



Tympanic paragangliomas: a large case series and single institutional experience

Timothy Mclean¹, James Rudd¹, Stephen J. Kerr^{2,3}, Michael Gleeson¹, Rupert Obholzer¹

¹Department of Otolaryngology, Guy's and St. Thomas' Hospital, London, UK; ²The Kirby Institute, The University of New South Wales, Sydney, Australia; ³Biostatistics Excellence Centre, Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand

Contributions: Contributions: (I) Conception and design: T Mclean, R Obholzer; (II) Administrative support: T Mclean, J Rudd, SJ Kerr, R Obholzer; (III) Provision of study materials or patients: T Mclean, J Rudd, M Gleeson, R Obholzer; (IV) Collection and assembly of data: T Mclean, J Rudd, M Gleeson, R Obholzer; (V) Data analysis and interpretation: All authors; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Rupert Obholzer. Guy's Hospital, Great Maze Pond Road, SE1 9RT, UK. Email: rupert.obholzer@nhs.net.

Background: Head and neck paragangliomas (HNPGs), of which tympanic paragangliomas (TPGs) or glomus tympanicum are a subset, are rare and complex tumors. Our understanding of HNPGs is rapidly evolving especially in relation to the genetic basis of this disease. This study aims to review the clinicopathologic factors and treatment outcomes of a large series of TPGs to help inform future treatment decision making.

Methods: Guy's and St Thomas' Hospital Trust maintains a prospective database of HNPGs. A clinical review of this database was performed from 1984 until 2019. There were 349 cases of HNPGs. After applying inclusion and exclusion criteria there were a total of 56 cases with a clinical or pathologic diagnosis of a tympanic paraganglioma suitable for analysis.

Results: The average age at presentation was 53.4 years (SD \pm 13.1), with a male to female ratio of 1:17.7. There were genetic mutations or variants of uncertain significance (VUS) associated with TPGs found in four (7.1%) patients. Five (8.9%) patients with TPGs had multiple paragangliomas. Of all patients with TPGs, three (5.4%) had other HNPGs and two (3.6%) had other non-HNPGs. The difference in median pre- and post-operative air conduction (AC) threshold and bone conduction (BC) thresholds was a 7 dBHL and 1 dBHL improvement respectively. Progression free survival or treatment failure was calculated for TPGs with progression free survival probability at 5 years: 0.93 (95% CI: 0.73–0.98), and at 10 years: 0.88 (95% CI: 0.68–0.96).

Conclusions: Improved understanding of TPGs will lead to better assessment, management and patient outcomes.

Level of Evidence: Level IV.

Keywords: Tympanic paraganglioma (TPG); glomus tympanicum; head and neck paragangliomas (HNPGs); succinate dehydrogenase (SDH); case series

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Introduction

Tympanic paragangliomas (TPGs) are rare, histologically benign but locally invasive neoplasms originating in the middle ear (1-5). Until reports by Guild and Rosenwasser they

were not widely recognised or understood (6-8). TPGs are a subset of head and neck paragangliomas (HNPGs), which are uncommon neuroendocrine tumors (9), and derived from neural crest cells associated with parasympathetic paraganglia (10). TPGs arise along the tympanic branch of

the glossopharyngeal nerve or less commonly the auricular branch of the vagus nerve (3,5).

TPGs commonly present with pulsatile tinnitus and/or hearing loss (1-4). They characteristically demonstrate slow growth, which can be unpredictable, and eventually lead to complications (11-14). For TPGs, surgical treatment is still commonly held as the ideal management approach with the technical aspects being well established (3,4,15,16). However, there is still a lack of consensus about the optimal management of HNPGs (17). Our understanding of HNPGs, in particular the genetics of paragangliomas, has evolved rapidly over the last few decades (11,18). As a result, the approach to the assessment of TPGs has significantly changed in light of this (10). In spite of this, clinicopathologic and treatment data for TPGs is sparsely reported in the literature. Our study presents one of the largest longitudinal series of TPGs with a focus on the clinicopathologic factors and treatment outcomes.

We present this following article in accordance with the CARE reporting checklist (available at <http://dx.doi.org/10.21037/ajo-20-71>)

Methods

Study cohort

Guy's and St Thomas' Hospital Trust London, United Kingdom maintains a prospective clinicopathological database of HNPGs. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Quality Improvement and Patient Safety Committee at Guy's and St Thomas' Hospital Trust and individual consent for this retrospective analysis was waived. A retrospective review of the HNPG database was performed and this identified 349 cases with HNPGs managed from 1984 until 2019. Inclusion criteria for this study were all patients with a clinical or pathologic diagnosis of a TPG, giving 59 cases. Exclusion criteria included any patient with no demographic or clinicopathologic details in the database, and so 3 cases were excluded leaving a total of 56 cases suitable for analysis.

Clinicopathologic and treatment factors

A literature review was performed to determine significant clinical, pathologic, and treatment factors for TPGs including: gender, age at diagnosis, tumor location, multifocality, genetic testing, hormone secretion,

malignancy, follow-up date, death date, and cause of death.

The database listed a small number of cases with tumors that could be regarded as facial paragangliomas, and these were included in the tympanic paraganglioma group.

Treatment factors included: treatment type, treatment date, and treatment failure. The initial treatment window was defined as 2 years from first treatment date for any intervention or from diagnosis if an intervention was planned. The reason for this is that if multimodality or staged treatment was planned then it can take time to complete. Treatment failure, or progression, was defined as recurrence requiring further intervention after 2 years from initial treatment, or metastasis or death at any time after initial treatment has occurred.

Statistical analysis

The database is compiled into Excel Version 16.6.11 (Microsoft Corp., Redmond, Washington, United States of America) for Mac (Cupertino, California, United States of America) and analysed using Stata 16.0 (Statacorp, College Station, Tx, USA).

Time from diagnosis to progression was calculated, and patients who did not progress were censored at the last date of follow-up when no progression was confirmed. The Kaplan-Meier method was used to calculate disease free-survival probabilities, and the logrank test was used to formally test whether predictor covariates of interest were associated with progression. Factors tested included age at presentation, sex, whether or not the patient had multiple lesions, whether the tumour was secreting or had mutations, tumour size, and treatment modality. Malignancy was not tested as there were no malignant TPGs.

An analysis of treatment failure correlated to clinical and treatment factors was performed. The analysis was of 54 cases of TPGs as two were censored due to incomplete data. No statistically significant clinicopathologic or treatment factors were found that correlated with treatment failure for TPGs.

Results

Clinicopathologic

This study included 56 patients with TPGs, and each patient had only one TPG. The average age at presentation was 53.4 years (SD \pm 13.1), with a male to female ratio of 1:17.7 (*Table 1*).

Clinicopathologic features are detailed in *Table 2*. There

Table 1 Demographics of tympanic paragangliomas.

Variable	Outcome
Cases	56
Tumors	56
Age at presentation ± SD (years)	53.4±13.1
Gender (male:female)	3:53 (1:17.7)

Table 2 Clinicopathologic features of tympanic paragangliomas.

Variable	Outcome
Median [IQR] maximum dimension at presentation (mm)	9 [6–12] mm
Genetic mutation in HNPG	4 (7.1%)
Metanephrines/metadrenalines (total)	0–1
Metanephrines/metadrenalines (plasma)	0
Metanephrines/metadrenalines (urine)	0–1
Malignant HNPG	0

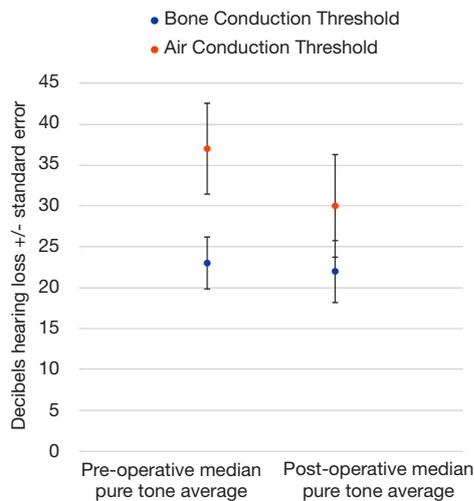


Figure 1 Audiologic outcomes for tympanic paragangliomas—median of the air conduction and bone conduction pure tone average thresholds both pre- and post-operatively.

was a slight right sided predominance of tumors at 52.9% seen in our series. The median tumor maximum dimension at presentation was 9 mm with interquartile range (IQR) of 6–12 mm. There was a genetic mutation or variants of uncertain significance (VUS) associated with TPGs found in four (7.1%) patients. Five (8.9%) patients with TPGs had

multiple paragangliomas. Of all patients with TPGs, three (5.4%) had other HNPGs and two (3.6%) had other non-HNPGs.

When patients have multiple paragangliomas there is uncertainty about which tumor is the source of the secretions, therefore it is only possible to give a range of the proportion of secretory tumors. A number of patients with TPGs, where secretion was detected, had multiple tumors including some with non-HNPGs. The proportion of tumors that were secretory for TPG ranged from 0–1.8%.

There were no TPGs associated with malignancy in this cohort of patients.

Hearing outcomes

There were 21 patients who had pre- and post-operative audiograms, and this data is illustrated in *Figure 1*. Air conduction (AC) and bone conduction (BC) thresholds were assessed across frequencies from 250 Hz, 500 Hz, 1 kHz, 2 kHz, 4 to 8 kHz both pre- and post-operatively. A pure tone average (PTA) was calculated using those frequencies. The median pre-operative AC PTA was 37 (IQR, 14–50) Decibels hearing level (dBHL). The median pre-operative BC PTA was 23 (IQR, 12.5–31) dBHL. The median post-operative AC PTA was 30 (IQR, 18–67) dBHL. The median post-operative BC PTA was 22 (IQR, 13.5–38.5) dBHL. The difference between the medians pre- and post-operative AC and BC PTAs was a 7 Db and 1 decibels improvement respectively. Only one patient suffered a greater than 20Db worsening in hearing thresholds, with a 61 Decibel deterioration of their PTA post-operatively. No patients ended up with an anacoustic ear.

Treatment

Details of treatment for the TPGs is outlined in *Table 3*. The mainstay of treatment was surgery, which was performed on 49 tumors (87.5%). Four cases were observed and the initial treatment for 2 cases could not be determined due to lack of data, and these were classified as ‘Other’ in *Table 3*. In one case treatment was by radiation and this was performed 40 years ago with the reasoning behind this treatment decision being unclear. The median tumor follow-up to progress or censoring was for 40 months (IQR, 15.8–89.3).

Progression free survival or treatment failure was calculated for TPG in *Figure 2*, with progression free survival probability at 2 years: 0.97 (95% CI: 0.82–0.996), at 5 years:

Table 3 Initial treatment of tympanic paragangliomas

Treatment modality	Patients
Observation	4
Surgery	49
Radiation	1
Multimodality	0
Other	2
Total	56

0.93 (95% CI: 0.73–0.98), and at 10 years: 0.88 (95% CI: 0.68–0.96). The incidence rate for failure for the entire sample is 5 over 288.2 PYFU; or 1.73 (95% CI: 0.872–4.2)/100 PYFU.

Complications

If hearing loss is excluded then complications included 4 tympanic membrane perforations, 1 case of external auditory canal stenosis and 1 case chronic mastoid cavity infection.

Discussion

The natural history of TPGs is usually one of indolent growth however, HNPG growth can at times be unpredictable (10,12,19). Due to their inherent proximity to the facial nerve and inner ear, the onset of facial palsy and sensorineural hearing loss may be associated with tumors of a small size (4). The aim of surgical intervention is to remove the tumor and thus prevent the complications of progressive tumor enlargement and to alleviate symptoms. For these reasons, treatment of TPGs is by surgery where possible, and conservative management is generally offered to patients unfit for surgery (3,4). Surgery for TPGs usually is curative and has a low morbidity profile and complete resection minimises the risk of morbidity secondary to the tumor, such as hearing loss or facial nerve palsy (2,4,20).

Clinical factors

The literature reports two different statistics with regards to age: (I) age at presentation and (II) age at first treatment, however it is often unclear which is being reported. The average age of TPGs reported in the literature range from 52.6–60.3 years, and a bimodal distribution has been

reported (2–4,14,21). This age range was consistent with the average age of presentation in our series of 53.4 years (SD \pm 13.1), and age was normally distributed in this study.

Our series noted a slight right sided predominance at 52.9%, but this has not been observed in the literature (2–4).

A female preponderance has been reported in the literature for HNPGs, with the overall male to female ratio of ranging from 1:1.7–4 (14,17,21–23). The gender distribution for the different HNPG subtypes varies, with females more commonly developing TPGs followed by jugular paragangliomas, vagal paragangliomas and carotid body tumors. The male to female sex distribution for TPGs in the literature ranges from 1:2.7–9.5, while it is higher in our series at 1:17.1 (3,4,14,15,21). There is a low germline succinate dehydrogenase (SDH) mutation rate associated with TPGs (3,14). This may explain the female preponderance, as male gender has been reported as a predictor for a mutation in SDH gene (24).

The median maximum tumor dimension at presentation in our series was determined via radiological means as the maximum dimension in any plane either axial, sagittal or coronal. TPGs are often diagnosed while small and our series supports this finding. This is thought to be due to TPGs eliciting symptoms, such as hearing loss or pulsatile tinnitus, at an earlier stage compared to other HNPG.

In our series, 5 (8.9%) patients with TPGs had multiple paragangliomas and this comprised of both HNPGs and non-HNPGs. There were no bilateral TPGs observed in our patients. In the literature, rates of multiplicity in cases with TPGs is low (4). This is explained by the fact that SDH mutations increase the rates of multifocal tumors and there is a low mutation rate observed for TPGs (3,14).

Pathologic factors

Genetic testing for HNPGs is relatively recent occurrence, after the discovery of the SDH variant association identified in hereditary paragangliomas in 2000 (25). Genetic screening now is an important part of the assessment and management for most HNPGs (10,18). However, there is no consensus regarding genetic testing in HNPGs, with some clinicians recommending selective testing while others advocating universal testing for all HNPGs (11,18,24,26). At our institution genetic testing for HNPG is being utilised with increasing frequency. Not all patients in this study underwent genetic testing because our series predates the introduction of genetic testing.

Pathogenic variants in SDH identified in patients with

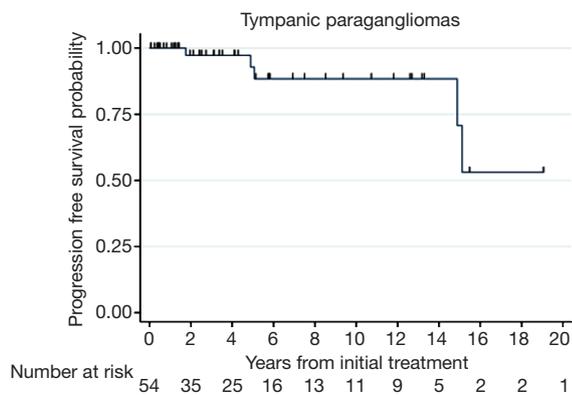


Figure 2 Kaplan Meyer overall survival curve for tympanic paragangliomas.

HNPG is associated with a positive family history, multiple tumors, younger age at presentation and male gender (24). These trends were not clearly seen in our series due to the low rates of pathologic SDH variants associated with TPG (7.1%). The lack of family history or pathogenic variants associated with TPG are consistent with the literature (3,14). Based on this study screening patients with TPGs for other paragangliomas or a predisposing germline mutation though not routinely needed should at least be considered on a case by case basis.

Metanephrines or metadrenalines can be tested in urine or plasma, with the latter test being easier and having a higher sensitivity and specificity (27). HNPGs are associated with the parasympathetic nervous system while non-HNPG are associated with the sympathetic nervous system and this accounts for the lower rates of secretion in HNPGs (28). The proportion of cases for all HNPGs where metanephrine secretion is detected is estimated in the literature to be 1–6% (14,17,21,29). Metanephrine secretion is almost never associated with isolated TPGs with the proportion secreting reported at less than 1%. The reason for this is uncertain but it may be related to the small size of TPGs (2-4,30). The proportion of metanephrine secreting TPGs in our series is estimated to range from 0–1.8% (Table 2). The range reflects the uncertainty around identifying the source of secretion in patients with multiple tumors. The lower limit of the range represents the proportion of secreting isolated TPGs. The upper limit of the range theoretically equals the proportion of secreting TPGs if in patients with multiple HNPGs then the TPG is always the source of metanephrines.

A limitation of our series is that it may underestimate secretion rates as there was incomplete testing of patients with TPGs and also some patients were tested using urinary tests which are less sensitive.

There were no TPGs associated with malignant change in our series (Table 2). Malignancy in paragangliomas can be difficult to determine as there are no definitive histopathologic criteria, but is defined by metastatic spread which in turn can be complicated by the multifocal nature of HNPGs (17,18). The overall malignancy rate in the literature for HNPGs varies widely from 0–19%, and differs by subtype (9,14,17,21,22,31,32). The rates of malignancy directly correlate with the proportion of genetic variants seen in each HNPG subtype (11,33,34), and that would help explain the fact that TPGs are not usually associated with malignancy (4).

Audiologic outcomes

TPGs commonly cause hearing loss. The hearing loss may be conductive or mixed hearing loss as TPGs often impinge on the ossicular chain and tympanic membrane (3). Less commonly there can be involvement of the inner ear causing a sensorineural hearing loss (4). In general, surgery would be expected to correct any conductive hearing loss and prevent a sensorineural hearing loss developing as a result of a TPG. Due to the location of TPGs there is a small but significant risk to hearing with surgery. In this study hearing thresholds were relatively well preserved, with the difference between pre- and post-operative median AC and BC mean PTA thresholds levels being a 7 Db and 1 Db improvement respectively, as seen in Figure 1. In the literature, reported hearing outcomes vary after surgery. Overall, with respect to hearing levels after surgery for TPGs there may be a small improvement, or deterioration, or they may remain unchanged, with a poor hearing outcome being an infrequent complication (3,4,15).

Treatment

The majority of patients (87.5%) in our series were treated with surgery with only 5 treatment failures, and this is similar to other series in the literature (3,4). The TPGs in our series were, on the whole, primarily treated at our institution. Of the 5 failures 40% (n=2) were both treated and then successfully salvaged with surgery at our institution. Another 40% (n=2) were operated on elsewhere and referred due to a recurrence requiring surgery. The last

failure was a patient with a TPG who initially requested conservative management, but then after 15 years of observation required surgery due to progressive tumor growth and associated symptoms. Exclusion of those last 2 categories of failures, either initially treated externally or who refused surgical management, would produce an even lower failure rate. Thus, surgical management of TPGs at a high-volume centre leads to excellent outcomes. There is a low recurrence rate and good long-term control reported in the literature which is comparable to that in this study (2-4,35). The low rate of treatment failure or disease progression limits a statistical analysis of factors contributing to failure.

The key to surgical management is a thorough pre-operative clinical and radiological assessment (3). The vascular supply to the TPGs is usually the inferior tympanic branch of the ascending pharyngeal artery, but may receive supply from other arteries including the caroticotympanic branches of the internal carotid artery (15). The surgical approach for TPGs is commonly via either a transcanal or transmastoid approach (2-4,10,14,16,36), with an emphasis on surgical access and addressing the tumor vascular supply (15,16).

Based on the outcomes reported in this study and the literature regarding TPGs, a minimum 5-year period of clinical follow-up after treatment would be advised (2,4,37,38). Post-operative imaging would be recommended if the patient becomes symptomatic or is suspected of developing another HNPG. Surveillance image may also be required in patients who are at risk of developing other paragangliomas (10,39-41).

Complications

Intra-operative complications are uncommonly reported in surgery for TPGs (3,4), however rare and serious complications have been reported (4). If changes in hearing level are excluded, our series had a low rate of complications at 10.7% with most being relatively minor in nature, such as tympanic membrane perforation or post-operative wound infection. As discussed previously only one patient had a greater than 20 Db deteriorating in hearing thresholds.

Our series has a number of limitations including being retrospective in nature and lacking a complete data set. Also approach to management of TPGs has evolved over time and this inherently reflected in our series. Despite these limitations our series provides insights into clinicopathologic and treatment of a rare disease.

Conclusions

TPGs are rare middle ear tumors that require a careful and thorough assessment. This study shows TPGs are associated with other paragangliomas and also germline SDH mutations, and that surgical treatment is safe and effective strategy and should be used where possible. Improved understanding of these tumors will hopefully lead to better patient outcomes.

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Footnote

Reporting Checklist: The authors have completed the CARE reporting checklist. Available at <http://dx.doi.org/10.21037/ajo-20-71>

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Quality Improvement and Patient Safety Committee at Guy's and St Thomas' Hospital Trust and individual consent for this retrospective analysis was waived.

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