The Journal of Laryngology & Otology (2017), ***131***, *580–584*.
© JLO (1984) Limited, 2017
doi:10.1017/S0022215117000809

REVIEW ARTICLE

Active surveillance management of head and neck paragangliomas: case series and review of the literature

L HARRISON[1], R CORBRIDGE[2]

[1]*Department of ENT, Head and Neck Surgery, Northampton General Hospital, and* [2]*Department of ENT, Head and Neck Surgery, Royal Berkshire Hospital, Reading, UK*

Abstract

Background: Head and neck paragangliomas are rare. They are usually slow-growing, benign, non-catecholamine secreting tumours, traditionally treated with surgical excision. Complications of surgical excision include lower cranial nerve palsies, stroke and death.

Method: A retrospective case note analysis was conducted of patients with head and neck paragangliomas treated with a watch-and-scan policy from March 2003 to September 2015, and the relevant literature was reviewed.

Results: Fifteen head and neck paragangliomas were identified. None of the patients developed a new lower cranial nerve palsy or progression of their presenting hearing loss during the follow-up period. Five patients displayed an increase in maximum linear dimension of 4 mm over an average of 57.4 months. A review of the literature showed that a watch-and-surveillance scan policy is evolving as a treatment option for head and neck paragangliomas without malignant risk factors.

Conclusion: Readily available surveillance scanning in head and neck paragangliomas enables the monitoring of head and neck paragangliomas, which may allow for avoidance of major surgery.

Key words: Paragangliomas; Head And Neck Neoplasms; Surgery; Medical Imaging

Introduction

Head and neck paragangliomas are rare and account for around 3 per cent of all paragangliomas.[1] Head and neck paragangliomas arise from neural crest derived cells found in the region of the parasympathetic paraganglia, and are frequently found in the vagal, tympanic and jugular paraganglia, as well as carotid bodies. Head and neck paragangliomas are usually slow-growing, benign, non-catecholamine secreting tumours, most frequently originating from the carotid body at the bifurcation of the common carotid. They can be locally aggressive and lead to lower cranial nerve palsies.

Around 3–5 per cent of paragangliomas will undergo malignant transformation.[2–4] Factors such as genetic background, tumour size, anatomical location and high metadrenaline levels are associated with malignant disease. Malignant potential is uncommon and difficult to predict. A rapidly enlarging neck mass, pain and younger onset age can be associated with underlying malignancy.[5–7] Histopathological features cannot reliably distinguish benign from malignant tumours, and malignancy is confirmed with the presence of regional or distant metastasis to non-endocrine tissue.[8]

In recent years, an active surveillance approach has emerged for those with head and neck paragangliomas, without malignant risk factors, who may be poor surgical candidates or have multifocal disease. Where possible, the traditional mainstay of treatment is surgical excision, which aims to prevent the local destruction of adjacent lower cranial nerves.[9] Surgical excision can offer a cure, but is associated with significant morbidity due to cranial nerve involvement. Further options include stereotactic radiosurgery and external beam radiotherapy. Radiotherapy has been shown to achieve local control, with less morbidity and similar oncological outcomes to surgery; however, the symptomatic control of hearing loss and pulsatile tinnitus is less promising.[10,11]

Readily available magnetic resonance imaging (MRI) is an accurate way of monitoring growth in head and neck paragangliomas without malignant risk factors. Currently, there is a paucity of evidence on the natural disease progression of head and neck paragangliomas; therefore, we report our experience on

Accepted for publication 18 January 2017 First published online 17 April 2017

https://doi.org/10.1017/S0022215117000809 Published online by Cambridge University Press

watch-and-surveillance scanning in head and neck paragangliomas.

Materials and methods

We retrospectively reviewed all head and neck paragangliomas managed with watch-and-surveillance scanning at two centres within the Thames Valley region, in the UK. Paragangliomas at all head and neck sites, including the carotid body, and jugulotympanic and vagal paragangliomas, were included. Patients were identified from the senior author's caseload using electronic medical records. All diagnoses were made using either MRI or computed tomography (CT).

Data obtained for each patient included demographics, anatomical site, presenting symptoms, development of symptoms such as cranial nerve palsy and hearing loss, rate of conversion to surgical or radiosurgical treatment, and paraganglioma growth rate between the date of the first presentation and the last follow up.

A literature search of the databases Medline, Embase, Cochrane Library and NHS Evidence, from inception to September 2015, was also performed to review the natural disease progression of head and neck paragangliomas.

Results

A total of 15 head and neck paragangliomas and 14 patients (10 females and 4 males) who underwent watch-and-surveillance scanning, with complete medical records, were identified for analysis. All patients presented from March 2003 to September 2015, with a range of 8 to 143 months' follow up. Mean age at presentation was 61 years (range, 39–79 years). Four cases were found incidentally, six presented with a neck lump and two with pulsatile tinnitus. Two patients with jugulotympanic paragangliomas presented with associated sensorineural hearing loss, and one patient with a carotid body paraganglioma presented with bilateral sensorineural hearing loss and tinnitus unrelated to the tumour. Magnetic resonance imaging was used for diagnosis with serial examination in 13 patients, and CT was used for 1 patient.

Three patients had bilateral head and neck paragangliomas in this series. Two of these patients received surgical treatment for their first head and neck paragangliomas, as they presented over three decades ago when surgery was the mainstay of treatment. The surgically treated tumours are not included in this study. One patient sustained left vocal fold palsy following the surgical excision of a left jugulotympanic paraganglioma and declined surgery to the right vagal paraganglioma. The other patient had surgery to a carotid body paraganglioma; a carotid body tumour was an incidental finding on the other side at a later date, which was treated conservatively. One patient with bilateral jugulotympanic paragangliomas was managed conservatively and therefore both paragangliomas were included in the series.

TABLE I
PRIMARY ANATOMICAL SITE OF HEAD AND NECK PARAGANGLIOMAS

Head & neck paraganglioma type	Cases (*n*)
Vagal paragangliomas	3
Jugulotympanic paragangliomas	6
Carotid body paragangliomas	6

Table I shows the primary anatomical sites of the head and neck paragangliomas.

Only one patient presented initially with lower cranial nerve palsy. This was a case of a jugulotympanic paraganglioma, which had affected the hypoglossal and vagus nerves. Percutaneous endoscopic gastrostomy was eventually required to prevent aspiration. Interesting, the three patients with vagal paragangliomas did not have vocal fold palsies at presentation.

None of the patients in the case series developed a new lower cranial nerve palsy or progressive hearing loss during the follow-up period. Furthermore, none of the patients were converted to surgical or stereotactic radiosurgery. The largest increase in size was an incidental carotid body tumour, which increased in maximum linear dimension by 10 mm over a period of 119 months; this patient had undergone previous surgery on a contralateral carotid body tumour.

The median follow-up duration across all cases in the series was 49 months. At the time of diagnosis, the median maximum linear dimension on imaging was 20 mm (range, 5–50 mm), in comparison to 22 mm at the time of the last follow up. Ten head and neck paragangliomas (67.7 per cent) remained stable, whilst five (33.3 per cent) demonstrated growth between presentation and last follow up. The median increase in maximum linear dimension between presentation and last follow up on imaging was 4 mm over an average time frame of 57.4 months.

None of the patients in the study died of their disease, although one patient died of unrelated causes. Common indications for initial observation of patients in this case series included co-morbidities, the likelihood of surgical morbidity and patient choice.

A review of the literature from inception to September 2015 revealed five articles where head and neck paragangliomas had been managed with active surveillance.[12–16] The results are summarised in Table II.

Discussion

Aetiology and pathogenesis

Head and neck paragangliomas are rare, slow-growing tumours. They accounted for only 0.012 per cent of cases in a large oncological surgical series of paragangliomas.[17] Head and neck paragangliomas originate from neuroendocrine cells arising from the parasympathetic autonomic nervous system, in comparison to thorax or pelvis paragangliomas, which usually arise

https://doi.org/10.1017/S0022215117000809 Published online by Cambridge University Press

TABLE II
FINDINGS FROM OTHER CASE SERIES FOR CONSERVATIVE MANAGEMENT OF HEAD AND NECK PARAGANGLIOMAS

Study (year)	Tumours (*n*)	Mean patient age (years)	Asymptomatic at presentation (*n*)	Cranial nerves with paresis at presentation (*n*)	Follow-up duration (months)	Tumours that grew (*n*)	Mean growth (mm per year)
Current study (2017)	15 total*	61	4	1	49	5	0.8
Kunzel *et al.*[12] (2014)	2 carotid body & 1 jugulotympanic paragangliomas	42.3	3	1 Xth & right XIIth CN paresis	156	1	Unknown
Carlson *et al.*[13] (2015)	8 jugulotympanic paragangliomas	Unknown	Unknown	Unknown	25.5	Unknown	Unknown
Langerman *et al.*[14] (2012)	47 total; 28 carotid body & 19 vagal paragangliomas	56	30	0	60	17 (38%)	2
Cosetti *et al.*[15] (2008)	4 total	74.5	9	Unknown	24–396	2	Unknown
Jansen *et al.*[16] (2000)	48 total; 20 carotid body, 17 vagal & 11 jugulotympanic paragangliomas	Unknown	32 (67%)	0	50	29 (60%)	0.83

*For breakdown, see Table I. CN = cranial nerve

from the sympathetic autonomic nervous system. Physiologically, one of the main differences between parasympathetic and sympathetic paraganglia is that the parasympathetic ones, which are found in the head and neck, rarely secrete catecholamines.[18]

Head and neck paragangliomas are associated with a genetic mutation of gene complexes that encode for succinate dehydrogenase, an enzyme complex bound to the inner membrane of mitochondria.[4] Up to 50 per cent of head and neck paragangliomas are familial,[4,19,20] and genetic mutations have been found in 92 per cent of patients with a positive family history. Those with multiple paragangliomas, a young age at diagnosis, male gender and malignant disease have a higher chance of genetic mutation.[20,21] In those where an SDH mutation is identified, close monitoring and screening of first-degree relatives is advocated.[4]

Incidence

Classically, head and neck paragangliomas present in the fourth and fifth decades of life, and affect more females than males.[10,22] In our series, the average age at presentation was 61 years and the tumours predominantly affected females. One explanation for this is the higher sensitivity of hypoxia in females as a result of the lower baseline haemoglobin level of 12–16 g/dl, in comparison to 14–18 g/dl in males. Hypoxia induces hyperplasia of the chemoreceptors, and paragangliomas are 10 times more prevalent at high altitude.[23,24] With this in mind, paragangliomas can be considered as more extensive hyperplasia rather than neoplasia.[23] Head and neck paragangliomas most frequently arise from the carotid body,[4] which is also evident in our series.

Investigation

Advances in imaging techniques have improved detection and surveillance of head and neck paragangliomas. Computed tomography and MRI are readily available cross-sectional imaging techniques. High-resolution contrast CT may have an advantage over MRI in delineating small jugulotympanic paragangliomas and extension of these tumours.[2] However, for most other localisations, MRI provides superior diagnostic information to CT, identified by a salt and pepper appearance in T1- and T2-weighted images.[2] Magnetic resonance imaging not only allows tumour detection, but also characterisation, and assessment of tumour extension and vessel encasement.[2] Magnetic resonance imaging also avoids exposure to ionising radiation, an important consideration in the context of surveillance.[25] A combination of unenhanced and contrast-enhanced three-dimensional time-of-flight magnetic resonance angiography can accurately detect small head and neck paragangliomas between 10 mm and 20 mm in size, which is particularly important in multicentric disease.[26,27]

Position emission tomography (PET) scanning techniques, including fluorodopa PET, somatostatin agonist PET-CT or fludeoxyglucose PET-CT, are highly

https://doi.org/10.1017/S0022215117000809 Published online by Cambridge University Press

sensitive in detecting head and neck paragangliomas. Obholzer *et al*. advocate PET scanning in all patients presenting with cervical paraganglioma, in order to identify multicentric disease.[8] Other authors have suggested PET scanning in those with a positive personal family history or succinate dehydrogenase genetic mutation, and in those with confirmed multifocality.[26]

Treatment and results

In 1989, van der Mey *et al*. compared the clinical outcomes of gross total resection with subtotal resection.[20] They found no improvement in clinical outcome, but a higher incidence of cranial neuropathy was apparent with gross resection. In that study, head and neck paragangliomas showed slow progression, and this is the basis on which the conservative management of head and neck paragangliomas has been explored.[20]

High rates of morbidity are associated with the resection of certain types of head and neck paragangliomas, particularly jugulotympanic paragangliomas, and those requiring infratemporal or lateral skull base approaches.[24,28] Post-operative disease control is variable: overall recurrence rates following surgery have been reported to be 57 per cent, and 83 per cent in those tumours greater than 2 cm.[9,29] A review of the literature by Cosetti *et al*., in 2008, showed post-operative control rates at between 80 and 95 per cent.[15] In many of these studies, those aged over 60 years old did not undergo surgical resection because of the significant morbidity and increased rehabilitative challenges in this age group.[15]

Many series have reported that complete resection of vagal paragangliomas results in the loss of vagus nerve function in the majority of cases.[13] Obholzer *et al*. report that, in their experience, no dissection plane exists between the entrance and exit of the vagus nerve, and, although there are reports that vagal nerve function is preserved, there is inevitable reduction of function.[8]

Regarding carotid body paraganglioma resection, an intra-operative mortality rate of 10 per cent has been reported.[15] Furthermore, post-operative mortality rates are as high as 4 per cent.[3,30] Other frequent functional deficits include Horner's syndrome, accessory nerve palsy, dysphagia, dysphonia and stroke. Pre-operative stenting of the internal carotid artery has been found to facilitate safe resection and avoid vascular injury.[31]

Interestingly, in those with head and neck paragangliomas, survival has been shown to not statistically differ from that of the general population.[30] Cosetti *et al*. reviewed 12 patients; 7 had undergone previous subtotal surgical resection and 4 were treated with observation. One of the patients treated with observation demonstrated growth after six years.[15] Carlson *et al*. advocated 'watch and wait surveillance scanning' as a viable treatment option in older patients following a review of 16 'glomus jugulare tumours'.[13] They showed stable appearances in 7 patients on radiological follow up over an average of 57.6 months, and reported an average growth rate of 0.8 mm per year in the remaining 5 patients. Furthermore, less than a third of patients in that series had a new or worsening lower cranial nerve deficit.[13]

Langerman *et al*. reviewed 47 cases of paragangliomas, including a combination of vagal and carotid body paragangliomas, and advocated surveillance scanning in those head and neck paraganglioma patients without worrisome symptoms, including those without lymphadenopathy, rapid growth or pain.[14] Their results showed that only 38 per cent of paragangliomas grew, in comparison to our series where there was 33.3 per cent increase in size at an average rate of 0.84 mm per year.[14] Reviewing existing studies, growth rate has been published at a rate of between 0.3 and 5 mm per year, with an average of 1 mm per year and a median doubling time of four years.[14,16]

In 2000, Jansen *et al*. compared different tumour sites, and found that jugulotympanic paragangliomas were significantly less progressive compared to other head and neck paragangliomas.[16] However, this may be related to the confined space within the petrous bone in which they are found. Sethi *et al*. found that vagal paragangliomas are more likely to demonstrate malignant features in the region of 19 per cent, compared to 6 per cent in carotid body tumours and 2–4 per cent in jugulotympanic paragangliomas.[32]

At present, it is almost impossible to differentiate between benign and malignant paragangliomas, as there are no reliable histological, cytological, molecular or immunohistochemical criteria for malignancy. Instead, malignancy is confirmed by the presence of metastasis in sites where paraganglia are not usually present, for example the liver and lymph nodes.[6,26] Historically, the behaviour of head and neck paragangliomas has been considered aggressive, but with recent studies and greater understanding they are now being increasingly recognised as more indolent, and the incidence of malignancy has been identified at between 3 and 19 per cent.[23,32]

Factors that should discourage against active surveillance include the presence of lymphadenopathy, rapid growth and pain. Evidence of familial predisposition to tumours as a result of a mutation in the succinate dehydrogenase gene, and younger age of onset, should prompt close monitoring, as there is an increased association with malignancy. Furthermore, in those undergoing active surveillance, the development of regional or distant metastasis, or a rapidly enlarging mass, should prompt intervention. The aforementioned study by Jansen *et al*., published in 2000, compared the clinical behaviour, and therefore the management, of head and neck paragangliomas with vestibular schwannomas.[16] They showed that tumours with a smaller volume at presentation, of between 0 and 0.8 cm^3, did not grow as much as those over 0.8 cm^3, and they found that a large proportion of tumours were not progressive, which is comparable to our study. All these factors can only partially predict the biological behaviour of each individual head and neck paraganglioma, but the

https://doi.org/10.1017/S0022215117000809 Published online by Cambridge University Press

absence of growth in a large proportion of these tumours suggests there is a role for active surveillance.

Limitations of this study include the small cohort and its retrospective nature.

Conclusion

This case series lends further weight to a new trend in active surveillance scanning. Careful consideration still needs to be given, as locally aggressive disease and malignant potential, although rare, have been reported. Embarking on surgical resection is associated with debilitating morbidity and even mortality, which could be unnecessary given the natural progression of many head and neck paragangliomas.

With readily available modern cross-sectional imaging, head and neck paragangliomas can be accurately monitored for disease progression. The slow growth rate of many head and neck paragangliomas, as well as the low possibility of developing cranial nerve deficits and the potential for multifocal disease, justifies the consideration of an 'active surveillance scanning' approach. Awareness of all treatment options for head and neck paragangliomas is necessary to adequately counsel patients and to ensure that an appropriate management choice is selected.

References

1 Sykes JM, Ossoff RH. Paragangliomas of the head and neck. *Otolaryngol Clin North Am* 1986;**19**:755–67
2 Van den Berg R. Imaging and management of head and neck paragangliomas. *Eur Radiol* 2005;**15**:1310–18
3 Havekes B, Corssmit EP, Jansen JC, van der Mey AG, Vriends AH, Romijn JA *et al*. Malignant paragangliomas associated with mutations in the succinate dehydrogenase D gene. *J Clin Endocrinol Metab* 2007;**92**:1245–8
4 Boedeker CC, Neumann HP, Maier W, Bausch B, Schipper J, Ridder GJ. Malignant head and neck paragangliomas in SDHB mutation carriers. *Otolaryngol Head Neck Surg* 2007; **137**:126–9
5 Patetsios P, Gable DR, Garrett WW, Lamont JP, Kuhn JA, Shutze WP *et al*. Management of carotid body paragangliomas and review of a 30-year experience. *Ann Vasc Surg* 2002;**16**: 331–8
6 Chapman DB, Lippert D, Geer CP, Edwards HD, Russell GB, Rees CJ *et al*. Clinical, histopathologic, and radiographic indicators of malignancy in head and neck paragangliomas. *Otolaryngol Head Neck Surg* 2010;**143**:531–7
7 Samji KB, Crown AL, Buxton-Thomas MS, Aylwin SJ, Schulte KM, Dizdarevic S. Necessity for long-term follow-up of patients with head and neck paraganglioma and mutation in the succinate dehydrogenase genes: an index case report and literature review. *Endocr Pract* 2012;**18**:e130–4
8 Obholzer RJ, Hornigold R, Connor S, Gleeson MJ. Classification and management of cervical paragangliomas. *Ann R Coll Surg Engl* 2011;**93**:596–602
9 Netterville JL, Jackson CG, Miller FR, Wanamaker JR, Glasscock ME. Vagal paraganglioma: a review of 46 patients treated during a 20-year period. *Arch Otolaryngol Head Neck Surg* 1998;**124**:1133–40
10 Jackson CG. Glomus tympanicum and glomus jugulare tumours. *Otolaryngol Clin North Am* 2001;**34**:941–70
11 Krych AJ, Foote RL, Brown PD, Garces YI, Link MJ. Long-term results of irradiation for paraganglioma. *Int J Radiat Oncol Biol Phys* 2006;**65**:1063–6
12 Kunzel J, de Tristan J, Mantsopoulos K, Koch M, Baussmerth M, Zenk J *et al*. Experiences in the treatment of patients with multiple head and neck paragangliomas. *Am J Otolaryngol* 2014;**35**:294–9
13 Carlson ML, Sweeney AD, Wanna GB, Netterville JL, Haynes DS. Natural history of glomus jugulare: a review of 16 tumours managed with primary observation. *Otolaryngol Head Neck Surg* 2015;**152**:98–105
14 Langerman A, Athavale SM, Rangarajan SV, Sinard RJ, Netterville JL. Natural history of cervical paragangliomas: outcomes of observation of 43 patients. *Arch Otolaryngol Head Neck Surg* 2012;**138**:341–5
15 Cosetti M, Linstrom C, Alexiades G, Tessema B, Parisier S. Glomus tumors in patients of advanced age: a conservative approach. *Laryngoscope* 2008;**18**:270–4
16 Jansen JC, van der Berg R, Kuiper A, van der Mey AG, Zwinderman AH, Cornelisse CJ. Estimation of growth rate in patients with head and neck paragangliomas influences the treatment proposal. *Cancer* 2000;**15**:2811–16
17 Lack EE, Cubilla AL, Woodruff JM, Farr HW. Paragangliomas of the head and neck region: a clinical study of 69 patients. *Cancer* 1977;**39**:397–409
18 Van Duinen N, Steenvoorden D, Kema IP, Jansen JC, Vriends AH, Bayley JP *et al*. Increased urinary extraction of 3-methoxytyramine in patients with head and neck paragangliomas. *J Clin Endocrinol Metab* 2010;**95**:209–14
19 Saldana MJ, Salem LE, Travezan R. High altitude hypoxia and chemodectomas. *Hum Pathol* 1973;**4**:251–63
20 van der Mey AG, Maaswinkel-Mooy PD, Cornelisse CJ, Schmidt PH, van de Kamp JJ. Genomic imprinting in hereditary glomus tumours: evidence for new genetic theory. *Lancet* 1989;**2**:1291–4
21 Baysal BE. Hereditary paraganglioma targets diverse paraganglia. *J Med Genet* 2002;**39**:617–22
22 Burnichon N, Abermil N, Buffet A, Favier J, Gimenez-Roqueplo AP. The genetics of paragangliomas. *Eur Ann Otorhinolaryngol Head Neck Dis* 2012;**129**:315–18
23 Jackson CG, McGrew BM, Forest JA, Netterville JL, Hampf CF, Glasscock ME 3rd. Lateral skull base surgery for glomus tumors: long-term control. *Otol Neurotol* 2001;**22**:377–82
24 Heath D. The human carotid body in health and disease. *J Pathol* 1991;**164**:1–8
25 Corssmit EP, Romijn JA. Clinical management of paragangliomas. *Eur J Endocrinol* 2014;**171**:R231–43
26 Taieb D, Kaliski A, Boedeker CC, Martucci V, Fojo T, Adler JR Jr *et al*. Current approaches and recent developments in the management of head and neck paragangliomas. *Endocr Rev* 2014; **35**:795–819
27 van den Berg R, Verbist BM, Mertens BJ, van der Mey AG, van Buchem MA. Head and neck paragangliomas: improved tumour detection using contrast-enhanced 3D time of flight MR angiography as compared with fat-suppressed MR imaging techniques. *Am J Neuroradiol* 2004;**25**:863–70
28 Neskey DM, Hatoum G, Modh R, Civantos F, Telischi FF, Angeli SI *et al*. Outcomes after surgical resection of head and neck paragangliomas: a review of 61 patients. *Skull Base* 2011;**21**:171–6
29 Fish J, Klein-Weigel MD, Biebl M, Janecke A, Tauscher T, Fraedrich G. Systematic screening and treatment evaluation of hereditary neck paragangliomas. *Head Neck* 2007;**29**:864–73
30 de Flines J, Jansen J, Elders R, Siemers M, Vriends A, Hes F *et al*. Normal life expectancy for paraganglioma patients: a 50-year-old cohort revisited. *Skull Base* 2011;**21**:385–8
31 Piazza P, Di Lella F, Bacciu A, Di Trapani G, Ait Mimoune H, Sanna M. Preoperative protective stenting of the internal carotid artery in the management of complex head and neck paragangliomas: long-term results. *Audiol Neurootol* 2015;**18**:345–52
32 Sethi RS, Sethi RK, Herr MW, Deschler DG. Malignant head and neck paragangliomas: treatment efficacy and prognostic indicators. *Am J Otolaryngol* 2013;**34**:431–8

Address for correspondence:
Ms Laura Harrison,
Department of ENT, Head and Neck Surgery,
Northampton General Hospital,
Northampton, UK

E-mail: lauraharrison707@gmail.com

Ms L Harrison takes responsibility for the integrity of the content of the paper
Competing interests: None declared

https://doi.org/10.1017/S0022215117000809 Published online by Cambridge University Press