The management of head-and-neck paragangliomas

Cristina Capatina, Georgia Ntali, Niki Karavitaki and Ashley B Grossman

Oxford Centre for Diabetes, Endocrinology and Metabolism, University of Oxford, Oxford OX3 7LE, UK

Correspondence should be addressed to A B Grossman
Email
ashley.grossman@ocdem.ox.ac.uk

Abstract

Paragangliomas (PGLs) are tumours originating from neural crest-derived cells situated in the region of the autonomic nervous system ganglia. Head-and-neck PGLs (HNPGLs) originate from the sympathetic and parasympathetic paraganglia, most frequently from the carotid bodies and jugular, tympanic and vagal paraganglia, and are usually non-catecholamine secreting. Familial PGLs are considered to be rare, but recently genetic syndromes including multiple PGLs and/or phaeochromocytomas have been more thoroughly characterised. Nowadays, genetic screening for the genes frequently implicated in both familial and sporadic cases is routinely being recommended. HNPGLs are mostly benign, generally slow-growing tumours. Continuous growth leads to the involvement of adjacent neurovascular structures with increased morbidity rates and treatment-related complications. Optimal management mostly depends on tumour location, local involvement of neurovascular structures, estimated malignancy risk, patient age and general health. Surgery is the only treatment option offering the chance of cure but with significant morbidity rates, so a more conservative approach is usually considered, especially in the more difficult cases. Radiotherapy (fractionated or stereotactic radiosurgery) leads to tumour growth arrest and symptomatic improvement in the short term in many cases, but the long-term consequences are unclear. Early detection is essential in order to increase the chance of cure with a lower morbidity rate. The constant improvement in diagnostic imaging, surgical and radiation techniques has led to a safer management of these tumours, but there are still many therapeutic challenges, and no treatment algorithm has been agreed upon until now. The management of HNPGLs requires a multidisciplinary effort addressing the genetic, surgical, radiotherapeutic, oncological, neurological and endocrinological implications. Further progress in the understanding of their pathogenesis will lead to more effective screening and earlier diagnosis, both critical to successful treatment.

Key Words
- paragangliomas
- therapy
- management
- surgery
- radiotherapy

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Introduction

Paragangliomas (PGLs) are rare tumours originating from paraganglia – small groups of neuroendocrine cells arising from the autonomic nervous system ganglia. The sympathetic paraganglia are mostly located along the sympathetic nerve chains bordering the vertebrae and in the pelvis, while the parasympathetic ones are primarily located in the head and neck and less frequently located in the thorax or pelvis. Tumours arising from the

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parasympathetic paraganglia are usually non-chromaffin and only rarely secrete catecholamines, when compared with their sympathetic counterparts (Barnes *et al*. 2004).

Head-and-neck PGLs (HNPGLs) are rare tumours, representing 0.012% of a large oncological surgical series (Lack *et al*. 1977); the estimated clinical incidence is 1/100 000 patients per year (Baysal 2002). The classical main sites of origin are as follows: carotid bodies (at the bifurcation of the common carotid artery); jugular paraganglia (close to the jugular bulb) and tympanic paraganglia (in the middle ear) – usually considered together (JTPGLs); and vagal paraganglia (along the vagus nerve). The most frequently found are the carotid body tumours (CBTs) and the least frequent are those arising from the vagus paraganglia (VPGLs). The relative frequencies across series in the literature vary widely: in a large reported series of 204 HNPGLs, 57% were CBTs, 30% JTPGLs and 13% VPGLs (Erickson *et al*. 2001).

Increasingly, due to their association with phaeochromocytomas and new genetic data, these tumours are being diagnosed by endocrinologists and oncologists, but much of the published literature is in more specialised ENT or surgical journals. We think that it will be useful to survey current data on the management of these tumours in order to assist clinicians in advising their patients on the most appropriate therapy.

Genetic background

HNPGLs were occasionally described in rare conditions such as von Hippel–Lindau disease (Zanelli & van der Walt 1996, Gaal *et al*. 2009), multiple endocrine neoplasia type 2 (Boedeker *et al*. 2009*a*), neurofibromatosis (DeAngelis *et al*. 1987) and Carney's triad (Carney *et al*. 1977). Until quite recently, most PGLs were considered sporadic, unless there was a positive family history (FH) or if co-morbidities characteristic of the known genetic syndromes were present. However, many newly characterised genes have been found to be mutated in many apparently sporadic PGLs. Currently, four genetic PGL syndromes are being described, all with autosomal dominant transmission. Three of these syndromes are associated with germline mutations in the gene complex encoding succinate dehydrogenase (SDH): PGL-1, PGL-3 and PGL-4, caused by mutations in *SDHD*, *SDHC* and *SDHB* respectively. All these mutations predispose to PGLs in all locations and/or phaeochromocytomas. HNPGLs are frequent in the PGL-1 syndrome due to *SDHD* mutations and are frequently multifocal and also in the PGL-3 syndrome due to *SDHC* mutations; they are more rare but more frequently malignant in the PGL-4 syndrome secondary to *SDHB* mutations. In the PGL-1 syndrome, genomic imprinting has consistently been described; the maternally derived allele is imprinted, so this means that only mutations inherited from the father are pathogenic (Niemann *et al*. 1999, Baysal *et al*. 2000, Astuti *et al*. 2001, Gimenez-Roqueplo *et al*. 2012). The causal mutation of the PGL-2 syndrome has only recently been described (*SDHAF2* gene; Hao *et al*. 2009), is very rare (Bayley *et al*. 2010) and its transmission is also consistent with genomic imprinting (Kunst *et al*. 2011).

Genetic screening

Apparently sporadic PGLs harbour *SDH*-related mutations in a significant proportion of the cases (30.6%); the likelihood of having a *SDH* mutation is best predicted by a positive FH, multicentricity and a previous phaeochromocytoma and, to a lesser extent, by young age, male gender and malignancy (Neumann *et al*. 2009). Therefore, sequential genetic screening guided by clinical predictive factors has been recommended, although parallel sequencing of multiple genes is carried out in some centres, including our centre (Young 2006, Burnichon *et al*. 2009). The loss of the normal immunohistochemical staining of paraganglial cells with antibodies against the SDHB protein has recently been found to be highly associated with germline mutations of all the SDH complex genes (van Nederveen *et al*. 2009). Greater experience is needed with this elegant potential screening tool, but it promises to become a routine part of the screening as immunonegativity for the SDHB protein is consistently associated with *SDH*-related tumours and is not found in sporadic or non-*SDH* mutation-related cases. In an international study, the penetrance of gene mutations has been found to be 48% for *SDHD* at 30 years of age and 73% by 40 years of age, vs 29 and 45% respectively for *SDHB* (Benn *et al*. 2006). Thus, the high penetrance of *SDHD* mutations suggests that they are rarely found in patients presenting tumours beyond 45 years of age (Cascon *et al*. 2009). In a large UK study, the majority of the mutations missed using an age cut-off were in the *SDHB* gene; these authors suggested that if genetic testing for *SDHB* is limited to younger patients on cost grounds, it should be complemented with SDHB immunostaining (Jafri *et al*. 2013).

It has been suggested that genetic testing for *VHL*, *RET* and *NF1* mutations may be considered if there is clinical suspicion (Boedeker *et al*. 2009*a*,*b*) and for *SDHAF2* in high-risk patients negative for other *SDH* mutations (Bayley *et al*. 2010), while two other newly described

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genes (*TMEM127* and *MAX*) are rarely implicated in HNPGLs (Gimenez-Roqueplo *et al.* 2012). However, as has been noted above, we routinely screen for all the genes currently implicated in HNPGLs other than *NF1*; the latter has a very large number of exons, and the clinical syndrome is (almost always) obvious.

Clinical presentation

HNPGLs rarely release catecholamines to produce a hypersecretory syndrome (<10%). In the vast majority of cases, they are discovered due to the mass effects dominated by the involvement of lower cranial nerves (CNs) IX and X; 10% are diagnosed incidentally (Erickson *et al.* 2001).

HNPGLs in the lower part of the neck (CBTs and some VPGLs) usually present as painless, sometimes pulsatile, neck masses. With further growth, they involve the lower CNs, leading to speech and swallowing deficits (hoarseness and dysphagia) and sometimes to aspiration (Miller *et al.* 2000, Offergeld *et al.* 2012). A preoperative CN deficit is frequently observed in VPGLs (25–36%) and JTPGLs (39–40%) and less so in CBTs (4–22%) (Powell *et al.* 1992, Netterville *et al.* 1998, Sajid *et al.* 2007, Neskey *et al.* 2011).

Intracranial extension is rare in CBTs (Rao *et al.* 1999) and more frequent in VPGLs – 22% (Netterville *et al.* 1998). JTPGLs are intracranial tumours, and it is often difficult to delineate their site of origin: tympanic tumours may extend towards the jugular bulb and posterior fossa, while jugular tumours can involve the temporal bone and extend into the middle ear. Intracranial invasion and involvement of the CN adjacent to the jugular foramen can lead to pulsatile tinnitus, an ear mass, hearing loss, pain and vertigo as major presenting symptoms in JTPGLs and high VPGLs (Cummings *et al.* 1984, Persky *et al.* 2002, Offergeld *et al.* 2012).

HNPGLs are most frequently diagnosed in middle-aged adults (mean age 41–47 years; Erickson *et al.* 2001, Jackson *et al.* 2001, Papaspyrou *et al.* 2009). Genetic cases are more than a decade younger (Burnichon *et al.* 2009). A FH should be sought in all the cases; positivity is highly variable among series, but can reach over 80% in populations with a high frequency of founder *SDHD* mutations (Hensen *et al.* 2011). A positive FH increases the risk of multifocality: up to 78% of the cases with a positive FH and 17–37% of the unselected cases are multicentric (Jackson *et al.* 1990, Netterville *et al.* 1998, Erickson *et al.* 2001, Plukker *et al.* 2001, Sajid *et al.* 2007, Papaspyrou *et al.* 2009).

Malignancy can only be ascertained in the presence of distant metastases. None of the markers in a large set of putative markers of malignancy can reliably predict malignancy, and tumour size is still the major indicator of risk, as it is for phaeochromocytomas (Korevaar & Grossman 2011). The risk of malignancy is higher in *SDHB* mutation carriers, while multifocality is more frequent in *SDHD* germline mutations (Burnichon *et al.* 2009). In large series, evidence of malignancy in 3–5% of the HNPGL cases (Manolidis *et al.* 1999, Jafri *et al.* 2013) with a lower risk for CBTs and JTPGLs (2–6%) and a higher risk (16%) for VPGLs has been found (Kahn 1976, Kloppel 2003). Distant metastases may occur even after 16 years of follow-up (Lees *et al.* 1981), so long surveillance is critical for a precise estimate of the real incidence. The most common site of distant spread is the cervical lymph nodes (68.6%; Lee *et al.* 2002); other sites are the bone, lung and liver (Moskovic *et al.* 2010).

The overall 5-year survival in malignant cases is generally good (59.5–84%; Manolidis *et al.* 1999, Lee *et al.* 2002, Moskovic *et al.* 2010), but it becomes disappointing (11.8%) if cases with only local spread are excluded (Lee *et al.* 2002).

Classification

Shamblin classification of CBTs

The CBT classification of Shamblin *et al.* (1971) is still in use and shows a good correlation with surgical complications and outcome (Plukker *et al.* 2001, Luna-Ortiz *et al.* 2005, Makeieff *et al.* 2008). Tumours classified as class I have no or minimal attachment with the carotid arteries. Class II tumours surround the carotid arteries, partially encasing them. Shamblin class III tumours surround the vessels, adhering firmly over their whole circumference, so vessel resection and reconstruction are needed to attempt total tumour resection.

Fisch classification of JTPGLs

JTPGLs have been similarly classified by Fisch & Mattox (1988): class A JTPGLs are located along the tympanic plexus on the promontory, and class B tumours invade the hypotympanum, but do not erode the jugular bulb, as opposed to class C tumours (C1 destruction of the jugular bulb/foramen; C2 invasion of the vertical carotid canal; C3 invasion of the horizontal carotid canal and C4 invasion of the cavernous sinus). In class D tumours, besides the various degrees of invasion described for class C, intracranial extradural or intradural extension occurs (De1 and De2 intracranial and extradural invasion of up to

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2 cm or more than 2 cm respectively; Di1, Di2 and Di3 intracranial and intradural extension of up to 2 cm, between 2 and 4 cm or more than 4 cm respectively).

Diagnosis

Plasma or 24-h urinary metanephrine or catecholamine concentrations should be measured in all HNPGLs, as they can (rarely) be secretory (Erickson *et al.* 2001). If catecholamine excess is demonstrated, an extensive workup should be performed to assess the possibility of synchronous phaeochromocytoma/sympathetic PGLs. Exclusive dopamine secretion was considered to be very rare, usually silent and possibly associated with a trend towards increased aggressiveness or malignant potential (Eisenhofer *et al.* 2005), but recently higher rates (16.75–23%) of solely dopamine secretion or secretion of its metabolites have been described with these tumours (van Duinen *et al.* 2010, Van Der Horst-Schrivers *et al.* 2010). Chromogranin A is only rarely secreted (van Duinen *et al.* 2011). Thus, such markers are only useful in the follow-up of selected tumours.

Imaging is of paramount importance in patients with a clinical suspicion of HNPGLs or in individuals from affected families. Standard anatomical imaging (computerised tomography (CT) and magnetic resonance imaging (MRI)) is widely used as the initial evaluation method (see Figs 1, 2 and 3). CT has a lower sensitivity (Erickson *et al.* 2001), but accurately defines possible bone invasion. In MRI studies, PGLs show a characteristic 'salt-and-pepper' pattern (due to their vascularisation) and intense post-contrast enhancement. Doppler-flow ultrasonography can be useful for the diagnosis and follow-up of CBTs (Rao *et al.* 1999).

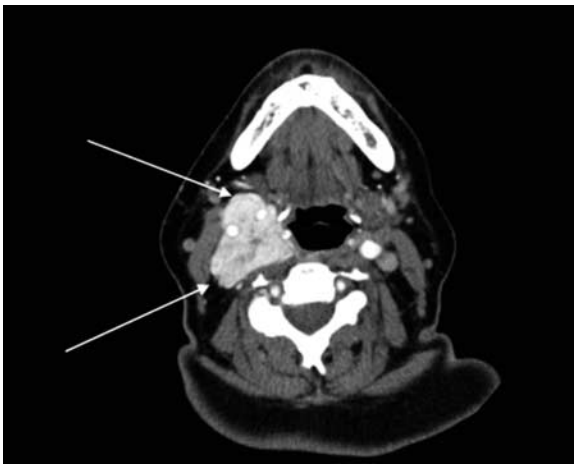

Figure 1
CT angiogram of the aortic arch and carotids a patient: a carotid bifurcation glomus tumour showing enhancement after contrast (arrows).

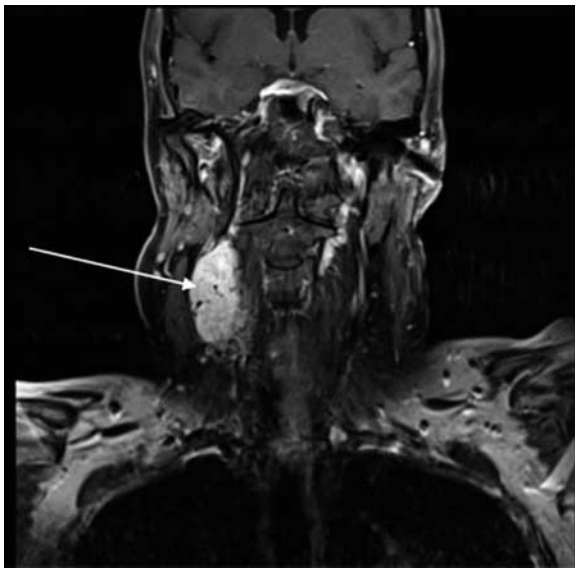

Figure 2
Cervical MRI of the patient illustrated in Fig. 1; the T1-weighted image shows the same lesion (arrow).

Angiography (digital-subtraction angiography (DSA) or MRI angiography) is a key method for diagnosis, defining the vascular anatomy preoperatively (tumour blood supply and extent of the involvement of the carotid arteries), ensuring safe preparation in the event of major vascular reconstructive surgery, demonstrating the patency of cerebral blood flow and identifying multicentric disease. MRI angiography is technically preferable and safer, but it has a lower sensitivity than DSA (van den Berg *et al.* 2000).

Whole-body screening with functional imaging studies can detect possible synchronous lesions in confirmed mutation carriers or those at a high-risk of familial disease (positive FH and young age). ^{123}I-MIBG (metaiodobenzylguanidine) scintigraphy, despite its high specificity, has a low sensitivity for the detection of HNPGLs. Its use for standard evaluation of HNPGLs is limited, and it is more frequently employed to assess tumour avidity for the tracer if radionuclide therapy is planned. Somatostatin receptor (SSR) scintigraphy has a better sensitivity, lower than that of standard anatomical imaging but offers whole-body scanning (Timmers *et al.* 2012, Gimenez-Roqueplo *et al.* 2013).

Positron-emission tomography (PET) has been used intensively as it can be used for the examination of the whole body with improved resolution, and it can detect small

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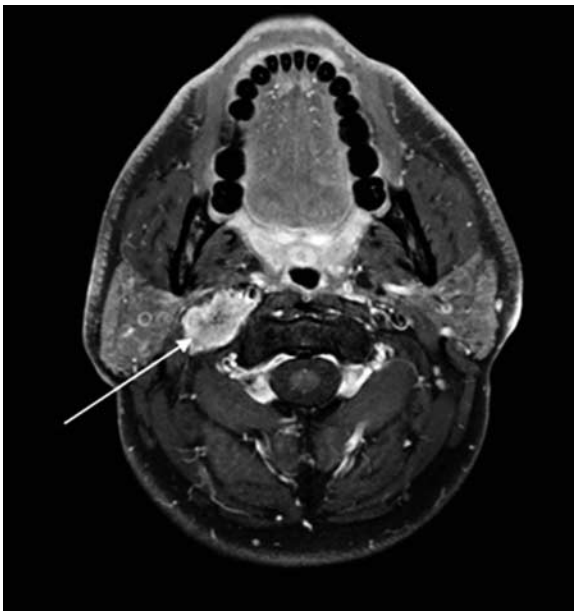

Figure 3
Neck MRI with gadolinium in another patient; the T1-weighted image shows a right-sided glomus jugulare tumour (arrow).

and metastatic lesions. ^{18}F-fluorodihydroxyphenylalanine (^{18}F-DOPA) PET has a very good sensitivity for the detection of both unselected (Gabriel *et al.* 2013) and *SDH*-related HNPGLs (King *et al.* 2011). In a small group of HNPGLs of unknown genetic status, ^{68}Ga-DOTANOC (DOTA-naphthyl-alanine conjugated with octreotide) PET/CT used for baseline evaluation is also significantly superior to CT, MRI and ^{131}I-MIBG scintigraphy for the detection of multicentric disease or distant spread (Sharma *et al.* 2013).

Where available, ^{18}F-DOPA–PET should be used as the first-line functional imaging method for the detection of suspected HNPGLs (while in sympathetic PGLs, ^{18}F-fluorodopamine PET/CT is advocated as the first-line detection method). If unavailable, ^{18}F-FDG- or ^{68}Ga-DOTA-peptide-PET or SSR scintigraphy (if PET is not available) should be used to complement anatomical imaging studies (Timmers *et al.* 2009, Blanchet *et al.* 2011; see Figs 4 and 5).

Natural history

The natural history of HNPGLs is estimated based on the surveillance of selected patients without significant symptoms and/or poor candidates for treatment. In a study, of the 47 presumed HNPGLs observed for 5 years, on average, 42% were stable and 38% slowly increased in size (mean annual growth 0.2 cm), while 20% decreased in size (any change in greatest dimension) (Langerman *et al.* 2012). Others have described a median growth rate of about 1 mm/year (0.3–5 mm) with a widely variable tumour doubling time (0.6–21.5 years), but overall 60% of the tumours increased by at least 20% of their original size over 1–8 years (average 4.2) (Jansen *et al.* 2000).

These results are generally considered reassuring, but the selection bias, short follow-up duration, lack of tumour-associated morbidity data and possible misdiagnosis or unrecognised malignant potential should be borne in mind.

Management

The main treatment modalities for PGLs include surgery and radiotherapy (external-beam radiotherapy (EBRT) or stereotactic radiosurgery (SRS)). The respective roles of chemotherapy and peptide receptor radionuclide therapy (PRRT) are yet to be clearly defined. Owing to the relatively mild natural history of HNPGLs, a long follow-up duration is needed before reaching a correct conclusion about the efficacy of any treatment.

Surgery

Whenever possible, complete surgical excision of the tumour is considered by many to be the favoured option of treatment in order to prevent morbidity associated with

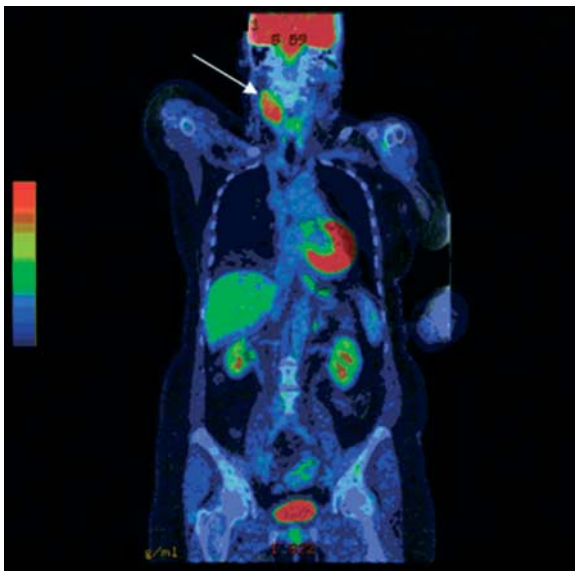

Figure 4
Whole-body ^{18}FDG-PET/CT of the patient illustrated in Figs 1 and 2 showing an ovoid, moderately FDG-avid mass centred on the right side of the neck (arrow), lying deep to the sternomastoid and displacing the right submandibular gland anteriorly.

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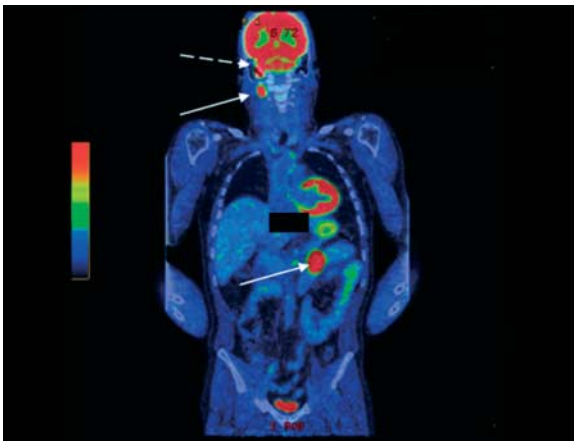

Figure 5
Whole-body ^{18}FDG-PET/CT of the patient illustrated in Fig. 3 showing besides the intensely FDG-avid right jugular paraganglioma (dashed arrow), a vagal paraganglioma (solid arrow), which is markedly FDG avid, and a left-sided phaeochromocytoma (solid arrow), which is also intensely FDG avid.

further tumour growth or later spread from an unrecognised malignant tumour. Overall, gross total resection (GTR) is achievable in 90–97% of the cases with a low surgical mortality rate (0–2.7%). However, surgery is associated with haemorrhagic, cerebrovascular and neurological risks (paresis of lower CN leading to swallowing and speech problems, aspiration, feeding tube or tracheostomy dependence, facial palsy and hearing loss; Erickson *et al.* 2001, Jackson *et al.* 2001, Kollert *et al.* 2006, Paris *et al.* 2006, Sevilla Garcia *et al.* 2007, Papaspyrou *et al.* 2009, Neskey *et al.* 2011, Obholzer *et al.* 2011). Adjuvant procedures to improve swallowing or hoarseness (e.g. vocal cord medialisation) are frequently used postoperatively, but complete rehabilitation of the complex neurological deficit is slow in younger patients and often impossible in the elderly (Netterville & Civantos 1993), and thus indications for surgery should always be considered with great care.

Particular surgical challenges are associated with different HNPGL locations

Carotid body tumours

Complete surgical resection is possible in the vast majority (85–100%) of CBTs and recurrences are rare (Lees *et al.* 1981, Gaylis *et al.* 1987, Rodriguez-Cuevas *et al.* 1998, Makeieff *et al.* 2008, Ma *et al.* 2009). However, surgical morbidity is still significant due to the high vascularity and proximity to essential neurovascular structures. Significant intraoperative bleeding occurs, especially in advanced tumours (mean blood loss of 2200 ml in Shamblin class III tumours; Plukker *et al.* 2001). To reduce bleeding, preoperative tumour embolisation has been advocated (Persky *et al.* 2002, Ulrich *et al.* 2009), but others have reported a lack of efficacy (Zeitler *et al.* 2010) and/or an increased risk of stroke (Westerband *et al.* 1998, Fruhmann *et al.* 2013), so its utility remains controversial. It is likely to be highly operator dependent and could be considered for large tumours, but only if there is appropriate local expertise.

The risk of transient ischaemic attack or stroke is higher in CBT surgery than in the surgery of tumours present in other locations. In an analysis of the postoperative outcome of 1181 patients, the cumulative incidence was found to be 6.3% (Anand *et al.* 1995), but was lower in more recent series, between 0 and 4.8% (Plukker *et al.* 2001, Luna-Ortiz *et al.* 2005, Sajid *et al.* 2007, Makeieff *et al.* 2008, Ma *et al.* 2009). A vascular surgeon should be an essential part of the surgical team as internal carotid artery injury occurs frequently (10–23%) and vessel reconstruction leads to significantly lower stroke and mortality rates vs ligation (Anand *et al.* 1995, Plukker *et al.* 2001). Advances in surgical techniques and a multidisciplinary approach have led to a dramatic overall decrease in surgical mortality rates – 1% in a recent UK multicentre study (Sajid *et al.* 2007) vs 3.2% in a literature review carried out in 1995 (Anand *et al.* 1995) and 12.82% in older series (Lack *et al.* 1977).

Early postoperative CN deficits (lower CN palsies or, rarely, Horner's syndrome) are frequent (19–50%), but a permanent deficit is less common due to progressive slow rehabilitation, 1–18% (Plukker *et al.* 2001, Patetsios *et al.* 2002, Persky *et al.* 2002, Sajid *et al.* 2007, Makeieff *et al.* 2008). In advanced cases (Shamblin classes II and III), the rate of permanent neurological deficit can be up to 38% (Luna-Ortiz *et al.* 2005). The Shamblin classification is significantly correlated with postoperative complications (Makeieff *et al.* 2008), intraoperative blood loss (Plukker *et al.* 2001) and vascular reconstruction need (Smith *et al.* 2006), so early detection is essential for safe management.

A particular complication in CBT surgery is blood pressure instability (as the carotid body physiologically functions as a baroreceptor): both hypotension (Kohler *et al.* 2004) and, with bilateral resection, severe resistant hypertension (baroreceptor failure syndrome) can occur (De Toma *et al.* 2000). Chemoreflex dysfunction (absence of a normocapnic hypoxic ventilatory response) is almost universal, but baroreflex dysfunction occurs inconstantly (Timmers *et al.* 2003).

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Vagus paraganglia

The probability of surgical cure in VPGLs is also very high: GTR is possible in 92.3–100% of the cases with a low mortality rate (0–2.7%) (Urquhart *et al.* 1994, Netterville *et al.* 1998, Jackson *et al.* 2001, Kollert *et al.* 2006). In a large literature review on VPGLs and JTPGLs published in 2012, Suarez *et al.* (2013*a*) described an average mortality rate of 1.3% with a GTR rate of 93.3%.

However, the neurological risks are higher than those for CBTs: CN palsies are more common after surgery for JTPGLs and high-located VPGLs due to the tumoural involvement of the jugular foramen. An immediate postoperative CN palsy rate can be as high as 96 and 100% respectively for these tumours (Neskey *et al.* 2011). The most affected component is the vagus nerve itself: in most series, a postoperative vagal deficit is almost universal (92–100%), by either paresis or necessary sacrifice during surgery (Urquhart *et al.* 1994, Netterville *et al.* 1998, Jackson *et al.* 2001, Bradshaw & Jansen 2005, Kollert *et al.* 2006, Zanoletti & Mazzoni 2006).

Other new CN deficits postoperatively occur in 23–61% of the cases for nerves IX, XI and XII (mostly IX) and in 15–17% for the facial nerves (Urquhart *et al.* 1994, Jackson *et al.* 2001, Bradshaw & Jansen 2005, Kollert *et al.* 2006, Zanoletti & Mazzoni 2006, Lozano *et al.* 2008). Severe aspiration as a consequence occurs in 10.2% of the cases (Suarez *et al.* 2013*a*). The majority of patients need complex rehabilitation management regarding speech, swallowing and facial nerve deficits, but during follow-up, these deficits often recover partially (Netterville *et al.* 1998).

Other significant complications include cerebrospinal fluid (CSF) leak, stroke and meningitis, present in 2.6, 2.2 and 0.4% of the cases respectively (Suarez *et al.* 2013*a*).

Other authors have suggested that the observation of VPGLs is associated with a better outcome: new CN palsy occurs in 7.5% of the cases (vs 60% postoperatively in the same series) and a 5% increase in size can be observed over 8.5 years (Bradshaw & Jansen 2005). However, in this series, 75% were familial cases and over half asymptomatic (therefore possibly less advanced), although 2.5% developed metastases during follow-up.

JTPGLs

Surgery is most challenging for JTPGLs as extensive exploration of the posterolateral skull base is required. In most studies, GTR has been achieved still in the majority of the cases (59–96%) with 0–5% mortality rate (no more than 2% in the most recent series), even for complex tumours. The GTR rate is generally lower in the Fisch C and D classes, and it decreases to 41% in class D tumours or 35% in those with a large intradural extension (Glassock *et al.* 1979, Jackson *et al.* 1990, Green *et al.* 1994, Gjuric *et al.* 1996, Briner *et al.* 1999, Moe *et al.* 1999, Forest *et al.* 2001, Tran Ba *et al.* 2001, Al-Mefty & Teixeira 2002, Saringer *et al.* 2002, Pareschi *et al.* 2003, Suarez *et al.* 2007, Huy *et al.* 2009).

A meta-analysis published in 2011 has computed a pooled estimate of tumour control with GTR and subtotal resection (STR) of 86 and 69% respectively (Ivan *et al.* 2011). In another review of the treatment results for JPGLs, the overall long-term tumour control irrespective of the degree of resection has been reported to be 78.2% with a 1.6% treatment-related mortality rate. The risk of recurrence after apparent GTR is 6.9% (Suarez *et al.* 2013*a*). However, in most surgical series, the follow-up duration is generally too short to allow all recurrences to be reported; with a longer follow-up duration (112 months), 18.8% can recur (Papaspyrou *et al.* 2009). The validity of pooling inhomogeneous data from different centres is questionable, but since large series are extremely rare, this approach offers some idea as to what to expect from surgery in these tumours.

The functional outcome following surgery is generally poor. At particular risk are the facial nerves (frequently mobilised in order to improve tumour exposure and removal) and hearing function. Immediate postoperative facial weakness is frequent, and long-term dysfunction is present in 14–33% of the cases (Briner *et al.* 1999, Huy *et al.* 2009). Hearing function either remains stable or deteriorates; it is subjectively improved in only 6–16% of the cases, while 39% may experience a deterioration (Glassock *et al.* 1979, Gjuric *et al.* 1996, Briner *et al.* 1999, Kunzel *et al.* 2012). Overall, up to 45.5% of the cases have some degree of hearing loss after surgery (Suarez *et al.* 2013*a*). The global risk of other postoperative CN deficits after GTR is also high: 38, 26, 40 and 18% of the cases for nerves IX, X, XI and XII respectively (Ivan *et al.* 2011). Adjuvant procedures (e.g. tracheostomy, feeding tube, vocal cord medialisation procedure and gastrostomy) are used frequently, with at least one procedure being needed in up to 30% of the cases (Gottfried *et al.* 2004). However, because CN deficits are common preoperatively in JTPGLs and trigger obscure compensation mechanisms, long-term feeding tube dependence is equally frequent after CBT and JPGL surgery (Neskey *et al.* 2011). Overall, the risk of a new permanent deficit is still low in complex, very advanced JTPGLs, and a high GTR rate (85%) can be achieved even in such cases (Al-Mefty & Teixeira 2002).

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Normal activity after JTPGL surgery resumes slowly, being observed in 72% of the patients at 6 months and 97% after 1–2 years, reflecting the slow but progressive return of neurological function (Briner *et al*. 1999).

Other complications occur in <10% of the patients (aspiration, infection and meningitis) with possibly higher rates for a CSF leak (11–14%) (Moe *et al*. 1999, Al-Mefty & Teixeira 2002, Lee *et al*. 2002, Gottfried *et al*. 2004, Kollert *et al*. 2006, Suarez *et al*. 2013*a*). In contrast to the risks for CBT surgery, the vascular risks are less significant, as these tumours mostly do not invade the carotids; the overall stroke rate is 1.6% (Gottfried *et al*. 2004). A rare but debilitating complication of JTPGL or VPGL surgery is the 'first bite syndrome', severe pain at the beginning of meal consumption (Netterville *et al*. 1998, Obholzer *et al*. 2011).

Tympanic PGLs are rarely reported separately; the results are generally more favourable, perhaps because they cause symptoms early and are diagnosed in less advanced stages. The GTR rate is 95–100% with <8% of the cases with non-severe complications and a significantly lower duration of operation and hospital stay. Hearing is generally is maintained (Jackson *et al*. 1990, O'Leary *et al*. 1991).

Radiotherapy

Radiotherapeutic options include conventional fractionated EBRT and SRS.

EBRT has been largely studied for the treatment of HNPGLs and several advantages over surgery have been outlined. Partial/complete symptom relief in the months after treatment occurs in most (52–100%) cases affected by tinnitus, dizziness/vertigo or pain. As opposed to surgery, a CN deficit present at diagnosis generally improves or remains stable (Cummings *et al*. 1984, de Jong *et al*. 1995, Huy *et al*. 2009).

Tumour control with radiotherapy is uniformly defined as a lack of tumour progression (although such an efficacy criterion in tumours with a natural slow growth is debatable); complete tumour remission is very rare, but a slow reduction of tumour volume occurs frequently. Local control occurs in 88–100% of the cases with variable follow-up durations (50 months–11 years). The control rate decreases significantly with time: 95–96% at 5 years and 88–94% at 10 years, but only 73% at 25 years. Disease-related mortality after radiotherapy is low (0–5.1%; Cummings *et al*. 1984, Hansen & Thomsen 1988, Powell *et al*. 1992, Verniers *et al*. 1992, Hinerman *et al*. 2001, Chino *et al*. 2009, Huy *et al*. 2009, Lightowlers *et al*. 2010, Suarez *et al*. 2013*a*).

Mild complications (mucositis, nausea, xerostomia and otitis media/externa) occur occasionally, but are of limited significance (Cummings *et al*. 1984, Verniers *et al*. 1992, Hinerman *et al*. 2008). The most important concerns, especially in young patients, are those regarding serious late effects. Brain or bone necroses are serious adverse effects, albeit being rare nowadays (0.8 and 2.6% respectively; Suarez *et al*. 2013*a*). A literature analysis carried out in 1984 has reported brain necrosis to be present in 1.44% of the cases, all receiving higher doses (63–75 Gy; Cummings *et al*. 1984). Bone necrosis is also correlated with massive radiation doses or concurrent infection (Sharma *et al*. 1984). Currently, the usual dose is 45 Gy (Hinerman *et al*. 2008, Huy *et al*. 2009), and larger doses are no longer used, except for the treatment of malignant tumours, where the response is very poor even then (Hinerman *et al*. 2008, Moskovic *et al*. 2010). The radiation-induced malignancy rate is difficult to assess, due to the variable follow-up durations and inconsistency of its ascertainment. Aggressive bone osteosarcoma, fibrosarcoma (Lalwani *et al*. 1993, Mumber & Greven 1995) and laryngeal carcinoma have been reported up to 25 years after treatment (Lack *et al*. 1977).

SRS has obvious advantages over EBRT (a single outpatient procedure and better anatomical targeting) and has been advocated as an alternative to surgery. Tumour control is achieved in larger series in 100% of the cases with 31–50% of the tumours slowly decreasing in size (decrease being variably defined). However, the median follow-up duration is short (2–4.8 years), so long-term true local control cannot be accurately assessed. Symptomatic improvement is frequent (29–70%), and a new CN deficit or worsening of a pre-existing CN deficit occurs rarely (0–15%) (Liscak *et al*. 1999, Foote *et al*. 2002, Pollock 2004, Lieberson *et al*. 2012). In a recent literature review, the overall control rate has been reported to be 98% (mean follow-up duration of only 31 months) with a 3% overall complication rate (mostly mild: nausea, vomiting and vertigo) (Lieberson *et al*. 2012).

In skull base tumours (the most surgically challenging), SRS efficacy has also been reported favourably. A review of the literature published between 1994 and 2004 and a very recent one have reported similar results: a 32–37% decrease in size, 61% remaining stable over an average follow-up duration of 39–41 months. Neurological improvement occurs in 24–39% of the cases, and a few cases experience worsening of conditions (only 2.8% permanent; Gottfried *et al*. 2004, Suarez *et al*. 2013*a*). However, new hearing loss is reported in up to 19% of the SRS-treated JPGL cases (probably due to bone radiation

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injury; Pollock 2004). JTPGL tumour control with SRS or EBRT is not statistically different, but the mortality due to disease or treatment has been reported to be significantly lower for SRS (Suarez *et al*. 2013*a*).

In a meta-analysis of treatment results for JPGLs, the tumour control rate for SRS with a long follow-up duration (mean 71 months) has been reported to be 95%, better than that of GTR (86% at a mean duration of 88 months) (Ivan *et al*. 2011). This led the authors to conclude that SRS offers better control with a lower risk and should be preferred, reserving surgery for the debulking of larger tumours in preparation for SRS (STR followed by SRS in the same analysis controlled only 71% of the cases, probably due to selection bias). Despite these favourable comparisons, no robust evidence of superiority (e.g. in randomised control studies) exists. Follow-up after SRS is relatively short, so long-term control may be overestimated and the complication rate underestimated. As HNPGLs are generally slow growing (over 90% grow by <0.5 cm/year; Langerman *et al*. 2012), a definitive assessment of long-term efficacy needs prolonged observation. In addition, the apparent lack of serious complications (e.g. secondary malignancies) needs long-term confirmation. Another limitation is that SRS can generally only be used successfully for the treatment of relatively small tumours (Foote *et al*. 2002, Chino *et al*. 2009), i.e. the most likely to be cured surgically without complications.

Treatment of malignant HNPGLs

Data from series of malignant HNPGLs are scarce. The outcome appears to be better with surgery and radiotherapy vs surgery alone. Younger patients tend to respond better, and the overall 5-year survival rate with complex therapy (surgery/radiotherapy/chemotherapy) may become 84% in young (<40 years) patients (Lee *et al*. 2002, Moskovic *et al*. 2010).

The results of 'standard' chemotherapy are modest (Massey & Wallner 1992, Patel *et al*. 1995, Pipas & Krywicki 2000, Moskovic *et al*. 2010), in line with theoretical arguments against the efficacy of classic chemotherapy for slow-growing tumours. Somatostatin analogue (SSA) treatment for receptor-positive tumours has also not shown a major benefit (Duet *et al*. 2005). The use of modern anti-angiogenic therapies holds some promise, as PGLs are highly vascular tumours; sunitinib (a tyrosine kinase inhibitor) has shown some positive benefits in PGLs not based in the head and neck (Joshua *et al*. 2009).

PRRT with radiolabelled agents (MIBG or SSA) is an option for the treatment of malignant or inoperable PGLs with high uptake for the specific radiopharmaceutical – up to half of the cases show symptomatic and partial tumour response (Mukherjee *et al*. 2001, Van Essen *et al*. 2006, Gonias *et al*. 2009, Zovato *et al*. 2012). No studies have evaluated the possible efficacy of PRRT in earlier stages, on a more limited malignant tumour load (perhaps on lower doses that might decrease the risk of severe toxic reactions).

Choice of therapy

For the majority of tumours, complete cure is the most desirable outcome, and surgery is most likely to produce this outcome. However, for tumours with a more indolent natural history, it is important to minimise post-treatment morbidity, and thus therapies offering local control with fewer adverse effects, such as radiotherapy, can sometimes be preferable. Robust evidence in favour of any one treatment method cannot be easily obtained, as randomised trials are rare, current management strategies involve a selection bias, and success criteria have been very differently defined for surgery vs radiotherapy. Overall survival is similar to that of the general population (de Flines *et al*. 2011), albeit with reduced quality of life (Havekes *et al*. 2008), so this is not a useful end point for comparison. Therefore, the optimal management of HNPGLs has generated considerable debate over the years, and recommendations have varied from the routine use of radiotherapy (Verniers *et al*. 1992, Cole & Beiler 1994) to simple observation for most patients (van der Mey *et al*. 1992).

In the light of current evidence, optimal management is highly dependent on the tumour (location, size, involvement of neurovascular structures, malignancy and hormone production), the patient (age, co-morbidities and symptoms) and the genetic status (implying potential for recurrence, malignancy or multicentric tumours). Pre-treatment assessment should include, where possible, a comprehensive FH, detailed anatomical and functional imaging (to assess location, bone and vascular involvement, multicentricity, functional status, association with other tumours and distant metastases) and a genetic analysis (mutation carriers are younger, with higher rates of multicentricity and malignancy) (Burnichon *et al*. 2009), as well as an assessment of co-morbidities.

Surgery has been recommended as the treatment of choice in most patients, especially if performed at tertiary centres with surgeons having high expertise and the availability of a multidisciplinary team. As has been noted above, most CBTs (Sajid *et al*. 2007,

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Makeieff *et al*. 2008), small, lower-cervical VPGLs (Urquhart *et al*. 1994), and class A and B temporal bone tumours (Moe *et al*. 1999, Suarez *et al*. 2007) can be cured surgically with an acceptable morbidity rate. Surgery is also the treatment of choice for all catecholamine-secreting PGLs (Young 2006). Advanced or skull base-located tumours are associated with the highest rate of complications and functional disability (with a low response to rehabilitation measures in the elderly). In such tumours, surgery is less effective and more likely to inflict serious damage (Moe *et al*. 1999, Pareschi *et al*. 2003). However, many complications are not permanent or do not significantly affect long-term function significantly (Briner *et al*. 1999). If an extensive CN deficit is present preoperatively, a radical procedure carries a low risk of additional neurological morbidity and offers a high chance of cure, even in advanced tumours (Al-Mefty & Teixeira 2002). In younger (i.e. most) patients, rehabilitation for a surgery-inflicted neurological deficit is more likely to be reversible.

Primary radiotherapy has also been recommended for skull base tumours (Jackson *et al*. 1990), and recent evidence suggests that it might also be an option for the treatment of CBTs (Suarez *et al*. 2013*b*). Indeed, tumour growth arrest following radiotherapy is as frequent as surgical cure, while morbidity is significantly lower (Suarez *et al*. 2013*a*,*b*). Nevertheless, local control decreases with time, and salvage surgery after unsuccessful radiotherapy is technically difficult due to radiation-induced fibrosis. Radiotherapy carries a risk of severe late complications and the possibility of unrecognised malignant potential: irrespective of the type of radiotherapy used, viable cells persist and late distant spread can occur (Chino *et al*. 2009). In advanced cases, radiotherapy alone implies large-field irradiation with possible deleterious consequences. It would seem reasonable to particularly recommend radiotherapy for older patients, whose risk of late recurrence or complications might exceed life expectancy, and those with bilateral large tumours and/or contraindications to surgery (Moe *et al*. 1999, Suarez *et al*. 2007, Evans & Collins 2008, Ma *et al*. 2009). While all types of radiotherapy may be effective, there appears to be an advantage for radiosurgery where this is technically possible.

For difficult surgical cases, STR followed by observation or radiotherapy is a reasonable approach, as debulking offers symptomatic improvement with a low morbidity rate (Cosetti *et al*. 2008) and facilitates the use of SRS on a smaller remnant. This conservative strategy has been reported to be successful in patients over 60 years of age (Cosetti *et al*. 2008), in those with advanced tumours (Moe *et al*. 1999) or in individuals with previously normal CN function (Tran Ba *et al*. 2001). However, 'intended' STR is rarely described in the literature (frequently STR is the suboptimal result of an attempted total removal), so the theoretical benefit cannot be adequately assessed. Routine adjuvant radiotherapy has not been proven to improve the control rate (Ivan *et al*. 2011), so radiotherapy should probably be reserved for the treatment of postoperative remnant growth.

But is any intervention always required? Observation alone has been recommended, especially in the elderly and/or asymptomatic patients. (Lieberson *et al*. 2012). There are studies that have been carried out in The Netherlands showing overall normal life expectancy in HNPGL patients and no survival benefit irrespective of treatment (van der Mey *et al*. 1992, de Flines *et al*. 2011): these have been often cited to support observation as a major management strategy. However, simple observation may be inappropriate; if the tumour has malignant potential, unpredictable tumour-associated morbidity may occur, and if the tumour progresses, there may be a need for a later, more hazardous intervention. Watchful waiting can be used in patients deemed to have a short life expectancy (due to age or serious co-morbidities), but it may not be ideal for smaller tumours that may be readily resectable and that may progress or become invasive.

Multicentricity needs to be assessed as it increases the risk of debilitating bilateral neurological deficit (post-operatively and/or by mass effect). Unilateral surgery is usually performed (on the smallest tumour or the side with less CN palsies); contralateral surgery is performed only if no significant CN deficit has occurred. Otherwise, radiotherapy, STR or observation and may be appropriate action only if the tumour becomes symptomatic or grows (Al-Mefty & Teixeira 2002). With genetic screening being more widely implemented, earlier discovery of multifocal tumours and improved treatment outcome are to be anticipated (Fruhmann *et al*. 2013).

For malignant tumours, surgery and adjuvant radiotherapy are offered for symptomatic relief and improved survival; systemic chemotherapy in unresectable disease and PRRT with radiolabelled agents in high-uptake tumours may be used in selected cases (Patel *et al*. 1995, Moskovic *et al*. 2010).

Follow-up protocol

In sporadic cases, annual head/neck MRI for the first 2 years (Papaspyrou *et al*. 2012) has been proposed.

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However, the risk of recurrence persists many years after treatment, with a median time to recurrence of 5.8 years (average 8.2) (Jackson *et al*. 2001); this suggests that a more extended imaging follow-up might be cost beneficial, for at least the first 5 years after treatment. For sporadic CBTs, an annual neck ultrasound initially and then every 5 years has been suggested (Fruhmann *et al*. 2013), but clinical observation must be maintained indefinitely. Where functional, annual biochemical assessments are required for at least 10 years (Papaspyrou *et al*. 2012).

In familial cases, the exploration of carriers should begin a decade before the earliest age at diagnosis in the family (Young & Abboud 2006). Annual clinical and biochemical assessments must be performed, with neck ultrasound, CT or MRI being performed every 1–2 years targeting mainly the locations most associated with the pathogenic mutation (Young & Abboud 2006). SSR scintigraphy is also recommended as an adjunct to anatomical imaging for the initial evaluation and follow-up (Gimenez-Roqueplo *et al*. 2013), but there is no currently validated protocol for long-term follow-up. Where available, DOPA–PET can be used for whole-body screening during follow-up; it should be employed every 2–3 years or to confirm suspicious findings on CT/MRI (Boedeker *et al*. 2009*a*,*b*, Papaspyrou *et al*. 2012). In any protocol, familial cases should be monitored for multicentric disease indefinitely (Erickson *et al*. 2001).

Conclusions

The optimal treatment strategy for HNPGLs has not been defined yet. While surgery can be highly effective, it is not uncommonly associated with a high morbidity rate, while radiotherapeutic approaches can prevent tumour progression, but have uncertain long-term consequences. We would in general favour a conservative approach, accepting the need for intervention where there is evidence of tumour progression or where there is concern regarding malignancy. Where surgery is employed, it should generally be confined to smaller tumours in younger patients, while radiotherapy may play a larger role with more invasive or extensive tumours in older patients. A multidisciplinary team is always needed from diagnosis to treatment and follow-up (geneticists, radiologists, vascular surgeons, nuclear medicine specialists, rehabilitation specialists, oncologists, endocrinologists and speech therapists). Further progress in the understanding of PGL pathogenesis is likely to lead to earlier detection, which is essential for successful management.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the review reported.

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References

Al-Mefty O & Teixeira A 2002 Complex tumors of the glomus jugulare: criteria, treatment, and outcome. *Journal of Neurosurgery* **97** 1356–1366. (doi:10.3171/jns.2002.97.6.1356)

Anand VK, Alemar GO & Sanders TS 1995 Management of the internal carotid artery during carotid body tumor surgery. *Laryngoscope* **105** 231–235. (doi:10.1288/00005537-199503000-00001)

Astuti D, Latif F, Dallol A, Dahia PL, Douglas F, George E, Skoldberg F, Husebye ES, Eng C & Maher ER 2001 Gene mutations in the succinate dehydrogenase subunit SDHB cause susceptibility to familial pheochromocytoma and to familial paraganglioma. *American Journal of Human Genetics* **69** 49–54. (doi:10.1086/321282)

Barnes L, Tse LLY, Hunt JL & Michaels L 2004 *Tumours of the paraganglionic system WHO Classification of Tumours, Volume 8 IARC WHO Classification of Tumours*. Geneva: WHO press.

Bayley JP, Kunst HP, Cascon A, Sampietro ML, Gaal J, Korpershoek E, Hinojar-Gutierrez A, Timmers HJ, Hoefsloot LH, Hermsen MA *et al*. 2010 SDHAF2 mutations in familial and sporadic paraganglioma and phaeochromocytoma. *Lancet Oncology* **11** 366–372. (doi:10.1016/S1470-2045(10)70007-3)

Baysal BE 2002 Hereditary paraganglioma targets diverse paraganglia. *Journal of Medical Genetics* **39** 617–622. (doi:10.1136/jmg.39.9.617)

Baysal BE, Ferrell RE, Willett-Brozick JE, Lawrence EC, Myssiorek D, Bosch A, van der Mey A, Taschner PE, Rubinstein WS, Myers EN *et al*. 2000 Mutations in SDHD, a mitochondrial complex II gene, in hereditary paraganglioma. *Science* **287** 848–851. (doi:10.1126/science.287.5454.848)

Benn DE, Gimenez-Roqueplo AP, Reilly JR, Bertherat J, Burgess J, Byth K, Croxson M, Dahia PL, Elston M, Gimm O *et al*. 2006 Clinical presentation and penetrance of pheochromocytoma/paraganglioma syndromes. *Journal of Clinical Endocrinology and Metabolism* **91** 827–836. (doi:10.1210/jc.2005-1862)

van den Berg R, Wasser MN, van Gils AP, van der Mey AG, Hermans J & van Buchem MA 2000 Vascularization of head and neck paragangliomas: comparison of three MR angiographic techniques with digital subtraction angiography. *AJNR. American Journal of Neuroradiology* **21** 162–170.

Blanchet EM, Martucci V & Pacak K 2011 Pheochromocytoma and paraganglioma: current functional and future molecular imaging. *Frontiers in Oncology* **1** 58. (doi:10.3389/fonc.2011.00058)

Boedeker CC, Erlic Z, Richard S, Kontny U, Gimenez-Roqueplo AP, Cascon A, Robledo M, de Campos JM, van Nederveen FH, de Krijger RR *et al*. 2009*a* Head and neck paragangliomas in von Hippel–Lindau disease and multiple endocrine neoplasia type 2. *Journal of Clinical Endocrinology and Metabolism* **94** 1938–1944. (doi:10.1210/jc.2009-0354)

Boedeker CC, Neumann HP, Offergeld C, Maier W, Falcioni M, Berlis A & Schipper J 2009*b* Clinical features of paraganglioma syndromes. *Skull Base* **19** 17–25. (doi:10.1055/s-0028-1103123)

Bradshaw JW & Jansen JC 2005 Management of vagal paraganglioma: is operative resection really the best option? *Surgery* **137** 225–228. (doi:10.1016/j.surg.2004.09.009)

http://erc.endocrinology-journals.org
DOI: 10.1530/ERC-13-0223

Published by Bioscientifica Ltd.

Briner HR, Linder TE, Pauw B & Fisch U 1999 Long-term results of surgery for temporal bone paragangliomas. *Laryngoscope* **109** 577–583. (doi:10.1097/00005537-199904000-00011)

Burnichon N, Rohmer V, Amar L, Herman P, Leboulleux S, Darrouzet V, Niccoli P, Gaillard D, Chabrier G, Chabolle F *et al*. 2009 The succinate dehydrogenase genetic testing in a large prospective series of patients with paragangliomas. *Journal of Clinical Endocrinology and Metabolism* **94** 2817–2827. (doi:10.1210/jc.2008-2504)

Carney JA, Sheps SG, Go VL & Gordon H 1977 The triad of gastric leiomyosarcoma, functioning extra-adrenal paraganglioma and pulmonary chondroma. *New England Journal of Medicine* **296** 1517–1518. (doi:10.1056/NEJM197706302962609)

Cascon A, Lopez-Jimenez E, Landa I, Leskela S, Leandro-Garcia LJ, Maliszewska A, Leton R, de la Vega L, Garcia-Barcina MJ, Sanabria C *et al*. 2009 Rationalization of genetic testing in patients with apparently sporadic pheochromocytoma/paraganglioma. *Hormone and Metabolic Research* **41** 672–675. (doi:10.1055/s-0029-1202814)

Chino JP, Sampson JH, Tucci DL, Brizel DM & Kirkpatrick JP 2009 Paraganglioma of the head and neck: long-term local control with radiotherapy. *American Journal of Clinical Oncology* **32** 304–307. (doi:10.1097/COC.0b013e318187dd94)

Cole JM & Beiler D 1994 Long-term results of treatment for glomus jugulare and glomus vagale tumors with radiotherapy. *Laryngoscope* **104** 1461–1465. (doi:10.1288/00005537-199412000-00006)

Cosetti M, Linstrom C, Alexiades G, Tessema B & Parisier S 2008 Glomus tumors in patients of advanced age: a conservative approach. *Laryngoscope* **118** 270–274. (doi:10.1097/MLG.0b013e318158194b)

Cummings BJ, Beale FA, Garrett PG, Harwood AR, Keane TJ, Payne DG & Rider WD 1984 The treatment of glomus tumors in the temporal bone by megavoltage radiation. *Cancer* **53** 2635–2640. (doi:10.1002/1097-0142(19840615)53:12<2635::AID-CNCR2820531211>3.0.CO;2-9)

DeAngelis LM, Kelleher MB, Post KD & Fetell MR 1987 Multiple paragangliomas in neurofibromatosis: a new neuroendocrine neoplasia. *Neurology* **37** 129–133. (doi:10.1212/WNL.37.1.129)

De Toma G, Nicolanti V, Plocco M, Cavallaro G, Letizia C, Piccirillo G & Cavallaro A 2000 Baroreflex failure syndrome after bilateral excision of carotid body tumors: an underestimated problem. *Journal of Vascular Surgery* **31** 806–810. (doi:10.1067/mva.2000.103789)

Duet M, Guichard JP, Rizzo N, Boudiaf M, Herman P & Tran Ba HP 2005 Are somatostatin analogs therapeutic alternatives in the management of head and neck paragangliomas? *Laryngoscope* **115** 1381–1384. (doi:10.1097/01.MLG.0000165806.99675.A9)

van Duinen N, Steenvoorden D, Kema IP, Jansen JC, Vriends AH, Bayley JP, Smit JW, Romijn JA & Corssmit EP 2010 Increased urinary excretion of 3-methoxytyramine in patients with head and neck paragangliomas. *Journal of Clinical Endocrinology and Metabolism* **95** 209–214. (doi:10.1210/jc.2009-1632)

van Duinen N, Kema IP, Romijn JA & Corssmit EP 2011 Plasma chromogranin A levels are increased in a small portion of patients with hereditary head and neck paragangliomas. *Clinical Endocrinology* **74** 160–165. (doi:10.1111/j.1365-2265.2010.03914.x)

Eisenhofer G, Goldstein DS, Sullivan P, Csako G, Brouwers FM, Lai EW, Adams KT & Pacak K 2005 Biochemical and clinical manifestations of dopamine-producing paragangliomas: utility of plasma methoxytyramine. *Journal of Clinical Endocrinology and Metabolism* **90** 2068–2075. (doi:10.1210/jc.2004-2025)

Erickson D, Kudva YC, Ebersold MJ, Thompson GB, Grant CS, van Heerden JA & Young WF Jr 2001 Benign paragangliomas: clinical presentation and treatment outcomes in 236 patients. *Journal of Clinical Endocrinology and Metabolism* **86** 5210–5216. (doi:10.1210/jc.86.11.5210)

Evans JM & Collins M 2008 Clinically diagnosed glomus vagale tumour treated with external beam radiotherapy: a review of the published reports. *Journal of Medical Imaging and Radiation Oncology* **52** 617–621. (doi:10.1111/j.1440-1673.2008.01941.x)

Fisch U & Mattox DE 1988 Infratemporal fossa approach type A. Classification of glomus temporale tumours. In *Microsurgery of the skull base*, pp136-152. Stuttgart, Germany: Thieme.

de Flines J, Jansen J, Elders R, Siemers M, Vriends A, Hes F, Bayley JP, van der Mey A & Corssmit E 2011 Normal life expectancy for paraganglioma patients: a 50-year-old cohort revisited. *Skull Base* **21** 385–388. (doi:10.1055/s-0031-1287681)

Foote RL, Pollock BE, Gorman DA, Schomberg PJ, Stafford SL, Link MJ, Kline RW, Strome SE, Kasperbauer JL & Olsen KD 2002 Glomus jugulare tumor: tumor control and complications after stereotactic radiosurgery. *Head & Neck* **24** 332–338. (doi:10.1002/hed.10005)

Forest JA III, Jackson CG & McGrew BM 2001 Long-term control of surgically treated glomus tympanicum tumors. *Otology & Neurotology* **22** 232–236. (doi:10.1097/00129492-200103000-00020)

Fruhmann J, Geigl JB, Konstantiniuk P & Cohnert TU 2013 Paraganglioma of the carotid body: treatment strategy and SDH-gene mutations. *European Journal of Vascular and Endovascular Surgery* **45** 431–436. (doi:10.1016/j.ejvs.2013.01.018)

Gaal J, van Nederveen FH, Erlic Z, Korpershoek E, Oldenburg R, Boedeker CC, Kontny U, Neumann HP, Dinjens WN & de Krijger RR 2009 Parasympathetic paragangliomas are part of the Von Hippel–Lindau syndrome. *Journal of Clinical Endocrinology and Metabolism* **94** 4367–4371. (doi:10.1210/jc.2009-1479)

Gabriel S, Blanchet EM, Sebag F, Chen CC, Fakhry N, Deveze A, Barlier A, Morange I, Pacak K & Taieb D 2013 Functional characterization of non-metastatic paraganglioma and pheochromocytoma by (18) F-FDOPA PET: focus on missed lesions. *Clinical Endocrinology* **79** 170–177. (doi:10.1111/cen.12126)

Gaylis H, Davidge-Pitts K & Pantanowitz D 1987 Carotid body tumours. A review of 52 cases. *South African Medical Journal* **72** 493–496.

Gimenez-Roqueplo AP, Dahia PL & Robledo M 2012 An update on the genetics of paraganglioma, pheochromocytoma, and associated hereditary syndromes. *Hormone and Metabolic Research* **44** 328–333. (doi:10.1055/s-0031-1301302)

Gimenez-Roqueplo AP, Caumont-Prim A, Houzard C, Hignette C, Hernigou A, Halimi P, Niccoli P, Leboulleux S, Amar L, Borson-Chazot F *et al*. 2013 Imaging work-up for screening of paraganglioma and pheochromocytoma in SDHx mutation carriers: a multicenter prospective study from the PGL.EVA Investigators. *Journal of Clinical Endocrinology and Metabolism* **98** E162–E173. (doi:10.1210/jc.2012-2975)

Gjuric M, Seidinger L & Wigand ME 1996 Long-term results of surgery for temporal bone paraganglioma. *Skull Base Surgery* **6** 147–152. (doi:10.1055/s-2008-1058638)

Glassock ME III, Jackson CG, Dickins JR & Wiet RJ 1979 Panel discussion: glomus jugulare tumors of the temporal bone. The surgical management of glomus tumors. *Laryngoscope* **89** 1640–1654. (doi:10.1002/lary.5540891015)

Gonias S, Goldsby R, Matthay KK, Hawkins R, Price D, Huberty J, Damon L, Linker C, Sznewajs A, Shiboski S *et al*. 2009 Phase II study of high-dose [131I] metaiodobenzylguanidine therapy for patients with metastatic pheochromocytoma and paraganglioma. *Journal of Clinical Oncology* **27** 4162–4168. (doi:10.1200/JCO.2008.21.3496)

Gottfried ON, Liu JK & Couldwell WT 2004 Comparison of radiosurgery and conventional surgery for the treatment of glomus jugulare tumors. *Neurosurgical Focus* **17** E4.

Green JD Jr, Brackmann DE, Nguyen CD, Arriaga MA, Telischi FF & de la Cruz A 1994 Surgical management of previously untreated glomus jugulare tumors. *Laryngoscope* **104** 917–921. (doi:10.1288/00005537-199408000-00001)

Hansen HS & Thomsen KA 1988 Radiotherapy in glomus tumours (paragangliomas). A 25 year-review. *Acta Oto-Laryngologica. Supplementum* **449** 151–154. (doi:10.3109/00016488809106399)

Hao HX, Khalimonchuk O, Schraders M, Dephoure N, Bayley JP, Kunst H, Devilee P, Cremers CW, Schiffman JD, Bentz BG *et al*. 2009 SDH5, a

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gene required for flavination of succinate dehydrogenase, is mutated in paraganglioma. *Science* **325** 1139–1142. (doi:10.1126/science.1175689)

Havekes B, van der Klaauw AA, Hoftijzer HC, Jansen JC, van der Mey AG, Vriends AH, Smit JW, Romijn JA & Corssmit EP 2008 Reduced quality of life in patients with head-and-neck paragangliomas. *European Journal of Endocrinology* **158** 247–253. (doi:10.1530/EJE-07-0464)

Hensen EF, Siemers MD, Jansen JC, Corssmit EP, Romijn JA, Tops CM, van der Mey AG, Devilee P, Cornelisse CJ, Bayley JP *et al.* 2011 Mutations in SDHD are the major determinants of the clinical characteristics of Dutch head and neck paraganglioma patients. *Clinical Endocrinology* **75** 650–655. (doi:10.1111/j.1365-2265.2011.04097.x)

Hinerman RW, Mendenhall WM, Amdur RJ, Stringer SP, Antonelli PJ & Cassisi NJ 2001 Definitive radiotherapy in the management of chemodectomas arising in the temporal bone, carotid body, and glomus vagale. *Head & Neck* **23** 363–371. (doi:10.1002/hed.1045)

Hinerman RW, Amdur RJ, Morris CG, Kirwan J, Mendenhall WM & Stringer SP 2008 Definitive radiotherapy in the management of paragangliomas arising in the head and neck: a 35-year experience. *Head & Neck* **30** 1431–1438.

Huy PT, Kania R, Duet M, Dessard-Diana B, Mazeron JJ & Benhamed R 2009 Evolving concepts in the management of jugular paraganglioma: a comparison of radiotherapy and surgery in 88 cases. *Skull Base* **19** 83–91. (doi:10.1055/s-0028-1103125)

Ivan ME, Sughrue ME, Clark AJ, Kane AJ, Aranda D, Barani IJ & Parsa AT 2011 A meta-analysis of tumor control rates and treatment-related morbidity for patients with glomus jugulare tumors. *Journal of Neurosurgery* **114** 1299–1305. (doi:10.3171/2010.9.JNS10699)

Jackson CG, Harris PF, Glasscock ME III, Fritsch M, Dimitrov E, Johnson GD & Poe DS 1990 Diagnosis and management of paragangliomas of the skull base. *American Journal of Surgery* **159** 389–393. (doi:10.1016/S0002-9610(05)81279-6)

Jackson CG, McGrew BM, Forest JA, Netterville JL, Hampf CF & Glasscock ME III 2001 Lateral skull base surgery for glomus tumors: long-term control. *Otology & Neurotology* **22** 377–382. (doi:10.1097/00129492-200105000-00018)

Jafri M, Whitworth J, Rattenberry E, Bradley L, Kilby G, Kumar AV, Izatt L, Lalloo F, Brennan P, Cook J *et al.* 2013 Evaluation of SDHB, SDHD and VHL gene susceptibility testing in the assessment of individuals with non-syndromic phaeochromocytoma and paraganglioma and head and neck paraganglioma (HNPGL). *Clinical Endocrinology* **78** 898–906. (doi:10.1111/cen.12074)

Jansen JC, van den Berg R, Kuiper A, van der Mey AG, Zwinderman AH & Cornelisse CJ 2000 Estimation of growth rate in patients with head and neck paragangliomas influences the treatment proposal. *Cancer* **88** 2811–2816. (doi:10.1002/1097-0142(20000615)88:12<2811::AID-CNCR21>3.0.CO;2-7)

de Jong AL, Coker NJ, Jenkins HA, Goepfert H & Alford BR 1995 Radiation therapy in the management of paragangliomas of the temporal bone. *American Journal of Otology* **16** 283–289. (doi:10.1016/0196-0709(95)90054-3)

Joshua AM, Ezzat S, Asa SL, Evans A, Broom R, Freeman M & Knox JJ 2009 Rationale and evidence for sunitinib in the treatment of malignant paraganglioma/pheochromocytoma. *Journal of Clinical Endocrinology and Metabolism* **94** 5–9. (doi:10.1210/jc.2008-1836)

Kahn LB 1976 Vagal body tumor (nonchromaffin paraganglioma, chemodectoma, and carotid body-like tumor) with cervical node metastasis and familial association: ultrastructural study and review. *Cancer* **38** 2367–2377. (doi:10.1002/1097-0142(197612)38:6<2367::AID-CNCR2820380625>3.0.CO;2-3)

King KS, Chen CC, Alexopoulos DK, Whatley MA, Reynolds JC, Patronas N, Ling A, Adams KT, Xekouki P, Lando H *et al.* 2011 Functional imaging of SDHx-related head and neck paragangliomas: comparison of 18F-fluorodihydroxyphenylalanine, 18F-fluorodopamine, 18F-fluoro-2-deoxy-D-glucose PET, 123I-metaiodobenzylguanidine scintigraphy, and 111In-pentetreotide scintigraphy. *Journal of Clinical Endocrinology and Metabolism* **96** 2779–2785. (doi:10.1210/jc.2011-0333)

Kloppel G 2003 Tumors of the adrenal medulla and the paraganglia. *Der Pathologe* **24** 280–286. (doi:10.1007/s00292-003-0635-8)

Kohler HF, Carvalho AL, Mattos Granja NV, Nishinari K & Kowalski LP 2004 Surgical treatment of paragangliomas of the carotid bifurcation: results of 36 patients. *Head & Neck* **26** 1058–1063. (doi:10.1002/hed.20105)

Kollert M, Minovi AA, Draf W & Bockmuhl U 2006 Cervical paragangliomas-tumor control and long-term functional results after surgery. *Skull Base* **16** 185–191. (doi:10.1055/s-2006-950386)

Korevaar TI & Grossman AB 2011 Pheochromocytomas and paragangliomas: assessment of malignant potential. *Endocrine* **40** 354–365. (doi:10.1007/s12020-011-9545-3)

Kunst HP, Rutten MH, de Monnink JP, Hoefsloot LH, Timmers HJ, Marres HA, Jansen JC, Kremer H, Bayley JP & Cremers CW 2011 SDHAF2 (PGL2–SDH5) and hereditary head and neck paraganglioma. *Clinical Cancer Research* **17** 247–254. (doi:10.1158/1078-0432.CCR-10-0420)

Kunzel J, Iro H, Hornung J, Koch M, Brase C, Klautke G & Zenk J 2012 Function-preserving therapy for jugulotympanic paragangliomas: a retrospective analysis from 2000 to 2010. *Laryngoscope* **122** 1545–1551. (doi:10.1002/lary.23268)

Lack EE, Cubilla AL, Woodruff JM & Farr HW 1977 Paragangliomas of the head and neck region: a clinical study of 69 patients. *Cancer* **39** 397–409. (doi:10.1002/1097-0142(197702)39:2<397::AID-CNCR2820390205>3.0.CO;2-C)

Lalwani AK, Jackler RK & Gutin PH 1993 Lethal fibrosarcoma complicating radiation therapy for benign glomus jugulare tumor. *American Journal of Otology* **14** 398–402.

Langerman A, Athavale SM, Rangarajan SV, Sinard RJ & Netterville JL 2012 Natural history of cervical paragangliomas: outcomes of observation of 43 patients. *Archives of Otolaryngology – Head & Neck Surgery* **138** 341–345. (doi:10.1001/archoto.2012.37)

Lee JH, Barich F, Karnell LH, Robinson RA, Zhen WK, Gantz BJ & Hoffman HT 2002 National Cancer Data Base report on malignant paragangliomas of the head and neck. *Cancer* **94** 730–737. (doi:10.1002/cncr.10252)

Lees CD, Levine HL, Beven EG & Tucker HM 1981 Tumors of the carotid body. Experience with 41 operative cases. *American Journal of Surgery* **142** 362–365. (doi:10.1016/0002-9610(81)90349-4)

Lieberson RE, Adler JR, Soltys SG, Choi C, Gibbs IC & Chang SD 2012 Stereotactic radiosurgery as the primary treatment for new and recurrent paragangliomas: is open surgical resection still the treatment of choice? *World Neurosurgery* **77** 745–761. (doi:10.1016/j.wneu.2011.03.026)

Lightowlers S, Benedict S, Jefferies SJ, Jena R, Harris F, Burton KE & Burnet NG 2010 Excellent local control of paraganglioma in the head and neck with fractionated radiotherapy. *Clinical Oncology* **22** 382–389. (doi:10.1016/j.clon.2010.02.006)

Liscak R, Vladyka V, Wowra B, Kemeny A, Forster D, Burzaco JA, Martinez R, Eustacchio S, Pendl G, Regis J *et al.* 1999 Gamma knife radiosurgery of the glomus jugulare tumour – early multicentre experience. *Acta Neurochirurgica* **141** 1141–1146. (doi:10.1007/s007010050411)

Lozano FS, Gomez JL, Mondillo MC, Gonzalez-Porras JR, Gonzalez-Sarmiento R & Munoz A 2008 Surgery of vagal paragangliomas: six patients and review of literature. *Surgical Oncology* **17** 281–287.

Luna-Ortiz K, Rascon-Ortiz M, Villavicencio-Valencia V, Granados-Garcia M & Herrera-Gomez A 2005 Carotid body tumors: review of a 20-year experience. *Oral Oncology* **41** 56–61. (doi:10.1016/j.oraloncology.2004.06.006)

Ma D, Liu L, Yao H, Hu Y, Ji T, Liu X, Zhang C & Qiu W 2009 A retrospective study in management of carotid body tumour. *British Journal of Oral & Maxillofacial Surgery* **47** 461–465. (doi:10.1016/j.bjoms.2009.06.006)

Makeieff M, Raingeard I, Alric P, Bonafe A, Guerrier B & Marty-Ane C 2008 Surgical management of carotid body tumors. *Annals of Surgical Oncology* **15** 2180–2186. (doi:10.1245/s10434-008-9977-z)

http://erc.endocrinology-journals.org
DOI: 10.1530/ERC-13-0223

Published by Bioscientifica Ltd.

Manolidis S, Shohet JA, Jackson CG & Glasscock ME III 1999 Malignant glomus tumors. *Laryngoscope* **109** 30–34. (doi:10.1097/00005537-199901000-00007)

Massey V & Wallner K 1992 Treatment of metastatic chemodectoma. *Cancer* **69** 790–792. (doi:10.1002/1097-0142(19920201)69:3<790::AID-CNCR2820690329>3.0.CO;2-U)

van der Mey AG, Frijns JH, Cornelisse CJ, Brons EN, van Dulken H, Terpstra HL & Schmidt PH 1992 Does intervention improve the natural course of glomus tumors? A series of 108 patients seen in a 32-year period *Annals of Otology, Rhinology, and Laryngology* **101** 635–642.

Miller RB, Boon MS, Atkins JP & Lowry LD 2000 Vagal paraganglioma: the Jefferson experience. *Otolaryngology – Head and Neck Surgery* **122** 482–487.

Moe KS, Li D, Linder TE, Schmid S & Fisch U 1999 An update on the surgical treatment of temporal bone paraganglioma. *Skull Base Surgery* **9** 185–194. (doi:10.1055/s-2008-1058145)

Moskovic DJ, Smolarz JR, Stanley D, Jimenez C, Williams MD, Hanna EY & Kupferman ME 2010 Malignant head and neck paragangliomas: is there an optimal treatment strategy? *Head & Neck Oncology* **2** 23. (doi:10.1186/1758-3284-2-23)

Mukherjee JJ, Kaltsas GA, Islam N, Plowman PN, Foley R, Hikmat J, Britton KE, Jenkins PJ, Chew SL, Monson JP *et al.* 2001 Treatment of metastatic carcinoid tumours, phaeochromocytoma, paraganglioma and medullary carcinoma of the thyroid with (131)I-meta-iodobenzylguanidine [(131)I-mIBG]. *Clinical Endocrinology* **55** 47–60. (doi:10.1046/j.1365-2265.2001.01309.x)

Mumber MP & Greven KM 1995 Control of advanced chemodectomas of the head and neck with irradiation. *American Journal of Clinical Oncology* **18** 389–391. (doi:10.1097/00000421-199510000-00005)

van Nederveen FH, Gaal J, Favier J, Korpershoek E, Oldenburg RA, de Bruyn EM, Sleddens HF, Derkx P, Riviere J, Dannenberg H *et al.* 2009 An immunohistochemical procedure to detect patients with paraganglioma and phaeochromocytoma with germline SDHB, SDHC, or SDHD gene mutations: a retrospective and prospective analysis. *Lancet Oncology* **10** 764–771. (doi:10.1016/S1470-2045(09)70164-0)

Neskey DM, Hatoum G, Modh R, Civantos F, Telischi FF, Angeli SI, Weed D & Sargi Z 2011 Outcomes after surgical resection of head and neck paragangliomas: a review of 61 patients. *Skull Base* **21** 171–176. (doi:10.1055/s-0031-1275251)

Netterville JL & Civantos FJ 1993 Rehabilitation of cranial nerve deficits after neurotologic skull base surgery. *Laryngoscope* **103** 45–54.

Netterville JL, Jackson CG, Miller FR, Wanamaker JR & Glasscock ME 1998 Vagal paraganglioma: a review of 46 patients treated during a 20-year period. *Archives of Otolaryngology – Head & Neck Surgery* **124** 1133–1140. (doi:10.1001/archotol.124.10.1133)

Neumann HP, Erlic Z, Boedeker CC, Rybicki LA, Robledo M, Hermsen M, Schiavi F, Falcioni M, Kwok P, Bauters C *et al.* 2009 Clinical predictors for germline mutations in head and neck paraganglioma patients: cost reduction strategy in genetic diagnostic process as fall-out. *Cancer Research* **69** 3650–3656. (doi:10.1158/0008-5472.CAN-08-4057)

Niemann S, Steinberger D & Muller U 1999 PGL3, a third, not maternally imprinted locus in autosomal dominant paraganglioma. *Neurogenetics* **2** 167–170. (doi:10.1007/s100480050078)

Obholzer RJ, Hornigold R, Connor S & Gleeson MJ 2011 Classification and management of cervical paragangliomas. *Annals of the Royal College of Surgeons of England* **93** 596–602. (doi:10.1308/147870811X13137608455172)

Offergeld C, Brase C, Yaremchuk S, Mader I, Rischke HC, Glasker S, Schmid KW, Wiech T, Preuss SF, Suarez C *et al.* 2012 Head and neck paragangliomas: clinical and molecular genetic classification. *Clinics* **67** (Suppl 1) 19–28. (doi:10.6061/clinics/2012(Sup01)05)

O'Leary MJ, Shelton C, Giddings NA, Kwartler J & Brackmann DE 1991 Glomus tympanicum tumors: a clinical perspective. *Laryngoscope* **101** 1038–1043. (doi:10.1002/lary.5541011213)

Papaspyrou K, Mann WJ & Amedee RG 2009 Management of head and neck paragangliomas: review of 120 patients. *Head & Neck* **31** 381–387. (doi:10.1002/hed.20967)

Papaspyrou K, Mewes T, Rossmann H, Fottner C, Schneider-Raetzke B, Bartsch O, Schreckenberger M, Lackner KJ, Amedee RG & Mann WJ 2012 Head and neck paragangliomas: report of 175 patients (1989–2010). *Head & Neck* **34** 632–637. (doi:10.1002/hed.21790)

Pareschi R, Righini S, Destito D, Raucci AF & Colombo S 2003 Surgery of glomus jugulare tumors. *Skull Base* **13** 149–157. (doi:10.1055/s-2003-43325)

Paris J, Facon F, Thomassin JM & Zanaret M 2006 Cervical paragangliomas: neurovascular surgical risk and therapeutic management. *European Archives of Oto-Rhino-Laryngology* **263** 860–865. (doi:10.1007/s00405-006-0074-2)

Patel SR, Winchester DJ & Benjamin RS 1995 A 15-year experience with chemotherapy of patients with paraganglioma. *Cancer* **76** 1476–1480. (doi:10.1002/1097-0142(19951015)76:8<1476::AID-CNCR2820760827>3.0.CO;2-9)

Patetsios P, Gable DR, Garrett WV, Lamont JP, Kuhn JA, Shutze WP, Kourlis H, Grimsley B, Pearl GJ, Smith BL *et al.* 2002 Management of carotid body paragangliomas and review of a 30-year experience. *Annals of Vascular Surgery* **16** 331–338. (doi:10.1007/s10016-001-0106-8)

Persky MS, Setton A, Niimi Y, Hartman J, Frank D & Berenstein A 2002 Combined endovascular and surgical treatment of head and neck paragangliomas – a team approach. *Head & Neck* **24** 423–431. (doi:10.1002/hed.10068)

Pipas JM & Krywicki RF 2000 Treatment of progressive metastatic glomus jugulare tumor (paraganglioma) with gemcitabine. *Neuro-Oncology* **2** 190–191.

Plukker JT, Brongers EP, Vermey A, Krikke A & van den Dungen JJ 2001 Outcome of surgical treatment for carotid body paraganglioma. *British Journal of Surgery* **88** 1382–1386. (doi:10.1046/j.0007-1323.2001.01878.x)

Pollock BE 2004 Stereotactic radiosurgery in patients with glomus jugulare tumors. *Neurosurgical Focus* **17** E10. (doi:10.3171/foc.2004.17.2.10)

Powell S, Peters N & Harmer C 1992 Chemodectoma of the head and neck: results of treatment in 84 patients. *International Journal of Radiation Oncology, Biology, Physics* **22** 919–924. (doi:10.1016/0360-3016(92)90788-J)

Rao AB, Koeller KK & Adair CF 1999 From the archives of the AFIP. Paragangliomas of the head and neck: radiologic-pathologic correlation. 1999 Armed Forces Institute of Pathology. *Radiographics* **19** 1605–1632.

Rodriguez-Cuevas S, Lopez-Garza J & Labastida-Almendaro S 1998 Carotid body tumors in inhabitants of altitudes higher than 2000 meters above sea level. *Head & Neck* **20** 374–378. (doi:10.1002/(SICI)1097-0347(199808)20:5<374::AID-HED3>3.0.CO;2-V)

Sajid MS, Hamilton G & Baker DM 2007 A multicenter review of carotid body tumour management. *European Journal of Vascular and Endovascular Surgery* **34** 127–130. (doi:10.1016/j.ejvs.2007.01.015)

Saringer W, Kitz K, Czerny C, Kornfehl J, Gstottner W, Matula C & Knosp E 2002 Paragangliomas of the temporal bone: results of different treatment modalities in 53 patients. *Acta Neurochirurgica* **144** 1255–1264. (doi:10.1007/s00701-002-1016-4)

Sevilla Garcia MA, Llorente Pendas JL, Rodrigo Tapia JP, Garcia RG, Surez FV, Coca PA & Surez NC 2007 Head and neck paragangliomas: revision of 89 cases in 73 patients. *Acta Otorrinolaringológica Española* **58** 94–100. (doi:10.1016/S0001-6519(07)74888-4)

Shamblin WR, ReMine WH, Sheps SG & Harrison EG Jr 1971 Carotid body tumor (chemodectoma). Clinicopathologic analysis of ninety cases. *American Journal of Surgery* **122** 732–739. (doi:10.1016/0002-9610(71)90436-3)

Sharma PD, Johnson AP & Whitton AC 1984 Radiotherapy for jugulo-tympanic paragangliomas (glomus jugulare tumours). *Journal of Laryngology and Otology* **98** 621–629. (doi:10.1017/S0022215100147188)

Sharma P, Thakar A, Suman KS, Dhull VS, Singh H, Naswa N, Reddy RM, Karunanithi S, Kumar R & Kumar R 2013 68Ga-DOTANOC PET/CT for baseline evaluation of patients with head and neck paraganglioma.

http://erc.endocrinology-journals.org
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Journal of Nuclear Medicine **54** 841–847. (doi:10.2967/jnumed.112.115485)

Smith JJ, Passman MA, Dattilo JB, Guzman RJ, Naslund TC & Netterville JL 2006 Carotid body tumor resection: does the need for vascular reconstruction worsen outcome? *Annals of Vascular Surgery* **20** 435–439. (doi:10.1007/s10016-006-9093-0)

Suarez C, Sevilla MA & Llorente JL 2007 Temporal paragangliomas. *European Archives of Oto-Rhino-Laryngology* **264** 719–731. (doi:10.1007/s00405-007-0267-3)

Suarez C, Rodrigo JP, Bodeker CC, Llorente JL, Silver CE, Jansen JC, Takes RP, Strojan P, Pellitteri PK, Rinaldo A *et al.* 2013*a* Jugular and vagal paragangliomas: systematic study of management with surgery and radiotherapy. *Head & Neck* **35** 1195–1204. (doi:10.1002/hed.22976)

Suarez C, Rodrigo JP, Mendenhall WM, Hamoir M, Silver CE, Gregoire V, Strojan P, Neumann HP, Obholzer R & Offergeld C 2013*b* Carotid body paragangliomas: a systematic study of management with surgery and radiotherapy. *European Archives of Oto-Rhino-Laryngology* [in press]. (doi:10.1007/s00405-013-2384-5)

Timmers HJ, Karemaker JM, Wieling W, Marres HA, Folgering HT & Lenders LW 2003 Baroreflex and chemoreflex function after bilateral carotid body tumor resection. *Journal of Hypertension* **21** 591–599. (doi:10.1097/00004872-200303000-00026)

Timmers HJ, Chen CC, Carrasquillo JA, Whatley M, Ling A, Havekes B, Eisenhofer G, Martiniova L, Adams KT & Pacak K 2009 Comparison of 18F-fluoro-L-DOPA, 18F-fluoro-deoxyglucose, and 18F-fluorodopamine PET and 123I-MIBG scintigraphy in the localization of pheochromocytoma and paraganglioma. *Journal of Clinical Endocrinology and Metabolism* **94** 4757–4767. (doi:10.1210/jc.2009-1248)

Timmers HJ, Taieb D & Pacak K 2012 Current and future anatomical and functional imaging approaches to pheochromocytoma and paraganglioma. *Hormone and Metabolic Research* **44** 367–372. (doi:10.1055/s-0031-1299712)

Tran Ba HP, Chao PZ, Benmansour F & George B 2001 Long-term oncological results in 47 cases of jugular paraganglioma surgery with special emphasis on the facial nerve issue. *Journal of Laryngology and Otology* **115** 981–987.

Ulrich S, Lehmann M, Ebmeyer J, Hamberger U, Reineke U, Dietrich U & Sudhoff H 2009 Direct percutaneous embolization of a carotid body tumor with Onyx. *HNO* **57** 1305–1310. (doi:10.1007/s00106-009-1960-x)

Urquhart AC, Johnson JT, Myers EN & Schechter GL 1994 Glomus vagale: paraganglioma of the vagus nerve. *Laryngoscope* **104** 440–445. (doi:10.1288/00005537-199404000-00008)

Van Der Horst-Schrivers AN, Osinga TE, Kema IP, Van Der Laan BF & Dullaart RP 2010 Dopamine excess in patients with head and neck paragangliomas. *Anticancer Research* **30** 5153–5158.

Van Essen M, Krenning EP, Kooij PP, Bakker WH, Feelders RA, de Herder WW, Wolbers JG & Kwekkeboom DJ 2006 Effects of therapy with [177Lu-DOTA0, Tyr3]octreotate in patients with paraganglioma, meningioma, small cell lung carcinoma, and melanoma. *Journal of Nuclear Medicine* **47** 1599–1606.

Verniers DA, Keus RB, Schouwenburg PF & Bartelink H 1992 Radiation therapy, an important mode of treatment for head and neck chemodectomas. *European Journal of Cancer* **28A** 1028–1033. (doi:10.1016/0959-8049(92)90448-B)

Westerband A, Hunter GC, Cintora I, Coulthard SW, Hinni ML, Gentile AT, Devine J & Mills JL 1998 Current trends in the detection and management of carotid body tumors. *Journal of Vascular Surgery* **28** 84–92. (doi:10.1016/S0741-5214(98)70203-4)

Young WF 2006 Paragangliomas: clinical overview. *Annals of the New York Academy of Sciences* **1073** 21–29. (doi:10.1196/annals.1353.002)

Young WF & Abboud AL 2006 Editorial: paraganglioma – all in the family. *Journal of Clinical Endocrinology and Metabolism* **91** 790–792. (doi:10.1210/jc.2005-2758)

Zanelli M & van der Walt JD 1996 Carotid body paraganglioma in von Hippel–Lindau disease: a rare association. *Histopathology* **29** 178–181. (doi:10.1046/j.1365-2559.1996.d01-505.x)

Zanoletti E & Mazzoni A 2006 Vagal paraganglioma. *Skull Base* **16** 161–167. (doi:10.1055/s-2006-949519)

Zeitler DM, Glick J & Har-El G 2010 Preoperative embolization in carotid body tumor surgery: is it required? *Annals of Otology, Rhinology, and Laryngology* **119** 279–283.

Zovato S, Kumanova A, Dematte S, Sansovini M, Bodei L, Di Sarra D, Casagranda E, Severi S, Ambrosetti A, Schiavi F *et al.* 2012 Peptide receptor radionuclide therapy (PRRT) with 177Lu-DOTATATE in individuals with neck or mediastinal paraganglioma (PGL). *Hormone and Metabolic Research* **44** 411–414. (doi:10.1055/s-0032-1311637)

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