

British Skull Base Society Clinical Consensus Document on Management of Head and Neck Paragangliomas

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Abstract

The management of head and neck paragangliomas (HNPGs) has changed significantly in recent years. There is, however, an absence of guidance in the literature regarding the optimal means of managing this challenging disease. This consensus document, developed by the British Skull Base Society, sets out recommendations for management of HNPGs. A preliminary document was produced on the basis of current practice in 3 large UK skull base centers, incorporating relevant peer-reviewed evidence. This document was then modified by discussion within these units, through a national survey of British Skull Base Society members, and through discussion with stakeholders. A consensus was reached on the management of all forms of HNPG. All patients should be managed by a multidisciplinary team and require initial surgical, endocrine, and genetic assessments as well as magnetic resonance imaging of the head, neck, chest, abdomen, and pelvis. Long-term preservation of function is the primary treatment goal, with conservative management the first choice treatment for most tumors. Radiotherapy is a safe, effective treatment for growing tumors in most cases, although there is a limited role for surgery. Screening of family members in high-risk groups is mandatory. These guidelines should help standardize high-quality care for patients with HNPGs.

Keywords

paraganglioma, treatment, surgery, radiotherapy

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Introduction

Terminology

Paragangliomas (PGLs) are extra-adrenal tumors arising from chromaffin cells. They have an incidence of around 0.5 per million, with a peak incidence between the ages of 30 and 50 years, although familial forms of the disease often present at a much younger age. There is a slight female preponderance.

The World Health Organization has classified PGLs and stated that the term *glomus tumor* should no longer be used.^{1,2} The term *paraganglioma* with a description of the

ganglion in which it arises should be used. The World Health Organization classification of head and neck PGLs (HNPGs) is as follows:

- Carotid body PGL
- Jugulotympanic PGL
- Vagal PGL
- Laryngeal PGL
- Miscellaneous PGLs

Broadly speaking, HNPGs can be divided into those originating within the temporal bone and those originating in the neck. With regard to temporal bone PGLs, there are several staging systems, including the Glasscock-Jackson and Fisch staging systems. The guideline group agreed that the Fisch staging system should be used, although it acknowledged that this has some limitations that need to be taken into consideration. The Fisch staging system is as follows:

- A: Mesotympanic
- B: Tympanomastoid
- C: Carotid canal involvement
 - 1: Limited involvement of carotid canal
 - 2: Involvement of the vertical portion of carotid canal

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- 3: Involvement of the horizontal portion of the carotid canal
- 4: Extension to foramen lacerum \pm cavernous sinus thrombosis
- D: Intracranial extension
 - e: Extradural
 - i: Intradural

Type A and most type B temporal bone PGLs arise from the tympanic plexus and are termed *tympanic PGLs*. In the majority, there is intact bone over the jugular bulb, with tumors arising in this location. Large tympanic PGLs may progress to involve the jugular bulb, in which case it may be difficult to differentiate a tympanic PGL from a jugular PGL. A small jugular PGL may spread superiorly without involvement of the carotid artery and be regarded as type B.

One of the limitations of this classification system is the lack of stepwise progression through the classes in some tumors. For example, a tumor that would otherwise be regarded as type C1 might have intradural involvement. Tumor class alone cannot therefore be used to determine management, and each case should be judged on its own merits.

There are other classification systems for cervical paragangliomas, including the modified Shamblin classification of carotid body PGLs³:

- Class 1: Not involving the carotid
- Class 2: Partially surrounding the carotid
- Class 3a: Completely surrounding the carotid
- Class 3b: Infiltration of the carotid wall irrespective of tumor size

The majority of PGLs are solitary, benign, and slow growing and often have minimal symptoms until large. Some tumors may, however, behave in a more aggressive fashion, demonstrating rapid growth or metastasizing. Certain genetic mutations are associated with more aggressive behavior, particularly *SDHB* mutations. Such tumors have been referred to as *malignant*. There is, however, no difference in histologic appearance of these tumors as compared with less aggressive tumors, and the term *malignant* should therefore be used bearing this in mind.

Predictors of growth include the following:

- Genetic status, including positive family history (detailed later)
- Age at presentation
- Tumor origin—risk of malignancy is greater in vagal PGLs than carotid body PGLs, which are in turn more likely to be malignant as compared with jugular or tympanic PGLs.

These guidelines aim to provide succinct guidance for clinicians on the management of all forms of HNPGs,

including associated distant disease, to improve knowledge and standardize clinical care. They are not intended to provide a comprehensive review of the literature.

Methods

An initial meeting including the 3 consensus group leads was convened, and a preliminary consensus document for management of HNPGs was produced as based on the practices of 3 large UK centers (Manchester, Cambridge, and London [Guy's and St Thomas' Hospital]). This document was circulated to all team members at these 3 centers, and modifications to the initial document were made following review of the current literature and preexisting clinical guidelines. The literature search was undertaken with PubMed. The search terms "paraganglioma," "glomus tumor," "head and neck," "genetics," "endocrinology," "investigation," and "treatment" were used. The aim was not to carry out a systematic review but to identify key publications relevant to the contemporary management of HNPGs. The following preexisting guidelines were reviewed:

- "National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology: Neuroendocrine Tumours" (2016)⁴
- "Pheochromocytoma and Paraganglioma: An Endocrine Society Clinical Practice Guideline" (2014)⁵
- "The North American Neuroendocrine Society Consensus Guideline for the Diagnosis and Management of Neuroendocrine Tumors: Pheochromocytoma, Paraganglioma and Medullary Thyroid Cancer" (2010)⁶
- "EANM 2012 Guidelines for Radionuclide Imaging of Pheochromocytoma and Paraganglioma"⁷
- "European Society of Endocrinology Clinical Practice Guideline for Long-term Follow-up of Patients Operated on for Pheochromocytoma or a Paraganglioma" (2016)⁸

The document was then circulated to the wider skull base community in the United Kingdom via the British Skull Base Society, and further modifications were incorporated. An electronic survey was circulated to clinicians within all the specialties involved in management of head and neck PGLs, asking for opinions on the points of potential controversy. This included questions around the logistics of running an HNPG multidisciplinary team (MDT) and what constitutes an MDT; what types of investigation and treatment the various types of HNPG should have; what the indications for treatment of the different forms of HNPG should be; what type of screening should be undertaken for new tumors in existing patients and for those at risk of developing PGL disease; and how outcomes should be audited and the results used to ensure high-quality care. A consensus meeting was then organized, and invitations for interested clinicians to attend were sent out through the

national associations of specialties dealing with PGL disease:

British Association of Head and Neck Oncologists
 Society for Endocrinology
 Vascular Society
 British Society for Genetic Medicine
 British Nuclear Medicine Society

At the consensus meeting (Liverpool, January 2018), the draft guidelines and the survey results were used to lead discussion around outstanding points of controversy. The consensus document was then modified and sent out to the specialist associations for comments, and final modifications were made. Responses were received from all. Patients were not invited to take part in the development of these guidelines, and we acknowledge that this is a potential limitation in the production of this clinical consensus document, given the emphasis on shared care for patients with PGLs. Future modifications of this document will be made in collaboration with patients.

Clinical Setting

PGL disease is complex, and all forms of HNPGL (including tympanic PGLs) should be managed by a MDT of clinicians that includes the following:

Core members

Skull base otolaryngology
 Head and neck surgery
 Clinical genetics
 Oncology (including radiotherapy)
 Endocrinology
 Vascular surgery
 Radiology
 Pathology

Extended members

Neurosurgery
 Endocrine surgery
 Nuclear medicine
 Speech and language therapy
 Audiology
 Dietician

The PGL team members will, in the main, work within a single center, although it is accepted that there may be clinicians with extensive experience in management of PGLs who work elsewhere. Such clinicians may continue to offer treatment for PGLs as long as they contribute to the MDT's audit process and can demonstrate good outcomes. They must bring all PGL cases to the MDT for discussion on a regular basis (per the recommendations detailed later). They should undertake PGL surgery only if their local team has the requisite specialties to effectively and safely do so; for example, embolization facilities must be available for all jugular PGLs, and if there is intracranial extension, neurosurgery must be involved. Similarly,

vascular surgery should be on-site if an otolaryngologist is considering removal of a carotid body tumor. Local management protocols should be in place to ensure that all patients receive appropriate care as defined by these guidelines.

Because of the complexity of the disease, the team should have extensive experience managing PGLs. The surgical, radiologic, and oncologic core members may work within either a head and neck or skull base MDT, and in most cases, these MDTs will be responsible for the day-to-day management of neck PGLs and temporal bone PGLs, respectively. Endocrine and clinical genetics assessments are required in all cases (including tympanic PGLs), and there should be well-defined pathways for the assessment by these core members of the team. The involvement of extended members of the team is required only in specific circumstances; for example, neurosurgery is needed for tumors where there is intracranial extension or other intracranial consequences of the disease.

Ideally, all core members of the team (with extended members if possible) should meet in a PGL-specific MDT on a regular basis (at least every 3 months), although it is accepted that this may not be possible in every center. The PGL MDT should discuss all new patients with HNPGLs, all patients with genetically positive or high-risk HNPGLs, all patients with growing or secreting tumors, or those who have previously required treatment. All current patients, whether or not they have active disease, should be discussed in the PGL MDT on at least an annual basis. A named clinician should have responsibility for running the MDT and be supported by an MDT coordinator, although it is accepted that this may not be possible in all centers.

Initial Assessment

Clinical Assessment

As a minimum, all patients should have an outpatient assessment with an otolaryngologist who is part of the MDT. The family history should be assessed with inquiries about tumors in other family members, including PGLs, pheochromocytomas, renal cancer, and gastrointestinal stromal tumors (**Table 1**).

Examination should include otoscopy, neck examination, assessment of cranial nerves (including flexible pharyngolaryngoscopy), and signs of any associated syndromes. Pure tone audiometry should be performed in both ears of the patients with PGLs involving the temporal bone.

Radiologic Assessment

All patients with an HNPGL should have a contrast-enhanced magnetic resonance imaging (MRI) of the head and neck to image the primary lesion. This includes tympanic PGLs. Temporal bone PGLs (jugular and tympanic) should also be imaged with high-resolution, thin-cut computed tomography (CT) of the skull base.

The other purpose of imaging is to assess the presence of synchronous and metachronous tumors as well as identify

Table 1. Common Genetic Mutations Seen in HNPGs with a Propensity for Development of Non-head and neck Tumors.

Gene	Inheritance	Phenotype	Frequency
<i>NFI</i>	AD	Café au lait spots, axillary freckling, Lisch nodules, peripheral nervous system neurofibromas. Mainly pheochromocytoma. HNPG rare	1% patients with <i>NFI</i> develop pheochromocytoma. 1% patients with pheochromocytoma
<i>RET</i>	AD	Multiple endocrine neoplasia type 2—medullary thyroid carcinoma, hyperparathyroidism, pheochromocytoma	50% of patients develop pheochromocytoma. 5% patients with pheochromocytoma
<i>VHL</i>	AD	Cerebellar and spinal hemangioblastomas, retinal angioma, pheochromocytoma, renal cell carcinoma, endolymphatic sac tumors. Extra-adrenal pheochromocytoma rare	Penetrance varies with mutation, up to about 20% individuals with <i>VHL</i> disease. 5%-10% patients with paraganglioma or pheochromocytoma
<i>SDHB</i>	AD	Pheochromocytoma and paraganglioma. High rate of malignancy. Have been associated with renal tumors and GIST	Penetrance, 40%-50%. 10%-15% patients with paraganglioma or pheochromocytoma
<i>SDHD</i>	AD: parent-of-origin effect	Pheochromocytoma and paraganglioma. Higher rate of HNPG. Usually nonmalignant, frequently multiple. Tumors develop only if inherited from father	Penetrance up to 75%. 5%-10% patients with pheochromocytoma or paraganglioma
<i>SDHC</i>	AD	Pheochromocytoma and paraganglioma. Mainly HNPG	Rare
<i>SDHA</i>	AD	Pheochromocytoma and paraganglioma. All locations described	Penetrance difficult to assess. Accounts for <1% inherited paraganglioma
<i>SDHAF2</i>	AD: parent-of-origin effect	HNPG	Penetrance unclear. Rare
<i>MAX</i>	AD: parent-of-origin effect	Pheochromocytoma and paraganglioma. Malignant cases have been described. Tumors develop only if inherited from father	Penetrance unknown. <1% patients with pheochromocytoma
<i>TMEM127</i>	AD	Pheochromocytoma often bilateral and multicentric. Malignancy rare. HNPG described but rare	Penetrance unclear. 1%-2% patients with pheochromocytoma
<i>FH</i>	AD	Usually associated with leiomyomatosis and renal carcinoma. Rare association with pheochromocytoma	Penetrance is unknown. Very rarely found
<i>KIF1Bβ</i>	AD	Phenotype unclear	Penetrance unknown. Very rare
<i>ELGN1</i>	AD	Paraganglioma and erythrocytosis	Insufficient data available
<i>EPAS1</i>	AD	Congenital polycythemia and paraganglioma	Insufficient data available
<i>MDH2</i>	AD	Pheochromocytoma	Single family described

Abbreviations: AD, autosomal dominant; GIST, gastrointestinal stromal tumor; HNPG, head and neck paraganglioma; PCC, pheochromocytoma; *VHL*, von Hippel–Lindau disease.

rare cases of metastatic disease. In light of this, all patients (including those with tympanic PGLs) should, at a minimum, also have imaging of the thorax, abdomen, and pelvis. Whole body MRI is preferred and should include coronal T1-weighted and STIR sequences of the whole

body and axial fat saturation T2-weighted sequences of skull base to kidneys (the latter to more readily identify and partially characterize lesions in the high-risk areas). Gallium DOTATATE positron emission tomography (PET) CT is an alternative method of screening the whole body for

synchronous tumors and has higher specificity than fluoro-deoxyglucose PET CT.⁹

There is no diagnostic role for catheter angiography. ¹²³Iodine-labeled metaiodobenzylguanidine (MIBG) scintigraphy only has a role where MIBG therapy is under consideration.

Identification of PGLs outside the head and neck should trigger referral to the appropriate member of the extended MDT.

Endocrine Assessment

Up to 10% of HNPGLs produce hormones. In head and neck tumors, this is primarily norepinephrine. All patients (including those with tympanic PGLs) should have plasma metanephrine levels measured at presentation (including adrenaline, normetadrenaline, and 3-methoxytyramine) because they may be a marker of aggressive tumor biology and may be associated with labile hypertension. Only 1 test is required to exclude a secretory lesion. Twenty-four-hour urinary metanephrine measurement may also be used, but this is less sensitive and logistically more difficult than plasma metanephrine measurement. Three-methoxytyramine is a more sensitive marker of secretory activity than adrenaline or normetadrenaline but of less cardiovascular significance.¹⁰ All patients with positive metanephrines require long-term endocrinology input.

Genetic Assessment

It is likely that 30% to 50% of pheochromocytomas and PGLs are caused by a single-driver germ-line mutation, although up to 10% of these will not be identified by current genetic testing techniques, because some patients have either rarer untested mutations or an as-yet-unidentified mutation.¹¹

Because of the high proportion of familial disease, genetic testing after appropriate counseling and informed consent is recommended in all patients with PGLs (including tympanic PGLs), even if there is no family history. Next-generation sequencing should be used for screening, and a recent consensus document made recommendations regarding which genes should be included in the test panel.¹² The pickup rate for the genes included in the panel is 99%. The possibility of identifying a variant of unknown significance during genetic testing is routinely discussed during pretest genetic counseling. The risk of this is around 10%.

Patients are at higher risk of familial disease, even in the absence of an identified mutation, if they

- Present at young age (<30 years)
- Have multiple tumors
- Have a family history of PGLs

Patients in these high-risk groups with mutation-negative results should be encouraged to enroll in national studies offering whole exome or genome sequencing.

There are currently at least 15 susceptibility genes that, when mutated, are associated with PGLs.¹² At least another

7 mutations are not associated with familial cases but have been identified from tumors in sporadic cases (somatic mutations). **Table 1** summarizes the most common mutations predisposing to PGL. *SDHD* mutations are the most common mutations in HNPGL. *SDHB* mutations are the most aggressive and are associated with malignancy in 23% of cases.¹³

Patients carrying these mutations are also at risk of other tumor types (**Table 1**). For example, mutations in *SDHB* may be associated with renal cell carcinoma (1-in-20 risk), papillary thyroid tumors, neuroblastomas, and gastrointestinal stromal tumors.

All PGL genes are inherited in an autosomal dominant manner. There is, however, variable penetrance: 79% for *SDHD* mutations and 22% to 28% for *SDHB* mutations up to the age of 70 years.¹³⁻¹⁵ The penetrance of other rarer mutations is unknown. It is important to note that *SDHD*, *SDHAF2*, and *MAX* mutations are subject to maternal imprinting and so are active only when inherited from the father.

The role of genetic testing is to stratify risk of aggressive tumor behavior and development of future tumors. Genetic counseling takes place prior to testing. It is also important to offer cascade genetic testing to all at-risk family members to identify those who would benefit from tumor surveillance and reproductive options, such as preimplantation genetic diagnosis.

There are currently inadequate data regarding the risk of having a familial form of the disease in patients with isolated tympanic PGLs, and the consensus group agreed that isolated tympanic PGLs should undergo the same genetic testing as other forms of PGL, until such time when there is evidence that the risk of familial disease is negligible.

Further Management

Following initial assessment, patient management should be discussed in either the skull base or head and neck MDT meeting depending on the tumor site. It may be appropriate to discuss the case in both MDT meetings if there are multiple tumors. In some centers, a wider MDT may be available, including members from both the head and neck and skull base MDTs as well as genetics and endocrinology. If such a wider MDT meeting is not available, then provisional management decisions should be made and then circulated to other members of the team for ratification.

Patient counseling plays a crucial role in ensuring that patients understand the extent of their disease, the likely natural history, and the risks and benefits of all management options. Shared decision making between patient and clinician is critical, bearing in mind that patients will have their own preferences regarding treatment and that management philosophies will vary among centers because of differences in local expertise and facilities. Specialist nurses play an important role in ensuring the holistic assessment and care of patients. This includes coordinating treatments, supporting patients and their family, and liaising with patient support groups.

The options for management include

- Active surveillance with serial imaging \pm plasma metanephrines
- Surgery
- Radiotherapy

Surveillance

The literature suggests that only around half of HNPGs show growth after diagnosis. The mean growth rate for jugulotympanic PGLs is 0.4 mm/y, and that for carotid body tumors and vagal PGLs is 1.6 mm/y.¹⁶ These rates are usually regarded as slow. Inter- and intraobserver error based on linear measurements from MRI can be up to 2 mm. It can therefore be difficult to identify these small changes from one year to another. Therefore, growth may be identified only after longer periods of surveillance and once it is >2 mm. For this reason, the majority of patients should undergo a prolonged period of surveillance to determine tumor behavior. The exceptions to this, where early treatment is appropriate, include the following:

- Tympanic PGLs
- Jugular PGLs with troublesome conductive hearing loss, pulsatile tinnitus, or impending or actual facial nerve weakness
- Significant brainstem compression
- Secretory tumors
- Clinical evidence of rapid growth
- Malignant disease
- Patient choice

Radiology

Individual HNPGs. All tumors under surveillance should undergo interval imaging with contrast-enhanced MRI of the head and neck. Initial imaging should be at 6 months and annually thereafter. This interval may be increased for tumors that have been stable. For example, a sporadic tumor could be scanned annually for 3 years, biennially for 6 years, and every 3 years thereafter. Surveillance may be stopped in elderly patients with isolated stable tumors.

Screening for New Tumors. In a patient with an isolated head and neck tumor for whom genetic testing is negative and initial screening imaging of the thorax, abdomen, and pelvis is clear, no further thoracoabdominal imaging is required. Patients with an isolated head and neck tumor in whom genetic testing is positive should have triannual MRI of the thorax, abdomen, and pelvis. Annual abdominal ultrasound may be used to screen for renal cell carcinoma in those with *SDHB* mutations. For recommendations regarding screening and management of multiple tumors/familial disease, see the Managing Multiple Tumors section and Managing Familial Disease section.

Endocrine

In a patient with a nonsecretory isolated head and neck tumor in whom genetic testing is negative and initial screening imaging of the thorax and abdomen is clear, no further endocrine follow-up is required. Secretory tumors are normally removed, and annual plasma metanephrines are recommended to screen for recurrence.

In those with an identified mutation or multiple tumors, surveillance should include annual plasma metanephrines (see Managing Familial Disease). If the plasma metanephrines are raised, then further imaging of the thorax, abdomen, and pelvis is indicated to assess for a new secreting tumor, with subsequent discussion of the results in the MDT. It should be noted that nonsecreting tumors can start secreting. Positive plasma metanephrines in a previously negative case does not therefore necessarily reflect new tumor development.

Outpatients

The majority of patients with HNPG should be seen annually to assess whether there is clinical progression—in particular, cranial nerve dysfunction. Where tumors have been stable for several years, the interval can be increased.

Active Treatment

The indications for active treatment differ according to tumor type. When treatment of an individual tumor is being considered, decisions should be made by the MDT in the context of the patient as a whole, with knowledge of the tumor size, rate of growth, mutation status, presence of malignancy defined by metastatic disease, secretory status, synchronous tumors, patient symptoms, and comorbidities, as well as patient choice. This is particularly important to consider for patients with bilateral disease who are at risk of bilateral lower cranial nerve palsies, as this can have a profound impact on quality of life and may require permanent tracheostomy and enteral feeding. Surgery and radiotherapy should be undertaken by clinicians who regularly manage PGLs.

Tympanic PGLs

Early surgical resection is the treatment of choice and should be undertaken by otologists experienced in tympanic PGL surgery. The consensus group did not feel that there was a requirement for the surgeon to be part of the main PGL MDT (ie, experienced surgeons who are not part of the main PGL MDT may undertake surgery on this type of tumor in their own center). The standard initial imaging protocol should be undertaken per other types of PGL. The patient should be referred to the PGL MDT for discussion so that a genetic and endocrine assessment can be undertaken and to facilitate audit.

In almost all cases, the aim of surgery is complete tumor resection with hearing preservation. Type A tumors are normally removed transcanal. Type B tumors usually require a combined transcanal and mastoid approach. Removal may

be facilitated by the use of the laser. There is no indication for embolization prior to surgery. Primary radiotherapy is not indicated.

Large tympanic PGLs may progress to involve the jugular bulb, in which case they should be managed as a jugular PGL.

Jugular PGLs

The main indications for treatment are tumor growth, symptom control or prevention of the development of symptoms, and cranial nerve palsies. The long-term aim of treatment is to preserve function while controlling tumor growth. While total surgical resection and radiotherapy provide equivalent long-term tumor control,¹⁷ the mainstay of treatment for growing tumors is radiotherapy, as the morbidity of treatment is usually significantly less than surgery.

Radiotherapy. The majority of growing or large tumors should be considered for fractionated radiotherapy, ideally with intensity modulated radiotherapy or fractionated stereotactic radiotherapy.¹⁸⁻²¹ Prescription doses of 45 to 50 Gy have been recommended for benign tumors, and local control is achieved in the majority of patients at 5 and 10 years. Growing small-volume tumors may be considered for treatment with stereotactic radiosurgery to a marginal dose of at least 12 to 14 Gy.¹⁸⁻²¹

Surgery. The role for surgery is generally to address symptoms that would not be adequately treated by radiotherapy and as salvage treatment following failure of radiotherapy. Resection should not put lower cranial nerve function at risk unless absolutely necessary. Indications for surgery include the following:

- Ear canal bleeding or persistent discharge
- Troublesome pulsatile tinnitus
- Conductive hearing loss
- Arteriovenous shunting
- Secreting tumors
- Significant brainstem compression
- Malignant disease
- Failure of radiotherapy to control growth

Surgery in these situations would generally be subtotal resection with the aim of preserving lower cranial nerve function. Postoperative radiotherapy should be considered, particularly for growth of residual disease.²²

In a small number of cases where the neural compartment of the jugular foramen is not involved, total resection may be offered as a primary treatment for growing tumors.

Surgery may also be favored if there is preexisting complete loss of function of the lower cranial nerves. Care should be taken in the latter group, as apparent lower cranial nerve palsies are often not complete and surgery with cranial nerve sacrifice may lead to additional disabling swallow issues with aspiration. In patients with normal preoperative facial function, transposition of the facial nerve should be carefully considered: while it improves access to the tumor

and minimizes the risk of facial nerve damage during resection, in itself it has a significant risk of long-term facial palsy. As a result, this technique is now rarely used.

The risk of postoperative morbidity following total tumor resection is significant, and recurrence rates are around 10%.²³⁻²⁶ The most common complications include injury to cranial nerves VII to XII, cerebrospinal fluid leak, and injury to the inner ear. The risk of cranial nerve injury following total resection (in those who still have function) is up to 80% for tumors larger than Fisch C4.^{23,24} Vascular injury is rare but may result in stroke or death.

Surgery should be preceded by embolization to minimize intraoperative bleeding and therefore minimize the risk of cranial nerve injury. If the goal of surgery is complete resection and the tumor is extensively involving the internal carotid artery, then preoperative assessment of the intracranial circulation should be undertaken, including balloon occlusion studies to determine whether preoperative occlusion of the carotid would reduce risk. Stenting of the internal carotid artery may be considered if balloon occlusion is not tolerated. Intraoperative sacrifice of the internal carotid artery should be avoided whenever possible.

With the exception of very limited type C1 disease, type C and D tumors require blind sac closure with removal of the malleus and incus. Unless there is significant preexisting cochlear injury, cochlear function should be preserved whenever possible. This allows hearing rehabilitation with bone conduction devices.

In the presence of intradural extension, a staged approach may be undertaken where the intracranial portion is removed initially and followed by the extracranial portion at a later date to minimize the risk of intracranial bleeding and persistent cerebrospinal fluid leak into the neck.

Vagal PGLs

Vagal PGLs tend to behave more aggressively than jugular PGLs and have a higher risk of metastasis (7%).²⁷

The evidence base for management is poor, but complete surgical resection and radiotherapy are both options and are equally effective in controlling tumor growth. Radiotherapy is the mainstay of treatment for small, growing tumors in the presence of a functioning vagal nerve and in all patients with contralateral vagal palsy. Contralateral disease status is paramount in the decision-making process, as bilateral vagal palsy (not isolated recurrent laryngeal nerve palsy) is likely to result in the need for permanent tracheostomy and enteral feeding.

Radiotherapy. Small-volume tumors may be treated with stereotactic radiosurgery. Larger tumors will require conformal fractionated treatment. Fewer publications report radiotherapy outcomes for vagal PGLs when compared with jugulotympanic PGLs. The same radiotherapy doses appear to be effective for tumors in both locations.²¹ For malignant tumors, the necessary dose is less well established, but higher doses should be considered as used for other malignant tumors (eg, 64-74 Gy).²¹

Surgery. Rapidly growing and/or large vagal PGLs and those in the context of an *SDHB* mutation are likely to behave more aggressively and may be more appropriately managed with surgical resection rather than radiotherapy to minimize future metastatic disease. It is rare to be able to preserve vagal function when vagal PGLs are resected, even if subtotal resection is planned. In view of this, the aim of surgery in most cases is total resection. Surgery may be preceded by embolization to minimize intraoperative bleeding, particularly for tumors extending into the jugular foramen, where vascular control is more challenging.

Carotid Body PGLs

Carotid body PGLs tend to behave more aggressively than jugular PGLs and have a higher risk of metastasis (2%-13%)²⁸ but less so than vagal PGLs. The majority of carotid body PGLs are not, however, associated with significant symptoms and are slow growing.

Conservative management should be considered initially and active treatment discussed if the tumor demonstrates growth, shows features of aggressive behavior, or is secretory or if cranial nerve function is already lost. In the latter case, care must be taken, as further deficit often occurs after removal of a tumor that was initially, mistakenly, felt to be associated with a complete cranial nerve palsy. Conservative management is not, however, risk free as there is a significant lifetime risk of complications (cranial nerve palsy) from conservative management.

Radiotherapy successfully controls growth in most cases. The risk of new cranial nerve palsy is low.¹⁷ There are risks of stroke and malignancy in the long term, although the opinion of the consensus group was that these were both low. Radiotherapy may be the favored treatment modality in the older age group with growing tumors, particularly if the tumor is large. This group is less likely to develop long-term complications.

Surgical resection has a similar tumor control rate to radiotherapy (up to 95% control depending on tumor size). The risk of new cranial nerve palsy is size dependent, with tumors <4 cm having a risk of 15% and tumors >4 cm having a risk of around 40%. Surgery may be the favored modality in the young patient, especially if the tumor is small.

Carotid body surgery should be performed by surgeons experienced in removing carotid body tumors. While the Vascular Society felt that only vascular surgeons should operate on carotid body tumors, the consensus group generally held the view that a head and neck surgeon and/or a vascular surgeon could carry out this surgery as long as they were appropriately experienced. The consensus group would encourage joint operating to minimize cranial nerve and vascular morbidity. It is acknowledged that there will be local variations in practice. A vascular surgeon should be available on-site on the day surgery if the tumor is being removed by an otolaryngologist—head and neck surgeon alone.

Preoperative embolization has been shown to reduce the vascularity of the tumor and should be considered for patients undergoing surgery. It should be carried out within 48 hours of surgery.

Managing Secretory Tumors

Secreting tumors need to be appropriately alpha blocked, particularly prior to surgery. Current evidence suggests that phenoxybenzamine is the most appropriate medication.²⁹ Beta blockade is rarely required, as secretory HNPGLs produce norepinephrine and not epinephrine. Beta blockade should therefore be reserved for persistent tachycardia after adequate alpha blockade and fluid resuscitation.

Managing Multiple Tumors

Management of multiple tumors is challenging. Particular care is needed to avoid bilateral neurologic impairment. Given this, the primary modality of treatment for patients with growing multiple tumors is radiotherapy. Surgery does, however, have a role in managing tumors arising in areas that have been previously irradiated. Surgery may be considered if there is a low risk of neurologic injury—for example, small carotid body PGLs and tympanic PGLs.

Posttreatment Surveillance

The risk of local recurrence following total surgical resection is <10%, but the risk of continued growth following subtotal removal is significant. The risk of growth following radiotherapy is also low. The MDT should, however, continue to remain vigilant for local recurrence and for the development of new PGLs outside the head and neck, particularly in those with multiple PGLs, metastatic disease, an isolated PGL treated with radiotherapy, or an identified genetic mutation. These groups should have long-term radiologic and clinical follow-up.

Head and neck PGLs treated with subtotal resection require a baseline MRI scan of the head and neck approximately 8 to 12 weeks following treatment and subsequent annual MRI scans of the head and neck for the first 3 years. The interval can be increased to alternate years for the subsequent 6 years and then every 3 years thereafter.

Annual plasma metanephrines are also appropriate in those with predisposition syndromes.

Patients with an isolated PGL and no identified genetic mutation who have undergone total resection can be discharged from follow-up after a period of radiologic observation, typically 5 years. Jugular PGLs have a higher risk of recurrence, however, and require more careful follow-up over a longer period.

Screening and Managing Familial Disease

Cascade genetic testing in families with a known genetic predisposition to developing PGLs can be offered in childhood. Those with a predisposition to develop PGLs can begin surveillance at the following time points: 8 years, with annual plasma metanephrines, and 15 years, with

whole body MRI every 3 years and abdominal imaging in the intervening years (magnetic resonance or ultrasound), aiming to detect tumors at an early stage. There is, however, a range of opinion on when screening should commence, with some authors suggesting commencement at a later stage.³⁰ Similarly, there are other possible imaging protocols for screening—for example, whole body MRI every 2 years. The consensus group felt that later commencement of screening risks delayed diagnosis of some tumors, particularly with an *SDHB* mutation. It also felt that the aforementioned imaging protocol offered an appropriate balance between early diagnosis and cost.

In individuals with no other risk factors for inherited disease (ie, isolated tumor, age >30 years, no family history), the group felt that there was no indication for testing family members of those who have a variant of unknown significance on genetic testing.

Managing Malignant PGLs

As outlined previously, malignant PGLs are defined by metastatic disease and tumor behavior rather than the histologic appearance of the primary tumor. Head and neck PGLs primarily metastasize to cervical lymph nodes, although distant metastases may develop in lung, bone, liver, and brain.²⁷ Tumors arising at atypical sites are likely to represent metastases.

Malignant disease is much more common in those patients with an *SDHB* mutation, although it has been observed with other mutations (eg, *SDHA*, *TMEM127*, and *VHL*).

Identification of metastatic disease is through cross-sectional and functional imaging, including PET, octreotide scans, and/or MIBG, as recommended after discussion by the PGL MDT. The treatment options for metastatic disease include peptide therapy with octreotide or MIBG, radiotherapy, and surgery. Suitability for peptide therapy is determined by tracer uptake by tumor on nuclear medicine imaging. Temozolomide is a further therapeutic option in malignant and metastatic PGL (eg, tumors in patients with *SDHB*).³¹

The behavior of the metastasis usually reflects that of the primary tumor with slow progression. Treatment is aimed at symptomatic relief and tumor control rather than cure.

Rehabilitation

Cranial nerve palsies should be actively rehabilitated and managed by the appropriate specialist team.

Assessing Outcomes

The MDT should audit its outcomes and benchmark against accepted standards of care. Potential outcome measures include

- Treatments
- Tumor control rates

- Need for further treatment
- Rates of cranial nerve functional preservation
- Rates of other complication
- Quality of life
- Adherence to management guidelines

Audit data should be centrally collected and the results peer reviewed by an audit committee with representation from all clinical stakeholders. Results should be fed back to the relevant team and placed in context with other centers for comparison. Acceptable outcome standards need to be set, and mechanisms for the identification of outliers need to be put in place. Mechanisms for ensuring that acceptable outcomes are maintained also need to be put in place.

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Supplemental Material

Additional supporting information is available in the online version of the article.

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