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Current Treatment of Paragangliomas of the Head and Neck

INVITED REVIEW
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ABSTRACT

Paragangliomas in the head and neck region (HNPGLs) are infrequently found neuroendocrine tumors. They usually originate from non-secretory parasympathetic ganglia (further verification is required). The majority arise in 4 distinct areas: carotid body, lateral temporal bone; mastoid and jugular foramen, and vagus nerve. The initial symptoms are frequently trivialized until an obvious painless mass, cervical, or pharyngeal, becomes obvious ± lower cranial nerve paresis or paralysis. Modern advances in diagnostics, imaging, histopathology, and genetics have resulted in a greater understanding of the natural history of HNPGLs, concluding that most tumors are benign and slow growing. More than 50% have a familial hereditary etiology, most commonly associated with germline mutations in the succinate dehydrogenase gene, several of which carry an increased risk of multifocal disease or metastasis; the remaining 50% are classed as sporadic. Many HNPGLs exhibit variable growth, most often slow annual growth, which encourages an initial period of observation for selected patients, e.g., small tumors, asymptomatic, and non-secreting. Surgery remains the optimum treatment for most patients presenting with larger tumors, rapidly enlarging tumors, secretory tumors, and/or symptomatic tumors. A reasonable alternative treatment option, which reports "excellent results," is the use of stereotactic radio-surgery. The results of theranostics trials are awaited and may change practice for inoperable, recurrent, or metastatic disease, where current response rates from conventional chemotherapy are disappointingly low. All patients diagnosed with a HNPGL should be referred to a specialist center for additional investigations, family education, and genetic screening and have their treatment managed in an algorithm-based approach, which has been shown to optimize outcomes.

Keywords: Paraganglioma, head and neck, carotid body, temporal bone, vagus nerve

Introduction

Paragangliomas (PGLs) are a group of neuroendocrine neoplasms that arise in the parasympathetic or sympathetic ganglia and are essentially the extra-adrenal counterpart of pheochromocytoma (PCC).[1] The World Health Organization (WHO) has deemed terms such as "glomus tumor" or "chemodectoma" should no longer be used and henceforth should be classified as non-epithelial neuroendocrine neoplasms (NEN).[2]

Head and neck paragangliomas (HNPGLs) comprise 65%-70% of all PGLs and account for <3% of all head and neck tumors.[3] Head and neck paragangliomas have an incidence of around 1-30 per 100 000 population, with a peak incidence between the ages of 40 and 70 years, with a 3-4 : 1 female preponderance.[2,4] Head and neck paragangliomas have been reported in more than 20 anatomical locations; the most commonly reported sites are carotid body tumors (60%) (CBTs), followed by temporal bone (29%) (TBPGLs) and vagus nerve (13%) (VPGLs). Other sites have been reported, which include the larynx, orbit, trachea, thyroid, and nasal cavity.[3]

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Owing to their origin in the parasympathetic ganglia, <95% of HNPGLs are typically non-secretory tumors.[1] This disease can occur as sporadic or hereditary forms; hence, genetic analysis plays a pivotal role in differentiating the forms.[4] Head and neck paragangliomas with a hereditary etiology (40%-50%) have a germline sequence, with the gene encoding succinate dehydrogenase (SDHx) complex being the most common sequence variation identified.[3,4] Hereditary PPGLs show autosomal dominant inheritance, commonly with reduced penetrance. Maternal imprinting with silencing of the maternal allele occurs for the SDHx subtypes (SDHD and SDHAF2), and thus, only mutations inherited from the father will cause disease. Because of incomplete penetrance, family history is inaccurate for identifying hereditary HNPGLs; hence, family sibling testing is required for the identification of mutation carriers.[4,5]

Current treatment of HNPGLs considers family history, the extent, aggressiveness and location of the tumor, its genetic origin, the molecular pathways involved, and especially DNA genetic testing of family members.[6] As HNPGL disease is complex, it is recommended that all patients diagnosed should be managed by a multidisciplinary team of clinicians, including a geneticist.[2] The current treatment strategies described for HNPGLs are broadly surgery, radiotherapy, and "watch-and-scan," recognizing that there is no universal best treatment. Surgery aims to remove the local tumor mass completely, radiotherapy aims to arrest local tumor growth, while active surveillance aims to avoid the potential morbidity of either surgery or radiotherapy while determining an appropriate time for intervention if necessary.[7,8] Manifestation of the distant site (<10%) "malignancy aggression" involving cervical lymph nodes and bone are uncommon events which are an ominous outcome for which specific treatment options are available.[9] Vagal PGs are most likely to demonstrate malignant features (7%-10%), followed by the carotid body (7%), and lesions from the tympanic-jugular PGs (2%-4%).[10] However, the current consensus of experts, because HNPGLs are solitary and benign in the vast majority of cases, survival is not a common endpoint reported in studies. The prognosis ranges from a normal life expectancy to a 5-year survival of <15% in patients with distant metastasis.[3]

MAIN POINTS

- *Head and neck paragangliomas are rare neuroendocrine tumor typically (95%) arising from non-secretory parasympathetic ganglia.*
- *The majority arise from 4 distinct areas: carotid body, lateral temporal bone, mastoid and jugular foramen, and vagus nerve.*
- *More than 50% have a familial hereditary etiology, associated with germline mutations in the succinate dehydrogenase gene.*
- *Presentation is initially subtle with minimal symptoms, until an obvious painless mass, with a lower cranial nerve paresis or paralysis.*
- *The peak incidence of is reported between 40 - 70 years, with a 3-4:1 female preponderance, but cases at a younger age are not uncommon.*
- *Surgery remains the optimum treatment for most patients presenting with larger tumors, rapidly enlarging tumors, secretory tumors and/or sympathetic tumors.*
- *Optimum outcomes have been reported when patients are investigated and advised in a specialist center, where treatment management in in a algorithm-based approach.*

Thus, the current primary treatment focuses on preserving function and the prevention of morbidity from progressive disease.[7,8,11]

Pathology

The histopathologic diagnosis of PGL is not difficult if the tumor is located in a typical site and when the patient displays classical symptoms associated with excessive catecholamines. Immunohistochemistry staining is crucial for pathological assessment.[2] However, diagnosing these tumors can be challenging when they appear in uncommon locations. They consist of solid nests called "zellballen" composing round and elongated cells with ample granular cytoplasm, which may be amphophilic or basophilic, set within a vascular framework. Additionally, they might exhibit acidophilic cytoplasm. While nuclear abnormalities can occur, mitotic activity is typically low, and necrosis is absent. Nonetheless, many pathologists argue that only chromogranin, synaptophysin, and S100 stains are necessary. Chromogranin and synaptophysin typically yield cytoplasmic positivity in tumor cells, whereas S100 staining, though it may stain tumor cells, offers distinct and intense positivity highlighting sustentacular cells within these tumors.[12]

A histopathological scoring system, correlating with metastatic potential, has been proposed: the Grading system for Pheochromocytoma and Paraganglioma (GAPP). This system is based on histological pattern, cellularity, comedo-type necrosis, capsular invasion, vascular invasion, Ki67 labeling index, and catecholamine type.[13] Tumors are graded on a scoring system with a maximum score of 10, categorized into well-, moderate-, and poorly differentiated. A study for PGLs showed a sensitivity of 100% and a specificity of 68%, with a PPV of 29% and an NPV of 100%.[14] This system does not take into account the underlying somatic or germline mutations, and while work continues with a classification system, to date the model GAPP is good at ruling out but poor at predicting metastatic potential.

Based on the WHO guidelines, all PGLs are considered malignant and thus at risk of metastasis, although metastasis can be difficult to identify given the wide distribution of paraganglia. As a "rule of thumb," metastasis is defined as PGLs in areas where paraganglia do not occur, i.e., lymph nodes and bone.[15]

Genetics

Neuroendocrine tumors show the highest degree of heritability in all neoplasms (approximately 40%-50%), and much progress has been made since the discovery of the mitochondrial complex II genes. Subunits of succinate dehydrogenase (SDHx) gene complex, including A, B, C, D, and AF2, have been most often identified as susceptible to the development of HNPGLs.[4] The discovery of succinate dehydrogenase subunit D (SDHD) gene in families with paraganglioma syndrome type 1 (PGL1) in 2000 helped in understanding the molecular mechanism of paraganglioma inheritance.[4,6,16] Five related types of hereditary paraganglioma syndromes (PGL) have been described, each of which has different risk profile and is related to different genes for HNPGLs (Table 1).[4,6] Therefore, knowledge of an individual's mutation status will inform treatment and ongoing surveillance. Multifocality of HNPGLs correlates with the SDHD mutational subtype, and metastases correlate with the SDHB subtype.[17]

Hereditary tumors can be suspected in the case of familial antecedents of the disease, multiple tumors, and early onset of disease (<40 years). Sporadic tumors are usually diagnosed in patients older than

Table 1. Clinical Features of Hereditary Head and Neck Paraganglioma Syndromes

Syndrome	Gene	Mode of Inheritance	HNPGL	Presentation	Multifocal	Secretor	Malignant
PGL 1	SDHD	Paternal	85%	85% CBT	55%-60%	Non	~10%
PGL 2	SDHAFT2	Paternal	100%		0	Non	0
PGL 3	SDHC	AD	Rare	Solitary	Rare	Non	0%
PGL 4	SDHB	AD	20%-30%		20%-25%	Possible	~30%
PGL 5	SDHA	AD	Rare		Rare	Unknown	Rare

AD, autosomal dominant.

40-50 years.[4] Multiple tumors, positive family history, age at diagnosis <40 years, presence of carotid body tumor, as well as bilateral presentation should be considered hallmarks of germline mutations in HNPGLs.[4] Until the turn of the millennium, hereditary syndromes associated with PCC and PGL were von Hippel-Lindau disease, multiple endocrine neoplasia type 2, and neurofibromatosis type 1, resulting from a germline mutation in the suppressor gene VHL, proto-oncogene RET, and NF1.[18] As more than 20 different known genes are responsible for hereditary HNPGLs whose prevalence varies from low to lifetime risk, in whom family history is unreliable, consensus recommends that all first-degree family members can benefit from genetic testing.[19]

Diagnosis

Presentation and Imaging

As the majority of HNPLGs are non-secreting, early clinical symptoms are soft and non-specific, resulting in a protracted time period (hoarse voice, swallowing symptoms, shoulder weakness, or Horner syndrome) until the typical presentation, which includes a painless enlarging neck mass, pulsatile tinnitus with cranial nerve palsies, or are identified as part of a family screening or as an incidental finding on imaging. The increasing use of CT and MRI imaging in patients with head and neck symptoms means that HNPLGs are also increasingly present as an incidental finding.[20,21] Because HNPLGs contain membrane-bound somatostatin type 2 receptor (SST-2), which makes them more easily detected with radiolabeled peptide receptor imaging, in situations such as multifocal, familial, recurrent, and metastatic, using nuclear imaging may identify more accurately the disease spread.[22]

Catecholamine Secretion

Sympathetic HNPGLs (<5%) secrete catecholamines, resulting in overactivity of the sympathetic system. Symptoms may present as the classic triad of diaphoresis, headaches, palpitations, and hypertension, but many do not. If these HNPGLs are left untreated, patients can experience heart attacks, arrhythmias, and stroke.[23]

The diagnosis of secretory HNPGLs is made by identifying catecholamines in the blood or urine (epinephrine (adrenaline), norepinephrine, and dopamine). While rare, there is sparse documentation of their true incidence rates. This may reflect inadequate biochemical screening following initial HNPGL diagnosis or a true lack of functional activity by tumors arising from parasympathetic ganglia. The concept that all HNPGLs either secrete or do not secrete catecholamines has been challenged, and it has been investigated that HNPLGs exhibit a continuum of hormone activity, influencing clinical presentation and the need for hemodynamic management.[24]

Advances in catecholamine metabolism have clarified why measurements of the O-methylated catecholamine metabolites, rather than the catecholamines themselves, are important for effective diagnosis. After completing their hormonal actions, catecholamines are metabolized to inactive compounds—norepinephrine breaks down into normetanephrine (NM) and vanillylmandelic acid (VMA), and epinephrine becomes metanephrine and VMA. The plasma test provides higher sensitivity than the urinary metanephrine test. For the rarer dopamine-producing HNPGLs, metabolites can be measured by levels of methoxytyramine (MTY), which is a human trace amine that occurs as a metabolite of the neurotransmitter dopamine, which can be important in some tumors and for the surveillance of patients at risk of metastatic disease. Plasma MTY has been shown to be positively related to tumor size but not related to the presence of SDHx mutations or tumor location. Recent findings have confirmed that increases in plasma MTY represent the main catecholamine-related biochemical feature of patients with HNPGLs.[25]

Current Treatment Options

Due to their origin, being located nearby or adherent to many critical neurovascular structures, natural tumor growth and/or surgical intervention may be associated with postoperative complications and/or sequelae with lifelong severe morbidity. Radiotherapy, with its modifications, is an alternative intervention but not without its own set of complications. There is no standard treatment for the management of HNPGLs, but employing an algorithm-based approach can help optimize outcomes.[7,11,26,27]

An example of decision-making is a series of 130 HNPGLs in 125 patients with HNPGLs accumulated in 2 tertiary care academic hospitals in the United States over the period 2011-2020 is described.[28] The tumor characteristics by location were as follows: CBT 55, temporal bone 43, vagal 24, and unspecified 8 (n = 130). The mean age was 56.26 years, and 93 (74.4%) were female. A total of 16 (12.8%) patients were syndromic, and most of the tumors were not hormonally active (n = 119, 95.2%), with a minority being catecholamine-s ecreting (n = 6). All of the hormonally active tumors underwent surgery. The factors that influenced the decision for surgery included the young, healthy patients, catecholamine-secreting tumors, and highly symptomatic tumor. The distribution of the 75 patients treated surgically was as follows: CBT 52% (39/75), TBPG 28% (21/75), VPG 13.3% (10/75), and others 6.7% (5/75). In the cohort of 39 patients who were under a "watch-and-scan," approach, 43.6% showed tumor growth, based on the definition of an increase in volume >15%. The tumor doubling time was 5.67 years when assessing only growing paragangliomas. It was noted that >50% of this group had no growth observed. The policy of the "watch-and-scan" strategy has now become widely advocated by clinicians, with decision being made on completion of a thorough investigation, which gives results on disease staging and identification of "at-risk" family members who may have SDHx genomic mutations. This period should be for an initial period of time (3-4 months) to assess tumor growth and symptom progression.[21,22,27-29]

Carotid Body Tumors

Development of Symptoms

A carotid body is a small collection of chemoreceptor cells that originates from the adventitia located at the carotid bifurcation. Expansion of a CBT, irrespective of etiology, in such a narrow, restricted space results in compression, encasement, and possibly invasion of the carotid arteries and cranial nerves, which occurs with tumor growth.

The presenting symptoms from an extensive systematic review report data recorded in 92 published studies (3458 patients). The most common presentation was a neck mass (75%), and of these, 86% of the masses were painless and asymptomatic. Other symptoms documented at presentation (14% overall) included cranial nerve palsy 3.5%, dysphagia 3.1%, and dysphonia 1.7%, and included syncope/dizziness, vertigo, tinnitus, transient ischemic attack (0.3%), and stroke (0.1%).[30]

Classification of Carotid Body Tumors

Carotid body tumors can be classified by etiology, location, catecholamine production, and anatomy. Sporadic etiology represents 65% of all CBTs, followed by the familial type 10%-25%, which usually affects younger patients, and the less frequent hyperplastic type (related to chronic hypoxia, respiratory diseases, and living at high altitudes). Carotid body tumors may be unilateral (most common) or bilateral (~5% sporadic and 30% familial cases). As <5% of HNPGL are catecholamine secretors, it is important that in these cases are identified early, prior to considering surgery. An anatomical classification was proposed by Shamblin et al, based on tumor characteristics regarding size and relationship with the carotid arteries, and it is surgically based (Table 2).[31]

Preoperative Selective Arterial Embolization

The use of preoperative selective embolization of the feeding vessels (the descending musculo-spinal branch of the ascending pharyngeal artery has been reported as very common) is practiced to reduce vascular and minimize neurological complications. The benefits of preoperative embolization remain to be clearly defined, with retrospective meta-analyses showing some or no effect.[32]

Surgical Treatment and Outcomes

A systematic review and meta-analysis of presentation and surgical management of 104 observation studies (mainly low-altitude environments) identified 4418 patients with 4743 CBTs, with a mean age of 47.3 years, and the majority being female (65%) [30] Bilateral tumors were reported in 9.6% of patients, while 4.1% were found to be malignant following histological review. Functional (catecholamine-secreting) tumors were reported in only 2.3% of patients. Details of the reported individual outcomes were reported in 99 studies (4306 patients), showing a mean 30-day mortality was 2.29% (95% CI 1.79- 2.93; $I^2=0\%$). In 92 studies (4061 patients), the mean proportion of patients developing a stroke at 30 days was 3.53% (95% CI 2.91-4.29; $I^2=0\%$). In 89 studies (4004 patients), the 30-day rate of death/stroke was 4.10% (95% CI 3.42-4.91; $I^2=3\%$).

Table 2. Classification of Carotid Body Tumors (Shamblin et al[31])

Grade	Anatomical Description
Shamblin I	Tumors are localized and easily resected.
Shamblin II	Tumors are adherent or partially surrounding the carotid vessels.
Shamblin III	Tumors are intimately surrounded or encase the carotid vessels.

Reporting postoperative complications based on Shamblin grade procedures (Shamblin I, II, and III), the data reported by only 12 studies (544 patients) revealed that the risk of stroke was 60% following Shamblin III, 25% for Shamblin II, and 15% Shamblin I.

Postoperative cranial nerve injuries (CNIs) have been reported by 99 studies (4327 patients) overall in 25.4% (95% CI 24.5 – 31.33). The most common CNIs were the hypoglossal nerve (CN X) (9.59%), while the vagus nerve (and/or its branches) was 8.07%. Twenty-six studies (1075 patients) reported the rate of CNIs according to Shamblin classification—Shamblin I was 3.76% (95% CI 2.62- 5.35), Shamblin II 14.14% (95% CI 11.94-16.68), and Shamblin III 17.10% (95% CI 14.82-19.65). The authors remarked that "considering the cohort of patients who suffered a CNI after CBT excision and in whom Shamblin status was known, the proportion of CNIs following Shamblin III tumor excision was 54% vs. 39% for Shamblin II and 7% for Shamblin I tumors." They also remarked "that CNIs are not generally considered to represent "serious" complications, but they can be extremely disabling to the patient and should not be underestimated."

It has long been recognized that the risks of surgery are high (large tumors) or the benefits are low (small, non-growing, tumors), and that conservative (non-surgical) treatment might be more appropriate. Monitoring tumors is best done by MRI or CT scanning until they reach a diameter of more than 2.5 cm. The best window for resection with a very low risk of complications is between 2.5 and 3.5 cm; larger tumors present a specific challenge and tend to have a more advanced Shamblin stage.[27] The long-term follow-up of patients with advanced CBTs usually achieves excellent oncologic outcomes with disease-free survival. However, survey results indicate that CNIs identified on clinical examination underreport patients' true postoperative deficits.[33]

Improvement in Shamblin Classification

Staging of CBTs by the Shamblin classification has been criticized over time, and modifications have been recommended by several surgical groups.[34] The fundamental limitation of the Shamblin classification is its exclusive assessment of the tumor extension in the horizontal plane. It was proven that as the CBT expands both in volume and approaches the skull base, it becomes a more accurate predictor of an increased likelihood of bleeding and cranial nerve complications.[35]

In the light of the above comments, two "improved" classifications have been proposed for the classification of CBTs.[36,37] The Mehanna classification, used a multicenter international cohort of CBTs, developed a new classification and risk stratification system, which was then validated on an independent cohort.[36] This classification has used anatomical landmarks to measure the vertical extent of CBTs into types 1-4 (upper body of hyoid, lower border of angle of mandible, up to but not superior to the aspect of body of C2 vertebrae, above the superior aspect of the body of C2 vertebrae). The authors conclude that this new system demonstrates a progressively increasing risk of developing complications with increasing stages. To progress with validation, the group has set up an International Prospective Database of Paraganglioma CBT cases. The Peking Union

Medical College Hospital (PUMCH) conducted a retrospective review of 116 CBTs using CT angiogram or MRI images. Classification (types I-V) was based on carotid arterial encasement and vertical extension of the tumor.[37] Type I indicates that the superior margin of the tumor was below the mandible angle. types II, III, and IV indicate that the superior margins of the tumor were above the mandibular angle but below the mastoid tip, with no encasement, partial encasement, and complete encasement to the internal and external carotid artery, respectively. Type V indicates that the superior margins of the tumor were above the mastoid tip. The authors concluded that future prospective studies with a larger number of patients are required to assess the validity and reliability of this proposed classification.

Malignant Carotid Body Tumors

A systematic review of the literature (20 publications with >5 CBT malignancies reported) concluded that the rate of malignant CBTs was 7.3%, diagnosed between the fourth and sixth decade, with a higher prevalence in women, mostly Shamblin III, with nodal and distant metastasis in 79.7% and 44.7%. These tumors were mostly Shamblin III, with cervical nodal and distant metastasis.[38] Malignancy should be suspected if the CBT is >4 cm, Shamblin III, painful or otherwise symptomatic, occurring at the extremes of age, bilateral, and multifocal disease, and if there are SDHx mutations present.[38] At surgery, if a cervical node is identified, performing a selective neck dissection (levels II-III clearance) should be considered, and adjuvant treatment should be considered based on histology.[38,39]

Temporal Bone Paragangliomas

Temporal bone paragangliomas (TBPGs) are highly vascular and usually benign neoplasms of the temporal bone. They are the second most common paragangliomas of the head and neck, accounting for 20%-30% of HNPGLs. The annual incidence of TBPGs has been reported as 0.07 per 100 000 population per year. There is a female preponderance, with a mean age at presentation in the fifth decade of life. There are 2 types of TBPGs, the tympano-mastoid paragangliomas (TMPs) and the tympano-jugular paragangliomas (TJPs). Temporal bone paragangliomas originate from the tympanic branch of the glossopharyngeal nerve (Jacobson's nerve) and the auricular branch of the vagus nerve (Arnold's nerve) are TMPs, while tumors originating from the paraganglia at the adventitia of the dome of the jugular bulb are TJPs.[40]

Germline Mutation

Temporal bone paragangliomas can be either sporadic or familial. In a multiethnic cohort of patients with sporadic TJPs, 25%-30% carried a germline mutation in the SDH gene. Specifically, TJPs in females were found in only 24% of cases associated with SDH loss, compared with 55% in male cases, and are associated with an earlier diagnosis.[25] In general, these patients present with advanced disease, and distant metastasis is found in a number of cases. It has been recorded that isolated TMPs very rarely have an SDHx mutation, with most being reported as sporadic tumors.[41,42] The age at presentation and growth rate of HNPGL patients below the age of 50 years are associated with a higher growth rate. Tympano-jugular paragangliomas median age at presentation is mid 55 years, while other HNPGLs present at younger ages. This finding might be explained by the low percentage of SDHx-related syndromic cases within the group of TJPs, as SDHx-mutated HNPGLs are known to present at relatively younger ages.[25] A female preponderance of TJPs has been reported and is rarely associated with germline SDHx mutations, suggesting a distinct mechanism to tumorgenesis.[25] Tympano-jugular paragangliomas occurs significantly more often in women (88%) and at presentation are significantly smaller than all other types of HNPGL. Tympano-jugular paragangliomas tumors with SDHx mutations are much larger at the time of presentation. Bilateral TJPs are more common in germline SDHx mutations. Metastatic disease occurs less often in patients with TJPs compared to other HNPGLs.[24] Temporal bone paragangliomas have a low risk of secreting catecholamines (1%-8%).[25]

Presentation

Presentation of TBPGLs is variable, most have been described commencing with an indolent behavior but occasionally with aggressive presentation that includes loco-regional invasiveness and distant metastasis. The most common symptoms are hearing loss and pulsatile tinnitus. As the tumor enlarges, patients present with cranial nerve (CN) dysfunction (CN IX-XII) with relevant symptoms to their muscle groups: shoulder weakness, hoarseness, dysarthria, and dysphagia. More than 60% of patients at the time of diagnosis have at least 1 cranial palsy.[20,26,40] With more extensive very large tumors, classified as "complex," TBPs can cause intracranial pressure, brain stem compression, and cranial nerve dysfunction (IV-VI). The term "Complex PGL" was introduced to describe a subset of TJPs which include multiple giant (>4 cm), malignant, neuropeptide-secreting lesions, and those previously treated with an adverse outcome—that is high-risk complications, prolonged hospital stay, and presents many surgical challenges.[43]

Classification

The most commonly used classification for TBPGs is the Modified Fisch classification into classes A, B, C, D, and V, based on the location and extension assessment by high-resolution computed tomography in 1979.[44] In 1999, Fisch reported a series of 136 patents with TBPGs and proposed a subclassification of classes C and D.[45] Sanna M from Italy, in 2010, proposed subclassifying Fisch class A and B into two subgroups, which reportedly would help with formulating a surgical plan.[46] Again in 2012, Sanna's group, after studying a group of 230 patients post-surgery, identified 8 patients who were found to have involvement of the vertebral artery by TBP and proposed the addition of a "V" category.[47] In 2012, Sanna, following a review of 45 patient charts with Fisch classification class C and D TJPGs with intradural extension, recommended that the De subcomponent of class D be removed, reflecting a simpler and more accurate reflection of the actual practices in many skull base centers[48,49] (Table 3).

Treatment

Treatment options consist of radiotherapy, including intensity-modulated (IMRT), stereotactic radiosurgery, proton therapy, or surgery, which may involve subtotal resection, total/gross total resection, or "wait-and-scan," or a combination.[26,50] Traditionally, the definitive treatment of TBPs has been surgical resection. However, the complexity of these tumors regarding their origin, extent, and variability in clinical presentation has inevitably led to a necessary critical discussion of treatment modality. Due to the relative proximity of location and vital neurovascular structures, tumor growth often leads to lower cranial nerve palsies. For this reason, different treatment strategies are being chosen in various centers. Over time, the radical surgical approach aimed at total excision of "all" or "complete" tumors, which is difficult and not always achieved, and not infrequently on postoperative scanning reveals that a lesser procedure has been

Table 3. Modified Fisch Classification of Temporal Bone Paragangliomas[44-49]

Class	Anatomical Location
Class A	Tumors confined to the middle ear: A1 Tumor margins clearly visible on endoscopic examination. A2 Tumor margins not visible on otoscopy. Tumor may extend anteriorly to the Eustachian tube and/or to the posterior mesotympanum.
Class B	Tumors confined to the tympanomastoid cavity without bone destruction of the infra-labyrinthine compartment of the temporal bone: B1 Tumors involving the middle ear with extension to the hypotympanum. B2 Tumors involving the middle ear with extension to the hypotympanum and the mastoid. B3 Tumors confined to the tympanomastoid compartment with erosion of the carotid canal.
Class C	Tumors extending beyond the tympanomastoid cavity, destroying bone of the infra-labyrinthine and apical compartment of the temporal bone and involving the carotid canal: C1 Tumors with limited involvement of the vertical portion of the carotid canal. C2 Tumors invading the vertical portion of the carotid canal. C3 Tumors with invasion of the horizontal portion of the carotid canal. C4 Tumors reaching the anterior foramen lacerum.
Class D	Tumors with intracranial extension: De1 Tumors with up to 2 cm dural displacement. De2 Tumors with more than 2 cm dural displacement. Di1 Tumors with up to 2 cm intradural extension. Di2 Tumors with more than 2 cm of intradural extension. Di3 Tumors with inoperable extension.
Class V	Tumors involving the vertebral artery (VA): Ve Tumors involving the extradural VA. Vi Tumors involving the intradural VA.

achieved. This has resulted in the introduction of the term “gross-total” or “sub-total” removal followed by postoperative radiotherapy to selected patients. The “sub-total” approach aims to preserve or limit cranial nerve palsies, allows for substantial tumor debulking and reduction of its mass effect, decompressing the bony periphery, and provides a smaller target volume for any subsequent radiation treatment, most usually stereotactic radiotherapy. This mode of treatment has increasingly been offered to many patients, resulting in “good quantity and quality of life” and providing a balance between surgical risk and tumor size reduction.[51-53]

Decision-Making

A review of the treatment outcomes of surgery and radiotherapy stratified per Modified Fisch Classification has reported that there is no “one-size-fits-all” approach, and that the key to successful TBPGs management is a personal approach, aiming for the best practice for each individual patient.[53-55] For Fisch class A and B tumors, surgery seems to be the best treatment option, which includes the majority of TMPs. Active surgical treatment should be offered to all symptomatic patients of all ages with early class disease that can be performed with minimal treatment morbidity TBJPs or Fisch Class B and C1 glomus tumors.[54] For patients who present with cranial nerve paralysis before treatment, the decision to undertake surgery is more likely to be tolerated better than patients whose cranial nerves are “normal functioning”; alternative options may be offered.[56] Patients’ age at presentation and their ability to tolerate unilateral postoperative lower cranial palsies are very demanding and permanent. It has been remarked that there is a set of converging criteria guiding the choice of “wait-and-scan” and active treatment that relates to the function of the IX and X cranial nerves (glossopharyngeal and vagus), the tumor growth rate, and the patient’s age.[57] For some patients, the “wait-and-scan” approach in the natural history of an untreated tumor will lead to the same neurological dysfunction but is more tolerated by most patients.[56] The major problem is defining the cutoff age to separate “young” patients from “elderly” patients. Traditionally, the elderly are those persons aged 65 years or older, but most authors refer to this group without an age definition and consider that aged 60 with no growth be recommended “wait-and-scan,” and patients with evidence of growth be treated with radiosurgery.[57,58] Many authors recommend that mutant-negative patients with single TBPGs presenting over 50 years of age, with minimal symptoms (hearing loss, pulsatile tinnitus), normal cranial nerve function or compensated cranial nerve palsies, and no imminent intracranial or vascular complication, a “wait-and-scan” approach can be recommended.[37,43] Clinicians who make a recommendation that a “wait-and-scan” policy is to be followed by the patient, this decision should be made in adherence to an agreed algorithm, which has been approved by members of the treating multidisciplinary team.[7,11,26,58-60]

Vagal Paraganglioma

Vagal paragangliomas (VPG) arise from the paraganglionic tissue within the perineurium of the vagus nerve (CNX). The incidence is estimated at 1 per 100 000 persons at risk per year. Vagal paragangliomas are >5% of HNPGs.[61] Vagal paragangliomas are benign tumors and can arise anywhere along the course of the vagus nerve, superiorly as a dumbbell lesion at the jugular foramen to the inferiorly located recurrent laryngeal nerve.[23]

Germline Mutation

Vagal paragangliomas are associated with a germline mutation of the SDHx gene which implies a familial predisposition and risk of multifocal disease. Up to 70% of VPG have a SDHx mutation, with a 50% mutation in females, and 85% mutation in males.[22] In those with genetic predisposition, multicentricity is found in 78%-85%.[45] Metabolically active VPG is considered rare, being diagnosed in 4%-5%.[26,46] The incidence of malignancy is estimated at 6.3%.[25]

Classification

As a result of developments in surgical techniques for skull base surgery, it has been possible to extend the cervical surgical cervical approach to include a transtemporal bone combined approach

Table 4. Classification of Vagal Paraganglioma[62]

Stage I	Tumors that lie in the parapharyngeal space without invasion of the jugular foramen.
Stage II	Tumors that invade the jugular vein without bone destruction.
Stage III	Tumors that deeply invade the jugular foramen and middle ear with bone destruction and variable involvement of the carotid canal (may overlap with classification of temporal bone tumors).

which has expanded the current classification that includes elements of the temporal bone classification (Table 4).[62]

Presentation

A cervical neck mass which may or may not be pulsatile, or it may present as a pharyngeal mass. Other symptoms include hoarseness from CNX paralysis or other lower CN palsies (X, XI, XII, VII, Horner's syndrome), along with their associated physical dysfunctions.[20,61]

Diagnosis

Early diagnosis of VPG is considered challenging, and diagnosis is best made by cross-sectional imaging, including CT and MRI with contrast.[61] MR angiography and perfusion angiography can estimate the degree of vascularity of the tumor and tumor flow dynamics and assess the degree of internal carotid involvement and intracranial vascularity. Serial imaging and functional imaging should be included in the initial work up of VPG to assess growth in a wait-and-scan strategy, and to identify multiple site involvement. The identification of catecholamine secretion should also be excluded as part of the initial assessment.[61]

Treatment Options

Because surgery, which has been the "standard of care" for HNPGs for some decades, more recently, due to the sequelae of surgery on a functioning cranial nerve (X vagus), resulting in 100% paralysis, less invasive strategies such as "wait-and-scan" or radiotherapy are always preferred.[63] Patients who are young, with no CN palsies, and non-secreting, should be recommended a "wait-and-scan" strategy—should the tumor mass be expanding or becoming more symptomatic, surgery should be advised. More elderly patients (>60 years) with several CN palsies after a "watch-and-scan" strategy, should they have an expanding tumor or increasing symptoms, should be offered radiotherapy. Patients with bilateral growing disease, secreting tumors, and CN palsies should be considered for surgery. Some patients (bilateral disease) may be unwilling or unfit for surgery and should consider radiotherapy or proton therapy. Some patients may be suitable for therapeutic nuclear medicine (theranostics).[61]

Multicentricity Head and Neck Paragangliomas

The management of patients with multicentric HNPGLs cannot be determined by an algorithm because many factors need to be considered, and the therapeutic option must be individualized. These factors include the age and general condition of the patient, the biological behavior of the tumor, tumor size and location, genetic results, bilaterality, lower cranial nerve function, and the potential morbidity of the treatment (surgery/radiotherapy).[64] Surgery is considered preferable for CBT and VPG—while the risks of cranial nerve paralysis with early-stage CBT are small, attempts at preserving the vagus nerve are seldom achieved. The optimal management of JVPG is more controversial. The risk of radiation-induced malignancy has to be considered in younger patients. The use of external beam radiotherapy and stereotactic radiosurgery have demonstrated similar chances of tumor control compared to surgery.[65] For, bilateral VPG, it is best to remove the largest tumor and "watch-and-scan" the contralateral side, considering irradiation if increasing in size with symptoms. For bilateral JTPGLs, a "watch-and-scan" approach should be followed for both tumors. If one begins to increase in size, then operate before the development of wide skull base invasion and irradiate the second side. The use of 3D modeling has been shown to be beneficial for establishing a surgical decision strategy (trauma-free excision) for patients with multiple HNPGLs.[66] Much advance has been made in the specialty of radiopharmaceutical theranostics that can target certain biological pathways and receptors, by appropriate pairing of radionuclide scintigraphy and radiotherapeutics. Early results have shown considerable therapeutic efficacy and tolerable toxicity in patients with multicentric, metastatic, and "inoperable" HNPGLs. Further investigations are needed.[67]

Conclusion

Head and neck paraganglioma are rare, typically benign, vascular neoplasms that embryologically originate from the extra-adrenal paraganglia of the neural crest. Due to their rarity, there is often a delay in primary referral, leading to advanced-stage disease at diagnosis. Additionally, patients face a lifelong risk of developing multiple independent tumors, multicentric tumors, post-treatment local tumor recurrence, as well as the potential risk of local and distant metastasis. Therefore, all patients with HNPGLs should be managed and treated in a regional or central center where a wide range of specialist expertise is available and further research can be undertaken. Combining several tertiary hospital institutions, larger-scale prospective data are necessary to help improve our understanding of long- and short-term outcomes and to establish treatment protocols.

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