of cases. The very rare mediastinal PGL have been shown to be frequently related to *SDHB*/*D* mutations (100% for non-cardiac mediastinal PGL and 77% for cardiac PGL) [25].

The identification of *SDHx*-related pathogenesis has several clinical implications, including the possibility of screening for other synchronous associated neoplasia. Gastrointestinal stromal tumors associated with PGL (Carney Stratakis syndrome; OMIM 606864) occur mostly in individuals with a germline pathogenic variant in *SDHA* or *SDHC* and often occur in the stomach and are multifocal (>40%). Pulmonary chondromas can rarely also occur (Carney triad; OMIM 604287) and/or with adrenal cortical adenoma and esophageal leiomyoma [26]. Renal clear cell carcinoma is part of the tumor spectrum of hereditary PHEO/PGL syndromes, particularly in individuals with pathogenic variants in *SDHB* and *SDHD*. Other tumors including papillary thyroid carcinoma, pituitary adenomas, and neuroendocrine tumors have been described in *SDHx* germline pathogenic variants, even if the risk of developing these tumors has not been established. Mutations in *FH* and *HIF2A* genes can also predispose to multifocal thoracic-abdominal PGL. Patients with *RET*, *NF1*, *VHL* and *MAX* mutations most often develop PHEO and rarely thoracic-abdominal PGL, as well as patients with the germline mutations in *TMEM 127* [27].

The results of genetic testing also impact the likelihood of metastatic potential. *SDHB* has been recognized as independent risk factors for metastatic disease, since *SDHB* mutations were detected in 35–55% of metastatic PGL [6]. However, in a meta-analysis of Eisenhofer [28], the same PGL location at thoracic-abdominal levels has also been associated with risk of metastatic disease and decreased overall survival. For non-cardiac mediastinal PGL, the rate of metastatic disease was 60%, half of which was related to *SDHB* and *SDHD* mutations.

Work-up and radiological imaging

Most of hereditary sympathetic PGL hypersecrete catecholamines, causing secondary hypertension or typically a paroxysmal hypertension accompanied by an abrupt onset of headaches, palpitations, diaphoresis, anxiety and chest pain. However, these tumors can mimic a variety of conditions, earning the title of “great mimic”. Actually, about 30% of patients with sympathetic PGL are either normotensive or experience only orthostatic hypotension. Other symptoms of catecholamine excess may include pallor, hyperglycemia, flushing, anxiety, nausea and/or vomiting. Further, an unusual hypertensive peak during an invasive procedure (general anesthesia, surgery, or interventional radiological procedure) suggests a workup for PGL.

In case of clinical suspicion of a sympathetic PGL, biochemical testing is required. Plasma free or urinary daily fractioned metanephrines are the tests of choice to screen for symptomatic catecholamine-secreting tumors [3]. While half of PHEO have an adrenergic biochemical phenotype, thoracic-abdominal PGL produce predominantly or exclusively norepinephrine.

Plasma-free metanephrines have higher sensitivity (96–100%) to rule out a diagnosis of cathecolamine-secreting tumor compared to 24-h urine fractionated metanephrines (77–90%), but a lower specificity (85–89% vs 93–98%). Moreover, some medications may potentially cause falsely elevated test results.

Metanephrines levels greater than 2–3 times the upper normal limit carry a near 100% positive predictive value for sympathetic PGL. Similarly, a metanephrine level that is less than one time the upper limit of normal has a very high negative predictive value. In *SDHB* and *SDHD*-related PGL, dopamine and its metabolite methoxytyramine should be tested [3].

Tumor localization in sympathetic PGL includes CT and MRI, the latter being preferred in pregnant women and for lifelong screening. The functional imaging techniques provides a higher specificity than radiological imaging and are particularly recommended for diagnosis of multifocal or metastatic disease. The sensitivity of 123I-metaiodobenzylguanidine (MIBG) SPECT for detection of PHEO is excellent (nearly 100%), but is low for extra-adrenal thoracic-abdominal PGL (56%–75%) and metastases, since it is limited by poor anatomical resolution and long imaging times; moreover, a significant number of sympathetic *SDHx*-related PGL lack the uptake of the radionuclide [3,29]. Accumulation of 123I-MIBG can be decreased in necrotic tumors or by several drugs including sympathomimetics, tricyclic antidepressants, and some α and β-adrenergic receptor blockers that should be withheld for about 2 weeks before. In case of MIBG avid lesions 123I-MIBG is very useful to identify patients that may benefit from treatment with therapeutic doses of 131I-MIBG.

In recent years, imaging using 18F-DOPA, 18F-FDG and 68Ga-labeled somatostatin analogs PET-CT has achieved better sensitivity and resolution than SPECT scintigraphy. 18F-DOPA PET has a high sensitivity for the localization of non-metastatic PGL (98–100%), while it is lower in *SDHB*-related metastatic PGL (sensitivities 20–45%). The sensitivity of 18F-FDG PET for non-metastatic PGL ranges between 92 and 100% and its specificity at 90%; it becomes highly sensitive (97%) for the detection of PGL metastases, especially in *SDHB*-related cases [30]. Thus, the use of 18F-FDG PET to preoperatively screen for metastatic disease in patients with PGL, in PHEO, high levels of plasma or urinary 3-metossityramine, and in high-risk patients carrying a *SDHB* germline mutations has been suggested [6].

Surgical approaches and results of treatment

Abdominal sympathetic PGL

The most common locations of abdominal sympathetic PGL is adjacent to the aorta. Surgery is the mainstay of treatment for abdominal PGL and represents the only chance of cure; approaches to resection may be either laparotomic or minimally invasive (endoscopic).

Minimally invasive adrenalectomy through transperitoneal approach or posterior retroperitoneal approach is the standard for removal of benign PHEO [3]. Safety and efficacy of minimally invasive adrenalectomy, in term of reduced pain, blood loss, hospital stay, and surgical morbidity, is well-documented in several large series. If bilateral surgery for concomitant PHEO is required, a cortical-sparing adrenalectomy should be taken into consideration in order to avoid the lifelong sequelae of adrenal insufficiency, since it may achieve a steroid independence in 78% with a 3-year estimated recurrence rate in the remnant adrenal of 3% [31].

Given the even more rarity of extra-adrenal PGL, few reports beyond small case series focusing on surgical treatment and outcome of sympathetic extra-adrenal hereditary PGL have been reported; most of these studies are biased by the inclusion of either PHEO and/or HNPGL. Moreover, the genetic origin of these tumors has not been often mentioned, since most mutations have been discovered only in recent years and have not been systematically detected.

The largest series in the pre-laparoscopic era was reported by O'Riordain [32] who described 66 cases during a 40-year period (1952–1992) managed at the Mayo Clinic. Extra-adrenal tumors were solitary and multiple in 52 and 14 patients, respectively, and 55 patients had retroperitoneal tumors related to the abdominal aorta between the diaphragm and aortic bifurcation. They reported one operative mortality following resection of a PGL due to damage to the celiac trunk in a patient with a retropancreatic tumor. Malignancy (metastatic disease or locally invasive disease) occurred in 36% of

patients; tumor size greater than 5 cm resulted as a strong predictor of persistent or recurrent disease and mortality, with survival of 59% at 15 years.

Given the greater risk of malignancy for abdominal PGL compared to PHEO, the concerns of multicentricity and relation to major vascular structures such as the inferior vena cava and aorta, the role of laparoscopic resection for PGL remains debated. However, advances in preoperative localization, genetics and laparoscopic techniques have allowed the removal of PGL by minimally invasive techniques, although experience remains limited and most studies involved only case reports.

Currently, endoscopic removal is considered the preferred surgical approach in experienced hands, when it is anatomically feasible [33–35]. In fact, even if they rarely invade surrounding structures, they may have several very short arterial vessels coming directly off the aorta, or they can lie deep in the pelvis adjacent to structures that require protection, such as the ureter and/or the iliac vein. Although there are less published data than for laparoscopic adrenalectomy, minimally invasive procedures for abdominal extra-adrenal PGL seems to reduce postoperative morbidity, hospital stay and costs with better cosmetic results compared with conventional laparotomy. The conversion rate of endoscopic to open surgery is about 5%, the reasons being large size of the tumor, malignancy, and bleeding. Mitchell in 2011 [33] described the experience with laparoscopic resection of 3 abdominal PGL, with emphasis on the use of intra-operative ultrasonography. Although there were nor intraoperative complications nor conversions to an open approach, they reported one internal hernia beneath the third portion of the duodenum, requiring reoperation and an extended hospital stay. In 2013, Goers [36] reported an experience of both open and laparoscopic resection of 15 PGL during a 13 years period, focusing on surgical outcome. Complications occurred in one patient in the laparoscopic group (wound infection) and in 3 patients in the open group (hypovolemic shock requiring transfusion, subhepatic abscess requiring percutaneous drainage, and an incisional hernia). Moreover, they observed comparable surgical outcome between laparoscopic resection of PHEO and PGL (tumor size, blood loss, need of intensive care unit, and total length of postoperative stay), except for operative times which were significantly longer in the PGL Group. In fact, not surprisingly, the longer operative times are due to a number of challenges in the resection of PGL, including the variability in their location, greater difficulty in operative exposure and proximity to the major structures such as aorta, vena cava, renal vessels and ureter. The study, however, was limited by the small number of cases and its retrospective nature.

In a recent, even retrospective, study analyzing a series of 108 patients undergoing surgery for PHEO ($n = 95$) and abdominal extra-adrenal PGL ($n = 13$), Falhammar [37] found that almost half of the patients with PGL had an initial laparoscopic approach but two-thirds of them required conversion to an open procedure; the length of post-operative hospital stay was twice as long as for PHEO. A fifth of the patients had complications during or early after surgery (bleeding, infection, damage to other organs, cardiovascular events), but without statistically significant differences between PHEO and PGL patients. No differences in malignancy at pathology reports were found between the two groups, with similar recurrences and death rate.

To date, the largest reported series described 161 laparoscopically resected PHEO/PGL in 126 patients [38]. Among these patients, 27 PGL were removed: 12 were solitary, 2 were multiple, and 5 were multiple familial PGL resected in conjunction with PHEO. PGL were removed by transabdominal laparoscopy in 16 cases and by the retroperitoneal endoscopic approach in 11 cases. In laparoscopic procedures, retroperitoneal PGL were easily reached after mobilization of the mesocolon and mesentery. The retroperitoneal approach with “no touch technique” seemed to be better than transperitonal one. They recommended a retroperitoneal endoscopic approach for suprarenal PGL, in bilateral tumors, in patients with earlier abdominal surgery, to avoid adhesions, while a transperitoneal approach might be preferred for infrarenal tumors.

Nevertheless, the 2014 Endocrine Society guidelines stated that, since PGL are more likely to be malignant and frequently found in areas difficult for laparoscopic resection, they should require open resection more likely than PHEO, even if some cases can be safely resected laparoscopically by experienced surgeons [3].

Several series have demonstrated the higher prevalence of malignancy in extra-adrenal PGL compared to PHEO, mostly in presence of high levels of 3-methoxythyramine [6]. Moreover, primary malignant tumors and malignant recurrences are frequent in *SDHB* mutation carriers and may also occur in *FH* and *MDH2* mutation carriers. Since the relevant genotype–phenotype associations in

hereditary PGL, Kebebew and coauthors [39] recently performed a prospective study on the impact of preoperative genetic testing information on surgical management of patients with PHEO and PGL. They found that the presence of a germline mutation and the tumor size were significantly associated with the surgical approach used (open versus minimally invasive approaches) and the extent of adrenalectomy (total versus cortical-sparing adrenalectomy). A minimally invasive surgical approach and cortical-sparing adrenalectomy was preferred in patients with specific germline mutations (*NF1*, *RET*, and *VHL*) associated with a low risk of malignancy. In contrast, germline mutations in *SDHB*, *TMEM127*, or *FH* confer a higher risk of recurrence, presence of extra-adrenal disease, and/or metastatic disease, requiring an open surgical approach with regional lymphadenectomy. They concluded that an endoscopic approach should be avoided in patients with large tumors, with high-risk germline mutations such as *SDHB*, surgically unfavorable anatomy (multiple small PGL arising at the root of the small bowel mesentery), or radiographic or clinical evidence of local invasion.

Finally, minimally invasive surgical techniques in case of multiple synchronous or metachronous abdominal extra-adrenal PGL could be challenging, especially in case of iterative surgery when open surgery is more likely required.

Persistence and recurrence are found more frequently in syndromic PGL following resection of the primary tumour. Recurrences are defined as new tumoral events, such as the reappearance of disease after complete tumor eradication or new tumors that arise in previously unaffected paraganglia. An increased risk of recurrence has been found in hereditary disease, larger tumor and PGL (compared to PHEO) [6].

Proper presurgical preparation of catecholamine-secreting sympathetic PGL patients by a multidisciplinary team is pivotal to guarantee the best possible outcome. An essential part of preoperative management is a cardiovascular evaluation, since these patients may have compromised cardiac function such as subclinical left ventricular failure. In addition, in these patients a proper medical treatment is recommended to prevent fatal sequelae of unpredictable instability in blood pressure. The most used drugs to minimize perioperative complications are selective α-adrenergic receptor blockers (Doxazosin), since they are associated with a lower preoperative diastolic pressure and intraoperative heart rate, better postoperative hemodynamic recovery, and fewer adverse effects such as reactive tachycardia and postoperative hypotension compared to non-selective α-blockers [3]. β-adrenoreceptor blockade is indicated to control tachycardia and tachyarrhythmias but should only be started after installment of proper α-adrenoreceptor blockade, since hypertensive crisis due to unopposed stimulation of α-adrenergic receptors may occur. Calcium channel blockers have mainly been used as add-on drug to α-adrenoreceptor blockade although some studies found them also effective and safe as monotherapy [40].

The long-term postoperative management has not been addressed in detail. However, a postoperative lifelong annual follow-up to screen for local or metastatic recurrences or new tumors should be performed in high-risk hereditary PGL patients [6].

Genitourinary sympathetic PGL

Genitourinary sympathetic PGL are rare tumors accounting for less than 1% of all PGL. The urinary bladder is the most common site (79.2%), followed by the urethra (12.7%), pelvis (4.9%), and ureter (3.2%). Symptoms range from the typical micturition-induced attacks of headache and palpitations. Reported treatment options for localized or locally advanced bladder PGL include radical cystectomy, partial cystectomy and transurethral resection. However, transurethral resection achieves recurrence because PGL are not mucosal tumors. For this reason, cystectomy is the preferred operation given the possibility of multifocality and tumor recurrence, especially if the tumor is deeply invasive [41].

Thoracic sympathetic PGL

Intrathoracic PGL represent less than 2% of sympathetic PGL. The location near the pulmonary artery, vena cava, atrioventricular groove, and atria may be explained by the close proximity of paraganglionic cell nest. Primary cardiac PGL are rare, with an estimated rate of approximately 50% of all intrathoracic PGL.

The prognosis for mediastinal PGL is dependent on the success of resection. Since the tumors are frequently functional and secrete large amounts of catecholamines, primarily norepinephrine, patients typically receive preoperative alfa-adrenergic blockade to counteract the effects of catecholamine release during surgical manipulation. Although successful treatment using an endoscopic approach has been described, resection of thoracic/mediastinal PGL usually requires an open approach. Surgical resection is often technically complicated because PGL are highly vascularized tumors and adhere tightly to surrounding tissues. In addition, they can extend into the atrioventricular groove, atria, and ventricles and may receive vascular supply from the right coronary artery (58%) or circumflex coronary artery (41%). The surgical procedure frequently requires cardiopulmonary bypass, sometimes with deep hypothermic cardiac arrest [42].

The survival rate for patients with a successful complete resection is 84.6% whereas patients with incomplete resections have a survival rate of 50%. Among severe intraoperative complications of patients with mediastinal PGL, uncontrollable bleeding has been reported most frequently. Wang reviewed 158 intra-thoracic PGL from 132 reports and noted 5 intraoperative deaths (3.1%) due to bleeding, and 5 patients died shortly after the operation (hospital mortality rate 6.3%) [43]. Preoperative tumor embolization to prevent bleeding appears as an attractive treatment for some highly vascular tumors. However, when it comes to functioning PGL, a potential risk associated with embolization is the induction of hypertensive crisis or wide fluctuations in blood pressures, or both, due to procedure-induced massive catecholamine secretion.

Other treatments

Palliative radionuclide treatment may be considered in patients with metastatic disease and unresectable lesions. It can be performed using beta-emitting isotopes coupled with MIBG or somatostatine analogue [44]. External radiotherapy may be considered for treatment of inoperable PGL and especially for palliation of painful bone metastases.

Chemotherapy, aimed to tumor size reduction and control of symptoms due to catecholamine secretion, is usually reserved to patients with local advanced and/or metastatic disease, with unresectable lesions, resistant to treatment with radionuclide therapy. The most used chemotherapy regimen was a combination of cyclophosphamide, vincristine, and dacarbazine; other chemotherapic regimens have been tested in other trials, but currently none has demonstrated effectiveness. Chemotherapy and radionuclide therapy often provide symptomatic and biochemical control but are less effective in causing survival increase [45].

Targeted therapy has been evaluated in malignant PGL, but all patients have experienced disease progression. Receptor tyrosine kinase inhibitors acting on several targets (VEGF, PDGF, and c-KIT), with antiangiogenic and antitumor activity have been tested in the treatment of malignant PGL, with some promising results. Molecular targeted therapies are promising strategies, but further studies on tumor biology, discovery of novel targeted drugs, and new trials are needed to achieve more effective treatments [46].

Summary

The last decades have shown an enormous progress in the knowledge and clinical care of PGL. To date, germline mutations can be detected in at least one third of patients affected by PGL and strong genotype–phenotype associations have been recognized. Therefore, genetic testing and counseling should be considered in all PGL to provide the optimal outcome for patients and relatives. In fact, the improved knowledge of the genetic background contributed to a better understanding of the pathophysiological pathways and influenced diagnostic and therapeutic strategies. The best modern biochemical diagnostic test should be used, including measurements of metanephrines and 3-methoxytyramine in plasma or daily urine. Moreover, in addition to anatomical imaging by CT or MRI, new promising functional imaging modalities such as PET using 68Ga-labeled somatostatin analogs or DOPA will probably routinely used in the near future. Accurate localization plays a critical role in the management of PGL, especially in determining the multifocality and the feasibility of surgery. Surgery remains the treatment of choice but can be associated with some relevant morbidity.

Therefore, surgery is usually performed if complete tumor excision is feasible, particularly in younger patients, in the case of large HNPGL that soon may or already present with cranial nerve deficits, and catecholamine-secreting PGL to prevent cardiovascular consequences. Post-surgical prolonged follow-up for timely detection of recurrent or metastatic disease is needed.

Conflict of interest statement

The authors declare no conflict of interest.

Practice points

- Search for clinical signs and symptoms that require biochemical testing for PGL
- Consider syndromic features related to hereditary PGL
- Use as initial biochemical test plasma or urinary metanephrines
- Choice of functional imaging should be based on location and genetic background
- Consider genetic testing in all patients: PGL phenotype is influenced by genotype
- Preoperative evaluation and medical preparation (including α-adrenoceptor blockade) are essential for catecholamine-secreting PGL
- Surgery is considered the treatment of choice, even if must be balanced with the risks of morbidity
- Timing, extent and surgical approaches may be tailored according to the age of patient, genotype, PGL location and multifocality
- Prolonged postsurgical follow-up is mandatory for all patients.

Research agenda

- Assessment of long-term outcome after surgical treatment of abdominal PGL: given the rarity of the disease, multicenter studies are needed to overcome the limitations of available evidence
- Genotype/phenotype correlation analysis, further research on genetics, tumor biology and molecular markers of malignancy are needed
- New trials are needed to assess the role of novel targeted drugs and more effective treatments in inoperable variants
- Assessment of a standardized follow-up protocol tailored according to patient and disease characteristics is needed.

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