Consensus Statement and Guidelines on the Management of Paragangliomas of the Head and Neck

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ABSTRACT

Paragangliomas (PGLs) of the head and neck (H&N) are uncommon tumors that either arise spontaneously or as part of an inherited syndrome. Hereditary PGL is an autosomal-dominant tumor predisposition syndrome in which an affected individual has greatly increased risk of developing PGL at any or several sites in the autonomic nervous system. The mode of inheritance for some is affected by maternal imprinting. These tumors are generally very slow growing, often taking a decade to double in size. A few are or can become malignant and can metastasize widely. Because of their site of origin, patients with these tumors may develop cranial nerve deficits that have a significant impact on their quality of life. Patients may present to specialists from widely differing disciplines, and some of these may not appreciate the full implications of their patient's disease. As a result, management can become fragmented or inappropriate, and some aspects of care may even be overlooked. This article is the distillation of consensus opinion derived from current published and unpublished data in this field, with particular reference to the management of temporal bone PGLs. We propose guidelines for the management of both sporadic and hereditary PGLs. A multidisciplinary team approach to the management of this complex disorder is advocated. Progress could be made by adopting these guidelines and by widespread dissemination of standardized information. Collaborative research should be promoted with the aim of harnessing advances in molecular genetics to develop targeted therapies for patients, particularly those with hereditary PGL.

KEYWORDS: Head and neck paraganglioma, management, surgery, genetics, molecular biology

Paragangliomas (PGLs) of the head and neck (H&N) develop from neural crest tissue and may arise sporadically, as part of an inherited syndrome, or in association with other tumor syndromes that have a predisposition to the development of pheochromocytomas (e.g., multiple endocrine neoplasia type 2 [MEN 2], von Hippel-Lindau disease [vHL], and neurofibromatosis type 1

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[NF1]). The estimated incidence is 1 in 300,000.[1] Four hereditary PGL syndromes have been described (hereditary PGLs 1–4). The succinate dehydrogenase (*SDH*) genes *D*, *C*, and *B* are found at 1p36, 1q21, and 11q23, respectively, and have been implicated as responsible for hereditary PGL 1, 3, and 4 syndromes, respectively.[2] The genetic mutation responsible for hereditary PGL 2 has not yet been identified. The *SDH* genes are known to be tumor suppressors as mutations cause overexpression of hypoxia-inducible factor 1α that results in proliferation of paraganglion tissue.

Paragangliomas are classified according to their site of development. The most common one is the carotid body tumor (CBT) PGL that arises at the bifurcation of the internal and external carotid arteries in the neck. Other sites of tumor development in the head are the vagus nerve (glomus vagale, vagal PGL), tympanic plexus (glomus tympanicum, tympanic PGL), and the wall of the jugular bulb (glomus jugulare, jugular PGL). Paragangliomas have also been reported in the temporal bone associated with the facial nerve. As it is sometimes difficult to be quite certain of the precise origin of tumors in the temporal bone, a collective term—temporal PGL—is sometimes used. Paragangliomas that develop in the abdomen, adrenal, or extra-adrenal areas are termed *pheochromocytomas* because they usually secrete vasoactive peptides. It is most uncommon for H&N PGLs to be endocrinologically active and secrete vasoactive amines.

Regardless of site, PGLs grow very slowly.[3] Tumor doubling times in the order of 10 years are to be expected. This slow natural growth history must be factored into any clinical decision concerning management. Equally, the results of any treatment aimed at controlling disease progression must be carefully considered in light of the expected natural history. Prolonged follow-up data in excess of 10 years are essential before any treatment modality can be considered to be effective.

There are no accepted pathological or immunohistochemical markers for distinguishing between malignant and benign PGLs. Therefore, H&N PGLs and pheochromocytomas are only determined to be malignant if metastases to non-neuroendocrine tissue are demonstrated. The most common site of metastatic spread for H&N PGLs is cervical lymph nodes. Common systemic sites include bone, lung, and liver. In the H&N, malignancy is most commonly found in vagal PGLs (16 to 19%), followed by CBT PGLs (~6%). Malignancy in jugular PGLs or tympanic PGLs is extremely rare.

MOLECULAR BIOLOGY

Succinate dehydrogenase (SDH) with its four subunits—A, B, C, and D—plays an important role in the Krebs cycle and, as part of the mitochondrial complex II, in the aerobic electron transport of the respiratory chain.[4,5] *SDHA*, a flavoprotein, and *SDHB*, an iron-sulfur protein, together constitute the catalytic domain, whereas *SDHC* and *SDHD* encode membrane anchors that allow the complex to participate in the respiratory chain as complex II. Mitochondrial complex II is thought to function as a tumor suppressor because defective mitochondrial complex II results in the overexpression of several hypoxia-inducible genes that are believed to result in proliferation of paraganglia.[6] Since the identification of *SDHD*, *SDHC*, and *SDHB* as classic tumor suppressor genes in 2000 and 2001, studies from research groups around the world have identified a total of 120 variants.[7,8]

Approximately 30% of apparently sporadic H&N PGLs are caused by a germline mutation in one of the genes *SDHB*, *SDHC*, and *SDHD*. Mutations of *SDHA*, however, are related to Leigh syndrome, which is characterized by severe neurodegeneration.[9] Compared with sporadic H&N PGLs, tumors in *SDHB*, *SDHC*, and *SDHD* mutation carriers develop at a significantly younger age. Patients with hereditary PGLs 1 and 4 have a very high lifetime risk for H&N PGLs, as well as thoracic and abdominal pheochromocytomas. The *SDHB* mutation carriers are more likely than *SDHD* mutation carriers to develop extra-adrenal

pheochromocytomas and malignant disease, whereas *SDHD* mutation carriers have a greater propensity to develop H&N PGLs and multiple tumors. Head and neck PGLs associated with *SDHC* mutations are almost exclusively benign and seldom multifocal. More CBTs have been found in *SDHC* mutations than in sporadic H&N PGLs.

INHERITANCE

Molecular genetic screening for *SDHB*, *SDHC*, and *SDHD* gene mutations is recommended for all apparently sporadic H&N PGLs to identify the risk of inheritance. There is a parent-of-origin-dependent inheritance in subjects with *SDHD* gene mutations (hereditary PGL 1).[10] The risk for manifestation of the disease phenotype is only increased if the mutation is inherited through the paternal line. Maternal transmission does not cause tumor development. Therefore, children of female *SDHD* mutation carriers do not require clinical surveillance.[11] If a mutation carrier themselves, they will pass on the mutation to their offspring in an autosomal-dominant fashion. In other words, the gene may be expressed several generations later.

CLINICAL PRESENTATION

Patients with cervical PGLs usually present with either a mass in the neck or a husky voice. A few experience impairment of swallowing. As these tumors develop in the parapharyngeal space, many achieve considerable size before becoming apparent. Similarly, cranial nerve deficits are acquired slowly, and it is not uncommon to find IX, X, XI, or XII cranial nerve palsies that had gone almost unnoticed.

By contrast, PGLs in the temporal bone usually present earlier because the principal symptom is pulsatile tinnitus. This may or may not be accompanied by a conductive hearing loss caused by the tumor filling the middle ear cavity. Cranial nerve palsies (nerves VII, IX, X, XII,) are also seen in patients with temporal bone PGLs but are generally not that common and usually indicate extensive disease. Tumors that extend into the petrous apex may cause VI nerve deficits and trigeminal neuralgia. A conductive or mixed hearing loss associated with a pulsatile red mass behind the tympanic membrane or of a red mass arising from the hypotympanum—the "rising sun" sign—is the most frequent clinical sign. In more advanced tumors, prominent vascularization of the floor of the external auditory canal may be visible. Occasionally tumors present as a polypoid mass that blocks the external auditory canal. Erosion of the labyrinth and associated vertigo is unusual, and, very rarely, bleeding from the ear may happen.

IMAGING

Detailed imaging is essential for management planning. This should include high-resolution computed tomography (CT) with bone windows, gadolinium-enhanced magnetic resonance imaging (MRI), and, in all but the smallest tumors, angiography. Whole-body positron emission tomography (PET), using either ^{18}Fluorine L-3,4-dihydroxyphenylalanine (^{18}F-DOPA) or ^{18}fluoro-deoxy-D (^{18}FD)-glucose, is highly sensitive in the detection of PGLs. It can alert the clinician to previously unsuspected multifocal or metastatic disease. As PGLs present to, or are referred to, highly specialized or focused clinicians, this whole-body technique has the advantage of highlighting those patients and their families that would be better managed by a multidisciplinary team. Furthermore, PET can detect tumors that are extremely small and may have been missed by other imaging modalities. In this way, the correct diagnosis and accurate staging can be established.[12] Temporal bone PGLs are classified according to the scheme devised by Fisch and Mattox[13] (Table 1).

Table 1 Classification System of Temporal Bone Paragangliomas

Class A	Tumors arise along the tympanic plexus on the promontory of the middle ear. Blood supply is from the tympanic artery, a branch of the ascending pharyngeal artery. They produce minimal erosion of the promontory.
Class B	Tumors originate in the canalis tympanicus of the hypotympanum and invade the middle ear and mastoid. The carotid foramen and canal are intact. These tumors invade bone, but the cortical bone over the jugular bulb is intact. The distinction between class B tumors and a C1 tumor may be difficult.
Class C	Tumors arise in the dome of the jugular bulb and destroy the overlying cortical bone. They spread inferiorly along the jugular vein and lower cranial nerves, posteriorly into the sigmoid sinus, superiorly toward the otic capsule and IAM, laterally to the hypotympanum and middle ear, medially to the jugular foramen and CPA.
	Subclassification is made according to the degree of erosion of the carotid canal:
	• C1: erode carotid foramen but do not invade the carotid artery
	• C2: destroy the vertical carotid canal between the carotid foramen and carotid bend
	• C3: grow along the horizontal portion of the carotid artery but do not reach the foramen lacerum
	• C4: grow to the foramen lacerum and along the carotid artery to the cavernous sinus
Class D	Tumors that have intracranial extension are further subclassified as follows:
	• De: intracranial but extradural:
	De 1: displace posterior fossa dura < 2 cm
	De 2: displace posterior fossa dura > 2 cm
	• Di: intracranial with intradural extension:
	Di 1: intradural extension < 2 cm
	Di 2: intradural extension > 2 cm
	Di 3: intradural extension that makes the tumor unresectable

IAM, internal auditory meatus; CPA, cerebellopontine angle.

Jugular PGLs produce a characteristic "moth-eaten" pattern of bone destruction on CT of the temporal bone. The key point that differentiates jugular from tympanic PGLs is dehiscence of the jugular bulb in the hypotympanum, which is best seen in coronal bone-windowed CT sections. Computed tomography also provides valuable detail of bone involvement around the carotid artery and inner ear.

With MRI, the "salt and pepper" appearance on long TR/long TE images is typical. The "pepper" component represents the multiple areas of signal void, interspersed with the "salt" component, which is seen as hyperintense foci (due to slow flow) on both long TR and short TR images. It has been reported that jugular PGLs are the only neoplasms of the skull base to exhibit the "dropout" phenomenon (seen in time-intensity curves) after intravenous injection of high-dose gadolinium.[14] Magnetic resonance imaging is capable of determining intracranial extension accurately in 95 to 98% of cases.

Magnetic resonance angiography (MRA) is helpful in determining the patency of the contralateral sigmoid sinus and internal jugular vein. Digital subtraction angiography (DSA) is essential for the majority of large tumors to assess the vascular anatomy because these may require preoperative vascular intervention such as embolization, balloon occlusion of the internal carotid artery (ICA), a bypass procedure, or the insertion of an intravascular stent. The most common feeding vessels arise from the ascending pharyngeal artery (inferomedial tumor compartments), posterior auricular artery, stylomastoid artery, and occipital artery (posterolateral tumor compartment). Large temporal bone PGLs may derive additional blood supply from branches of the internal maxillary, internal carotid, and contralateral carotid and vertebral (via meningeal or pial branches) arteries. In the latter case, a pial artery supply indicates transdural involvement.

Encasement of the ICA by tumor is evaluated by a combination of MRI and MRA. Narrowing and irregularities of the arterial lumen are strongly

suggestive of infiltration of its wall. Vascular encasement by temporal bone PGLs is usually seen at the distal cervical and petrosal segments of the ICA. Collateral cerebral blood flow must be assessed by four-vessel angiography with cross-compression in the first instance. If it is likely that the ICA will need to be sacrificed or occluded before tumor resection, a 15-minute balloon test occlusion (BTO) should be performed. If no neurological deficit develops, permanent balloon occlusion (PBO) can be undertaken. In situations where PBO is not possible, consideration of an external-internal carotid artery bypass followed by PBO or reinforcement of the ICA with a stent might be appropriate.[15]

If surgery is appropriate, preoperative embolization of the PGL is advised in all large jugular PGLs and vagal PGLs. Embolization has been shown to reduce bleeding, improve visualization of the tumor, and decrease surgical time.[16] This should take place at least 2 to 7 days before the anticipated surgery. Several materials have been used for embolization, ranging from particles to glue.

Postoperative MRI is advisable to exclude or monitor any residual or recurrent tumor. An interval scan protocol of 1, 3, and 5 years with subsequent scans at 5-year intervals thereafter is appropriate.

TREATMENT

There is still considerable debate over the best management for patients with PGLs. It is widely thought that the elderly or infirm are best managed conservatively and, at least initially, a "watch and wait" policy with serial scans and clinical examination is appropriate for many. Fit patients with small solitary PGLs that can be removed without inflicting significant neurological deficits are better treated by surgery. In experienced hands, large cervicotemporal PGLs can be removed completely with minimal morbidity. However, this degree of surgical skill is not widely available, and what some clinicians accept as minimal morbidity varies from institution to institution and country to country. The one serious issue on which all are agreed is that patients with multifocal tumors must be assessed very carefully because surgical intervention may jeopardize the long-term function of their larynx and their ability to swallow and hear. In other words, quality of life can be profoundly affected.

RADIOTHERAPY

Radiotherapy, either by gamma knife, stereotactic techniques, or external beam, has been advocated by some.[17] In several patients the tumor can be stabilized for significant periods of time, and the patients may avoid any surgical intervention or additional neurological deficits. Most surgeons will have seen patients for which radiotherapy failed to control their disease. These patients either present a decade or more after initial treatment with extremely advanced tumors, for which surgery has little to offer, or with excruciating pain caused by osteoradionecrosis of the skull base. It is generally agreed that radiotherapy does have a role in the management of multifocal disease, where the principal aim of the clinician is to preserve function and quality of life for as long as possible.

SURGERY

The surgery of H&N PGLs has evolved with advances in microsurgical and interventional radiological techniques, intraoperative monitoring, and improvements in postoperative care. Surgical resection remains the only means by which a PGL can be completely and reliably eliminated.

Paragangliomas limited to the tympanic cavity and tympanomastoid area (class A and B tumors) are removed by standard otologic techniques using endaural or postauricular exposure. Complete removal can be achieved for the vast majority with

minimal morbidity. For larger tumors, class C and D, the infratemporal fossa approaches described by Fisch[18] are recognized as the gold standard method of resection. By anterior transposition of the facial nerve, a direct lateral exposure of the jugular bulb is achieved with control of the sigmoid sinus and internal carotid artery. Intraoperative facial nerve monitoring is a standard of care. It has had a positive influence on the preservation of facial function. The same probably applies for the other lower cranial nerves. Vagal monitoring with needle or surface electrodes placed in the larynx may also benefit some patients.

Long-term study results of surgical resection of class C tumors using the infratemporal fossa type A (IFT-A) approach have reported complete elimination of tumor in 83% of patients with preservation of normal postoperative facial function in 65 to 80%.[19,20] An analysis of facial nerve outcomes following anterior rerouting from the first genu, as in IFT-A, shows that 41% of patients achieve a House-Brackmann grade I or II in the short term and 73% after long-term follow-up. Short-segment anterior rerouting from the second genu is thought by some to give superior functional results, with 47% achieving grade I or II function in the short term and 93% at long-term follow-up[21].

To minimize or completely avoid manipulation of the facial nerve throughout the surgery, posterolateral approaches that avoid anterior transposition of the facial nerve are favored by some. These approaches are mainly applicable to smaller class C tumors and have limitations with larger tumors.[22–24] The outcomes for patients with smaller tumors from using these techniques are comparable to those treated using the IFT-A technique.[22,23] The decision on how to tailor the management of the facial nerve in these cases is entirely dependent on the extent of anterior tumor spread and required active management of the ICA.

Regardless of the surgical technique used, tumor infiltration or encasement of cranial nerves is present without evidence of preoperative cranial nerve deficit in 50% of cases.[25] The major problems in jugular PGL surgery are removal of tumor from the pars nervosa of the jugular foramen and management of the ICA when it is encased by tumor. The resection of tumors arising in the jugular foramen carries the high risk of sudden and permanent vagal palsy with subsequent swallowing and aspiration problems. These functional deficits are not well tolerated by the elderly. For these patients, an extended period of recovery is often experienced, perhaps as long as 1 to 2 years. A very few are never able to compensate and require parenteral nutrition. An even smaller number may require a permanent tracheostomy. Younger patients are more robust and are usually able to overcome these handicaps.

Aggressive treatment of significant ICA involvement by PGLs remains controversial and is rarely necessary. If a temporary balloon occlusion is well tolerated by a patient with an extensive PGL, preoperative PBO with subsequent carotid resection is an acceptable method of treatment for those with a solitary PGL. Patients with inadequate collateral cerebral blood circulation present a major surgical risk and should be given the option of either a high-flow external carotid–middle cerebral artery bypass followed by PBO or ICA reinforcement with a stent.

Transdural tumor spread into the posterior fossa has been reported in 14 to 72% of series. Intradural tumor is normally addressed after removal and devascularization of the extracranial component. Although small intradural extensions can be removed at the same time as the temporal bone component, staged surgery is advised for larger extensions. Intracranial extension correlates well with the stage of a jugular PGL; however, this is not always the case. An intradural extension does not necessarily indicate that a facial nerve rerouting procedure, such as the IFT-A approach, should be done, but that is usually the case. The addition of a transcondylar approach has enabled good access to the lower clivus and anterior foramen magnum and provides a direct view of the tumor-brainstem interface while providing adequate control of the vertebral artery and vertebrobasilar junction.[26] In these very advanced cases, the use of vascularized tissue transfer for the reconstruction of dural defects after

extensive resections significantly reduces the risk of postoperative cerebrospinal fluid leaks.

Gross total tumor removal is achieved in 83 to 91% of patients in specialist centers. The most common sites for residual tumor to be found are in the cancellous bone around the tumor margins, in the cavernous sinus, on the brainstem, and adjacent to the lower cranial nerves.

Most would agree that cavernous sinus involvement with ophthalmoplegia (III, IV, and VI deficits) represents unresectable disease. Other situations where surgery is unwise are: very dominant sigmoid sinus, inadequate collateral cerebral circulation, and any patient with significant comorbidities. In these situations, palliative treatment modalities, including radiotherapy and sometimes subtotal resection and postoperative stereotactic radiotherapy, are viable options. Early rehabilitative programs for patients with multiple lower cranial nerve deficits following surgery are vital.

COUNSELING AND SCREENING

Molecular genetic screening for *SDHB*, *SDHC,* and *SDHD* gene mutations is recommended for all apparently sporadic H&N PGLs to identify risk of inheritance. All H&N PGL patients and first-degree relatives of patients with gene mutations should be offered genetic counseling and regular screening.[27] At the outset, all should undergo a thorough physical examination and have PET and H&N MRI together with 24-hour urine collections for vanilmandelic acid (VMA) excretion studies. In those with the *SDHB* mutation, raised VMA excretion products, or an abnormal PET study, an abdominal CT is advisable. In this way, a pheochromocytoma would be detected. Isotope studies using octreotide or MIBG (metaiodobenzylguanidine) will identify unsuspected PGLs, but these would almost certainly be imaged by PET more effectively.

Follow-up screening should include an annual physical examination and VMA excretion study, interval H&N MRI every 2 years, and PET studies at least every 5 years. In the event of any clinical suspicion that a new PGL has developed, appropriate imaging should be undertaken. Although PGLs have been reported in children under the age of 10 years, this is extremely rare. In view of the cumulative risk of radiation exposure to young children, it is advised that screening of minors commence at ~10 to 12 years of age.

SPECIALIST MULTIDISCIPLINARY CLINICS

The management of each patient with H&N PGLs requires careful and individual consideration. Size, site, age, general health, preexisting symptoms, potential for multicentricity, transmission of a genetic mutation to successive generations, and the capacity for malignant degeneration play decisive roles in determining the optimal management strategy. These skill sets do not reside in any one individual. There is a strong case for multidisciplinary care in specialist centers. Each center should have a skull base team that consists of an otologist, neurosurgeon, neuroradiologist, and radiation oncologist. The center should also have a geneticist and endocrine and vascular surgeons. The overall lead should be taken by the most experienced and appropriate surgeon, usually a skull base surgeon, and regular, biannual multidisciplinary meetings should be held. A database of PGL patients should be kept, with appropriate consent obtained, to share information and tissue with international registries.

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