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HEAD AND NECK

A two-decade experience of head and neck paragangliomas in a whole population-based single centre cohort

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Abstract Paragangliomas are rare neuroendocrine tumours arising from neural crest-derived tissue. In the head and neck region typical locations are the carotid bifurcation, vagal nerve or jugulotympanic region. Paragangliomas are normally benign, and malignant transformation is rare. During the past decade the understanding of the genetic and molecular aetiology has had an important clinical impact on the management of PGs. This is a retrospective review of all histologically verified paragangliomas diagnosed and managed at an academic tertiary care referral centre between 1990 and 2010. Data on age, sex, symptoms, tumour location, management and follow-up were recorded. There were 64 patients with 74 tumours. Thirty-six per cent of the tumours were located in the carotid body region, 48 % in the jugulotympanic region and 15 % in the vagal nerve. One tumour was located in the dorsal neck. Most (95 %) of the patients were treated primarily with surgery and with curative intent. Definitive radiation therapy was primarily given to two patients. Recurrent or residual tumours were treated with surgery in three patients and with radiation therapy in nine patients. The typical long-term post-operative sequel was vocal cord paralysis. Local recurrence was found in 6 % of patients. Symptoms and findings related to paragangliomas are variable and management should be individualized. Surgery remains the primary choice of the current treatment options, but often is challenging and warrants a multidisciplinary approach. We present an algorithm on the management of head and neck paragangliomas based on current knowledge.

Keywords Head and neck neoplasms · Paraganglioma · Surgery · Genetic testing · Mutation · Succinate dehydrogenase

Introduction

Background

Paraganglia are cell clusters located throughout the body in the vascular and neuronal adventitia derived from specialized embryonic neural crest cells [1]. Extra-adrenal

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Table 1 The SDH susceptibility genes associated with HNPs

Gene	PG sdr	Inheritance	Multifocality	Malignancy	PCC/PG in abd.	Mean age	Refs
SDHA	–	AD	Undet.	Undet.	Undet.	–	[5]
SDHAF2	2	AD with PI	High	Low	Undet.	33	[5, 16]
SDHB	4	AD	Intermed.	31–71 %	High	33	[5, 16]
SDHC	3	AD	Low	Very low	Very low	38	[5, 16]
SDHD	1	AD with PI	Very high	Under 5 %	Intermed.	40	[5, 16]

PCC pheochromocytoma, *PG* paraganglioma, *Refs* references, *SDHx* succinate dehydrogenase subunits A-D, *AD* autosomal dominant, *PI* paternal inheritance, *Undet* undetermined, *Intermed* intermediate [5, 16]

paragangliomas (PGs) have been proposed to constitute 15–20 % of paraganglion system tumours [2, 3]. The incidence of all paraganglion system tumours has been estimated by Baysal to be around 1/300,000 [4]. Head and neck paragangliomas (HNPs) are parasympathetic and thus typically non-secreting as opposed to paragangliomas of the lower mediastinum, abdomen or pelvis [5].

Besides being rare, HNPs are slowly growing, highly vascular, and mainly benign tumours that commonly occur at the carotid bifurcation (carotid body tumours, CBTs), at the jugular bulb (jugular PGs, JPs), in the tympanic cavity (tympanic or petrous bone PGs, TPs), or as vagal PGs (VPs) [1, 6, 7]. Malignancy has been reported in less than 10 % of PGs and is determined by metastasis to non-endocrine tissue [3, 7, 8]. Several histological criteria for malignancy have been proposed, but none of these have proven to be conclusive [9].

Genetics

Pheochromocytomas (PCCs) and PGs are frequently associated with an inherited mutation causing susceptibility to paragangliomas [5, 10]. Population studies show that as many as 54 % of patients with seemingly sporadic HNPs have actually a germline mutation in a known susceptibility gene [5]. The risk for genetic background increases with a positive family history of PGs, if the patient is under 40 years, or if the patient also has a PCC or multiple PGs [1, 10]. Presently, ten susceptibility genes have been discovered [5]. The two most common are genes coding for the two succinate dehydrogenase subunits *SDHB* and *SDHD* causing paraganglioma syndromes PGL4 and PGL1 [11, 12]. Others include *SDHC, SDHAF2, SDHA, TMEM127, MAX* and *VHL, NF1* and *RET* (MEN2) [13]. Table 1 outlines the succinate dehydrogenase (SDH) subunit and cofactor genes associated with HNPs. The mode of inheritance for paraganglioma susceptibility is autosomal dominant; however, for SDHD and SDHAF2 this is modified by imprinting and mutations in these two genes cause paragangliomas only when the mutation is inherited from father [14, 15]. Determining the molecular genetic background enables identification of other family members at risk, the mode of inheritance and also predicts the risk of malignant PGs for which the only reliable predictor is a germline mutation in the *SDHB* gene [16].

HNP characteristics

Being neuroendocrine tumours, HNPs are capable of synthesizing a variety of hormonal substances. These, however, are rarely symptomatic unlike their adrenal, abdominal or thoracic counterparts [1, 5]. Primarily the symptoms depend on the location of the tumour, where cervical PGs present with a painless, slowly enlarging lateral neck mass, while tympanic, petrous bone or jugular PGs present with tinnitus and hearing loss as early symptoms [17]. Patients with jugular PGs often suffer from lower cranial nerve deficits as a result of the tumour compression on cranial nerves (CNIX–XI) exiting the jugular foramen [17]. While the average age at diagnosis is approximately 50 years, the sex distribution varies with the site of the tumour; the carotid body PGs are found more often in men (2:1) whereas for vagal PGs the distribution is reversed [1, 18, 19]. The mean tumour doubling rate has been found to be 4.2 years making the growth rate usually slow [6].

Imaging and treatment

HNPs are mostly diagnosed with a computed tomography (CT) or a magnetic resonance imaging (MRI) scan while synchronous carotid body PGs are excluded and carotid body PGs also identified with Doppler sonography [6]. Further functional imaging modalities should be considered such as ^{18}F-dihydroxyphenylalanine positron emission tomography (^{18}F-DOPA PET) if the risk for multiple PGs is high or the patient has an SDHx mutation-related HNP [20]. Fine needle aspiration and biopsy are rarely diagnostic and often risky due to the high vascularity of the tumour [6]. The main treatment of choice for HNPs is still surgical resection, the trend being to move away from radical resection toward function-preserving surgical tumour reduction [18]. Good post-operative results can be expected for CBTs

of Shamblin class I and II and TPs, whereas operations on other CBTs and HNPs frequently result in deficits of adjacent cranial nerves [21]. Local control of, e.g. JTPs, can be achieved using post-operative stereotactic radiotherapy (SRT) or conservative wait-and-scan strategy; such function-preserving therapy approach appears to offer the greatest benefit for patients [22]. Tumours' slow growth, usually benign nature and the tendency of hereditary HNPs to be multifocal may justify less aggressive treatment strategies for all types of HNPs [23, 24].

In this report, we present data on patients diagnosed with histologically verified HNPs in an academic tertiary centre in Finland over a 21-year period. We concentrate on the different management strategies and discuss post-surgery patient outcomes. In addition, we propose a HNP management guideline based on the current knowledge of genetics underlying HNPs (Fig. 1).

Materials and methods

We retrospectively reviewed the clinicopathological records of all histologically confirmed HNPs managed at the Helsinki University Central Hospital (HUCH), covering approximately 1.8 million inhabitants, in Helsinki, Finland, during a 21-year period between January 1, 1990 and December 31, 2010.

The patients were collected from the archives of the Department of Pathology and their medical, operative and pathologic records reviewed. In total 138 patients were included in the first search from the pathology archives, of which 64 patients filled the inclusion criteria of location in the head and neck area. Two patients were excluded, because their HNP was diagnosed at autopsy. Data on age, sex, symptoms, the timing of diagnosis, tumour location and quantity, embolization, genetic aetiology, Charlson's Comorbidity Index (CCI), management and follow-up were recorded [25].

Clinical follow-up time was defined as the time period from the time of treatment (i.e. surgery) to the last clinical evaluation or time of death. Overall and disease-specific survival data, consisting of date and cause of death, were provided by the Statistics Finland. Endpoints (overall survival, disease-free survival) were defined according to FDA guidelines [26]. Specifically, when calculating the disease-free survival, non-cancer deaths were censored.

Statistical analysis was carried out using a computerized software package (SPSS, version 19.0, Chicago, IL, USA). Median follow-up time was calculated using the "reverse K-M method" as described by Schemper and Smith [27].

This study was a registry-based study recording the current management of HNP patients during a specific time period with no additional interventions. Therefore, formal Research Ethics Board approval was not necessary. An institutional research permission was granted for the study protocol (§ 78, 27.3.2012).

Results

Patients

We analysed the clinicopathological data of 64 patients with at least one histologically confirmed HNP. There were, in total, 74 HNPs. Six patients had multiple HNPs, which are presented in Table 2. Based on our data the incidence rate was 1.8 new cases per 1,000,000 persons per year. Of the 64 patients, 23 (36 %) were male and 41 (64 %) female with a median age of 56 years at diagnosis (range 21–73 years). At the time of diagnosis, the patients had a median CCI of 0 (range 0–6). Three patients had malignant paraganglioma matching the World Health Organization (WHO) criteria for paraganglioma malignancy [8].

Presenting symptoms and locations of tumours

The most frequent presenting symptoms were hearing loss or tinnitus in 41 % ($n = 26$) and a symptomatic neck mass or an incidentally found palpable mass in the neck on physical examination 42 % ($n = 27$). Two (3 %) patients had high blood pressure as their main symptom while three (5 %) patients were studied for HNP due to positive family history. As a presenting symptom seven patients (11 %) had cranial nerve neuropathies. The cranial nerve deficits were mostly associated with JPs ($n = 4$), but also CBTs ($n = 2$) and TPs ($n = 1$) were involved. 27 (36 %) tumours were located at the carotid body bifurcation (CBT), 19 (26 %) at the jugular foramen (JP), 16 (22 %) in the middle ear/tympanic cavity (TP) while 11 (15 %) were vagal paragangliomas (VP). One tumour was located in the dorsal neck.

Genetic testing

During the clinical workup and treatment of the patients included in our series, genetic testing was not routinely used. Testing was performed only on clinical suspicion as judged by the treating physician. Mutations were identified in four patients as presented in Table 3.

Preoperative embolization

Preoperative embolization was utilized in 17 operations with HNPs: 50 % (7/14), 50 % (4/8), 22 % (4/18) and 7 % (1/15) of JPs, VPs, CBTs and TPs, respectively. In addition, one dorsal neck PG was also embolized preoperatively. Embolization was used without complications and

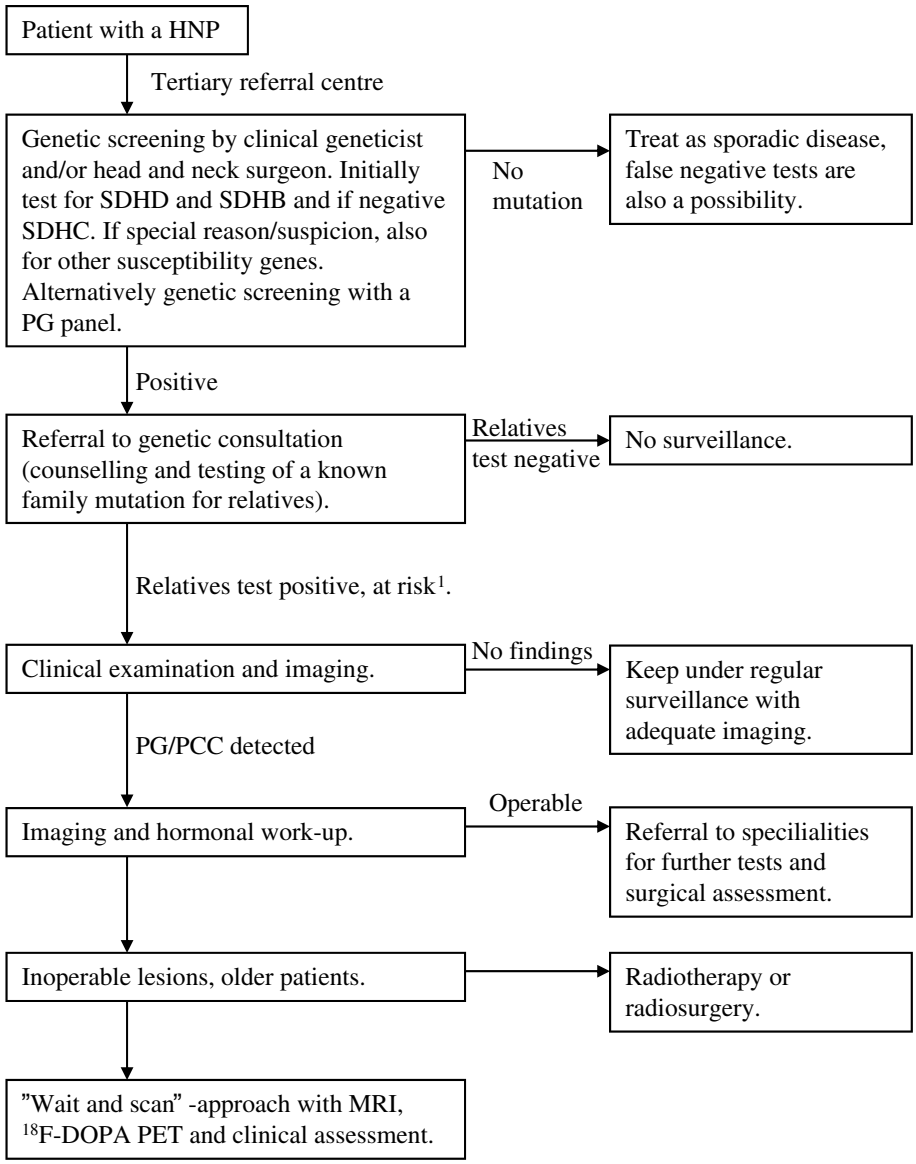

Fig. 1 Proposal for SDHx-related HNP patient's and his/her relatives' medical treatment. *1* If an SDHD mutation is inherited from mother no need for radiological screening, but genetic counselling should be given, because his/hers offspring are at risk. *HNP* head and neck paraganglioma [1, 5, 16, 20, 40–42, 45]

no difference in post-operative cranial nerve injuries was detected between embolized and non-embolized patients.

Primary surgical therapy

Sixty-two patients representing 68 tumours were treated with primary surgery. Two (3.1 %) patients received only radiotherapy for their HNPs. One patient declined surgery, whereas the other patient's tumour was considered inoperable. Patients with multiple HNPs received surgical treatment for selected tumours while some tumours were given radiotherapy or the "wait and scan" approach applied (Table 2). The median diameters for operated HNPs were 30 mm (range 20–70 mm) (CBT), 30 mm (range 13–40 mm) (JP), 7 mm (range 3–12 mm) (TP) and 60 mm (range 25–65 mm) (VP) according to the location of the tumour.

Internal carotid artery and cranial nerves were preserved whenever possible. Two of the 25 operated CBTs needed venous grafts to replace the internal carotid artery. A cranial nerve sacrifice was performed in 11 (17.2 %) operations. Nerve sacrifice was deemed necessary in 75 % of VPs ($n = 6$). In CBTs nerve sacrifice was needed in 11 % ($n = 2$) and in 50 % ($n = 3$) of multifocal HNPs. No cranial nerves were excised in JP or TP operations. However, in one TP operation, a controlled breakage of malleus' handle allowed access to the tumour; this was later repaired.

Follow-up and outcome

Patients were followed without a set guideline. In general, patients had a follow-up appointment at 6 months and 1 year after the operation. The median clinical follow-up

Table 2 Multifocal HNPs listed

Patient/sex	Age	Tumour locations	Malignant disease	Mutation	Hormonal activity	Treatment
7/M	39	CBT	Yes	SDHB	Yes	Surgery
		CBT				Surgery
		JP				Surgery
20/M	21	VP	No	SDHD	No	Radiation
		JP				Surgery
		CBT				Surgery
33/F	37	CBT	No	No	No	Surgery
		CBT				Surgery
		JP				F/U
53/F	38	VP	No	No	No	Surgery
		VP				Surgery
56/M	50	TP	No	No	No	Surgery
		CBT				F/U
		CBT				F/U
60/M	65	CBT	No	No	No	Surgery
		CBT				Surgery

M male, *F* female, *CBT* carotid body tumour, *JP* jugular paraganglioma; *VP* vagal paraganglioma, *TP* tympanic paraganglioma, *No* not tested, *F/U* follow-up

Table 3 Patients with an identified susceptibility gene

Patient	Age	Mutation	Malignant	Multiple	Locations	CA secretion
7/M	39	SDHB	Yes	Yes	Retroperitoneal PG, 2 × CBT and 1 × JP	Yes
44/M	47	SDHB	No	Yes	Abdominal PG and CBT	Yes
20/M	21	SDHD	No	Yes	CBT, JP and VP	No
18/F	24	SDHB	No	Yes	VP and urinary bladder PG	No

SDHx succinate dehydrogenase subunits A-D, *PG* paraganglioma, *CBT* carotid body tumour, *JP* jugular paraganglioma, *VP* vagal paraganglioma, *CA* catecholamine, *No* not tested or not found

time was 4.6 years (range 0–18.8 years). The median follow-up time of patient survival, obtained retrospectively from cause-of-death data, was 11.8 years (range 2.1–22.9 years).

Four (6 %) patients died of the disease. Two of them had malignant tumours and died of tumour progression. Also, one patient suffered a stroke on first post-operative day after surgery. During this procedure, no blood vessel graft was used and the carotid artery was not manipulated, but the internal jugular vein was ligated due to profuse bleeding. One patient developed a fatal myocardial infarction and pulmonary oedema on the third post-operative day. The survival times for patients with malignant HNPs were 15.7–3.6 years. One patient with malignant HNP has survived until the last day of follow-up of 11.9 years. In total 15 patients died during follow-up, 11 of these from causes unrelated to HNPs. The mean overall survival time was 17.8 years and the mean disease-specific survival time 21.3 years. The mean disease-specific survival of malignant cases was 11.5 years, significantly less than the mean disease-specific survival of benign cases at 22.1 years (log-rank test $p < 0.001$). The two patients that received only radiotherapy were alive at the last day of overall survival follow-up, with follow-up times of 6.8–7.8 years.

Secondary surgery and adjunctive radiotherapy

The mean disease-free time of surgically treated patients was 10.8 years (95 % CI 2.8–18.7), excluding patients with multiple HNPs that received primary radiation therapy to at least one tumour.

Altogether, in 13 (20 %) operations residual tumour tissue was left in situ perioperatively. If tumour tissue was found in post-operative radiological imaging within 6 months of the operation it was also considered to be a residual. Residuals were left in 25 % of patients with a VP, 50 % of patients with a JP, in 13 % of patients with a TP, and in 11 % of patients with a CBT. Residuals were followed up with CT and/or MRI scans and surgery and/or radiotherapy arranged if the growth of the residual tumour was detected.

Nine out of 13 residual tumours were treated. This included both of the malignant cases in our series. Two JP patients received surgery while another two (one

Table 4 Post-operational sequelae correlated with the location of the tumour

Location	Any sequelae (%)	Temporary	Long-term sequelae				
		Nerve dysfunction (%)	Hearing deficit (%)	Dysphagia/ hoarseness (%)	Horner's syndrome (%)	Facial nerve paralysis (%)	Multiple[a] (%)
VP	100	13	–	63	13	–	25
JP	86	29	–	13	–	6	21
CBT	67	39	–	17	6	–	6
TP	47	–	27	–	–	–	–
Multifocal	83	–	–	17	–	17	33

VP vagal paraganglioma, *JP* jugular paraganglioma, *CBT* carotid body tumour, *TP* tympanic paraganglioma, *Multifocal* multiple head and neck paragangliomas, *Temporary* under a year, *Long-term* over a year

[a] This group includes patients with several simultaneous long-term sequelae

malignant CBT and one large TP) received both radiotherapy and surgery. Four patients received radiotherapy only for their residual growth. Four patients were only followed up radiologically. One patient with a malignant residual tumour received adjunctive ^{131}Iodine-metaiodobenzylguanidine (^{131}I-MIBG) therapy after the tumour was re-resected.

During follow-up, four patients had a local recurrence (two JPs, one VP, and one TP). Three of these (two JPs and one VP) were given radiotherapy where the patient with a residual TP received secondary surgery.

Short and long-term post-treatment cranial nerve deficits

The short and long-term cranial nerve deficits included vocal cord paralysis, hoarseness, dysphagia, hearing loss, and Horner's syndrome. Many sequelae that were recorded at 6 months had recovered by the 12-month follow-up appointment. Table 4 links the post-operative cranial nerve deficits with the location of the tumour. In case of troubling hoarseness vocal cord medialization was performed, typically after at least a year of conservative management.

Short and long-term post-treatment local complications

Two patients (one JP and one TP) suffered from a post-operative eardrum perforation. Three patients received a tracheostomy at surgery; two of these had multifocal tumours. All patients were decannulated after recovering from the surgery.

Short and long-term post-treatment systemic complications

Aspiration pneumonia, sepsis and meningitis were uncommon in our patient cohort. Two patients had concurrent pneumonia and sepsis; one of these patients also had meningitis secondary to a JP operation.

Discussion

We analysed the management and follow-up data of HNP presenting a diagnostic and therapeutic challenge due to their rarity. Modern imaging (CT and/or MRI), careful clinical examination, and preferably genetic testing are needed before treatment is initiated [28]. Preoperative imaging, genetic tests results and patient's symptoms should all influence the planned treatment. If tumour removal is possible with minimal morbidity, surgery is the optimal choice [29]. For tumours that cannot be optimally resected or where surgical extirpation poses a high risk of severe and/or multiple cranial nerve damage, conventional radiotherapy or stereotactic radiosurgery should be considered [6, 29]. Surgery of HNPs should be discussed and planned preoperatively in a multidisciplinary environment with adequate rehabilitation possibilities to prevent unnecessary patient morbidity. There is a clear need for more organized and prolonged preoperative assessment, including genetic testing, and follow-up of HNP patients.

The sex distribution and median age in the present study were consistent with other studies [18, 19, 30, 31]. In accordance with previous studies, CBTs were the most common HNPs in our study, their percentage (37 %) being slightly lower than in other reports [31, 32]. CBTs were followed by JPs (26 %), TPs (22 %) and VPs (15 %) with the percentage of TPs and VPs showing higher prevalence than in other studies [31, 32]. The incidence rate of 1.8 cases per 1,000,000 per year is similar as previously reported [4]. Overall, our study presents accurate and statistically confirmed data covering important survival endpoints from an area of nearly 2 million inhabitants.

Boedeker et al. [6] suggest using preoperative embolization in patients with JPs, Shamblin class II and III CBTs and VPs with a diameter larger than three centimetres. In a study of 131 CBTs (104 Shamblin class II or III), Power et al. [33] found that preoperative embolization reduces intraoperative blood loss and may simplify the conduct

of the operation, but does not decrease the rate of cranial nerve injuries. Duffis et al. [34] conclude that preoperative embolization is an effective and safe adjuvant to surgical resection when the operator has adequate training, knowledge of anatomy and experience of procedures at hand. In our cohort of patients, embolization was used without complications and no difference in post-operative cranial nerve injuries was detected between embolized and non-embolized patients.

Fifty per cent of the resections on JPs were complete. The large percentage of subtotal resections can be explained by the avoidance of damaging cranial nerves and vasculature in the skull base. The extent of resection is restricted by post-operative sequelae that can be expected as shown in Table 4. In a review article of JPs and VPs by Suárez et al. [23], surgical control was achieved in 85 % of cases (including 14 % with subtotal resection). As highlighted by Suárez et al. [23], the benefits must outweigh the possible morbidity of the operation. A wait-and-scan approach as well as radiotherapy or radiosurgery should be considered for JPs that are subtotally resected or not suitable for surgery, i.e. when complete excision would likely lead to cranial nerve injuries [23]. Suarez et al. [23] suggest that indications for surgery and radiotherapy of JPs and VPs should be more strict and limited to those causing symptoms or being radiologically progressive (volume growth of over 20 % in 1 year). Stereotactic radiosurgery and especially gamma knife radiosurgery should be considered for JPs as these have been shown to dramatically reduce the radiation dose that falls on healthy tissue [35]. Still, even if good short-term control rates have been reported with stereotactic radiosurgery, there are yet no reports on the long-term follow-up data [35]. At our institution stereotactic radiotherapy, but not radiosurgery, is used.

In VP surgery, vagal nerve palsy is often unavoidable resulting in significant morbidity. If a patient has a VP but no cranial nerve deficits, surgery should not be done and instead, "wait and scan" approach is recommended [23]. The results of CBTs in the present study were in agreement with previous studies [36, 37]. CBTs' appropriateness for surgery has also been discussed by Suarez et al. [24] and surgery should be reserved for sporadic or familial unilateral diseases, where excision does not cause extra morbidity. Bilateral CBTs should be managed with a "wait and scan" approach or at least one tumour left intact to avoid bilateral carotid sinus denervation and the risk of baroreflex failure syndrome [38]. Treating one or both tumours with radiotherapy is another possibility [24]. In the present study, TPs were typically treated without complications and the follow-up was brief.

In our study, a malignant HNP was an adverse indicator for survival as two out of three patients with such a tumour died of the disease. There is no consensus on the optimal treatment of malignant HNPs. Mendenhall et al. [29] have suggested primary surgery followed by post-operative radiotherapy (60–70 Gy). However, detecting malignant forms of HNP is challenging, the metastases tend to grow slowly and they may be present at primary presentation or may not develop clinically apparent until decades later. Furthermore, their histology is not conclusive [3, 9]. Currently, the only known predisposing factor for malignancy is an SDHB mutation [3, 16, 39].

Since many residual HNPs and local recurrences appeared during the follow-up, we recommend a longer follow-up for HNP patients. Local recurrences in the present study were detected 2.5–10.8 years after the primary surgery, while our median follow-up time was 4 years. Based on this, even longer follow-up periods are justified. The genetic testing results should also be considered when determining the length of the follow-up and imaging methods. For patients with inherited paraganglioma susceptibility, the follow-up should be lifelong.

In the present study, there was no protocol for genetic screening of patients with HNPs, because genetic testing was not widely available for SDHx mutations in the 1990s. More importantly, generally accepted guidelines regarding whom to send for testing and genetic counselling are needed. Recent studies have suggested that all HNP patients should be screened for at least SDHD and SDHB and, if needed, SDHC mutations [5, 40, 41]. This should be done not only because it will significantly improve the chances of finding patients' at-risk relatives early on, but also because many genetic mutations may otherwise go undetected [5, 40, 41]. Finding a gene mutation is also important for patient follow-up, primary investigation and treatment to be planned correctly. Boedeker et al. [13] recommend a lifelong follow-up of SDHB, SDHC and SDHD mutation carriers with MRI of head and neck, thorax and abdomen and if needed with functional imaging.

CT or MRI scanning is advocated for primary anatomical imaging [20]. When choosing functional imaging for SDHx-related HNPs, ^{18}F-DOPA PET possesses the highest accuracy and is therefore the optimal screening method [1, 20, 40]. ^{18}F-DOPA PET also allows the screening of the whole body, which is particularly useful for patients with an SDHB mutation that predisposes to abdominal and thoracic PGs and PCCs [1, 40]. The golden standard for the best functional imaging of PGs of abdomen and thorax and PCCs has, however, not been decided. If strong suspicion for other PG or PCC arises, imaging should be planned with a nuclear medicine physician [42]. Because tumour size correlates strongly with surgical and post-operative complications, it would be advantageous to diagnose HNPs early on [16, 43]. Some residual tumours might only be detectable by angiography [44].

Based on our findings and the past decades development in the understanding of genetic background of HNPs and developments in functional imaging we suggest, that all HNP patients should be screened for SDHB, SDHD and, if needed, SDHC mutations [5, 13]. If these tests are negative, but a strong clinical suspicion remains then other susceptibility genes should be tested for. We have made a proposal for genetic testing and functional imaging pathway for HNP patients and their relatives. The pathway (Fig. 1) is based on the likelihood of SDHx-related mutations playing a major part in causing inherited and sporadic mutations leading to HNPs.

Conclusions

Surgical treatment of HNPs should be properly planned considering the patient's preoperative state and the expected morbidities following surgery. Patients with multiple HNPs form an especially challenging group where a combination of different treatment options should be considered. A 4-year follow-up of HNP patients is too short for all patients and individual genetic testing results will influence the screening protocol. For all patients with HPGs, family history should be collected and genetic consultation and testing organized, where appropriate. In the near future, if not already, genetic testing panels for patients with PGs, will greatly improve the efficiency of molecular genetic testing, and should be considered for all patients [45]. More follow-up data and studies are still needed regarding the sporadic and hereditary background of local recurrences and new tumours. Based on these results, patients with and without a susceptibility gene mutation need individually designed intervals for imaging and clinical follow-up visits.

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References

1. Martin TP, Irving RM, Maher ER (2007) The genetics of paragangliomas: a review. Clin Otolaryngol 32(1):7–11. doi:10.1111/j.1365-2273.2007.01378.x
2. Lenders JW, Eisenhofer G, Mannelli M, Pacak K (2005) Phaeochromocytoma. Lancet 366(9486):665–675 pii:S0140-6736(05)67139-5
3. Fliedner SM, Lehnert H, Pacak K (2010) Metastatic paraganglioma. Semin Oncol 37(6):627–637. doi:10.1053/j.seminoncol.2010.10.017
4. Baysal BE (2002) Hereditary paraganglioma targets diverse paraganglia. J Med Genet 39(9):617–622. doi:10.1136/jmg.39.9.617
5. Fishbein L, Nathanson KL (2012) Pheochromocytoma and paraganglioma: understanding the complexities of the genetic background. Cancer Genet 205(1–2):1–11. doi:10.1016/j.cancergen.2012.01.009
6. Boedeker CC, Ridder GJ, Schipper J (2005) Paragangliomas of the head and neck: diagnosis and treatment. Fam Cancer 4(1):55–59. doi:10.1007/s10689-004-2154-z
7. Lee JH, Barich F, Karnell LH et al (2002) National Cancer Data Base report on malignant paragangliomas of the head and neck. Cancer 94(3):730–737. doi:10.1002/cncr.10252
8. DeLellis R, Lloyd R, Heitz P (2004) World Health Organization classification of tumours. IARC Press, Lyon
9. Salmenkivi K, Heikkila P, Haglund C, Arola J (2004) Malignancy in pheochromocytomas. Apmis 112(9):551–559. doi:10.1111/j.1600-0463.2004.apm1120901.x
10. Jafri M, Whitworth J, Rattenberry E et al (2013) Evaluation of SDHB, SDHD and VHL gene susceptibility testing in the assessment of individuals with non-syndromic phaeochromocytoma, paraganglioma and head and neck paraganglioma. Clin Endocrinol (Oxf) 78(6):898–906. doi:10.1111/cen.12074
11. Baysal BE, Ferrell RE, Willett-Brozick JE et al (2000) Mutations in SDHD, a mitochondrial complex II gene. Hered Paraganglioma Sci 287(5454):848–851
12. Astuti D, Latif F, Dallol A et al (2001) Gene mutations in the succinate dehydrogenase subunit SDHB cause susceptibility to familial pheochromocytoma and to familial paraganglioma. Am J Hum Genet 69(1):49–54. doi:10.1086/321282
13. Boedeker CC, Hensen EF, Neumann HP et al (2013) Genetics of hereditary head and neck paragangliomas. Head Neck. doi:10.1002/hed.23436
14. Hensen EF, Jordanova ES, van Minderhout IJ et al (2004) somatic loss of maternal chromosome 11 causes parent-of-origin-dependent inheritance in SDHD-linked paraganglioma and phaeochromocytoma families. Oncogene 23(23):4076–4083. doi:10.1038/sj.onc.1207591
15. Kunst HP, Rutten MH, de Monnink JP et al (2011) SDHAF2 (PGL2-SDH5) and hereditary head and neck paraganglioma. Clin Cancer 17(2):247–254. doi:10.1158/1078-0432.CCR-10-0420
16. Myssiorek D, Ferlito A, Silver CE, Rodrigo JP, Baysal BE, Fagan JJ, Suarez C, Rinaldo A (2008) Screening for familial paragangliomas. Oral Oncol 44(6):532–537. doi:10.1016/j.oraloncology.2007.06.010
17. Offergeld C, Brase C, Yaremchuk S et al (2012) Head and neck paragangliomas: clinical and molecular genetic classification. Clinics (Sao.Paulo) 67((Suppl 1)):19–28
18. Kollert M, Minovi AA, Draf W, Bockmuhl U (2006) Cervical paragangliomas-tumor control and long-term functional results after surgery. Skull Base 16(4):185–191. doi:10.1055/s-2006-950386
19. Chino JP, Sampson JH, Tucci DL, Brizel DM, Kirkpatrick JP (2009) Paraganglioma of the head and neck: long-term local control with radiotherapy. Am J Clin Oncol 32(3):304–307. doi:10.1097/COC.0b013e318187dd94
20. King KS, Chen CC, Alexopoulos DK 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. J Clin Endocrinol Metab 96(9):2779–2785. doi:10.1210/jc.2011-0333
21. Shamblin WR, ReMine WH, Sheps SG, Harrison EG Jr (1971) Carotid body tumor (chemodectoma). Clinicopathologic analysis of ninety cases. Am J Surg 122(6):732–739
22. 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(7):1545–1551. doi:10.1002/lary.23268
23. Suarez C, Rodrigo JP, Boedeker CC et al (2013) Jugular and vagal paragangliomas: systematic study of management

with surgery and radiotherapy. Head Neck 35(8):1195–1204. doi:10.1002/hed.22976
24. Suarez C, Rodrigo JP, Mendenhall WM et al (2014) Carotid body paragangliomas: a systematic study on management with surgery and radiotherapy. Eur Arch Otorhinolaryngol 271(1):23–34. doi:10.1007/s00405-013-2384-5
25. Charlson ME, Pompei P, Ales KL, MacKenzie CR (1987) A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis 40(5):373–383
26. U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research (CDER) Center for Biologics Evaluation and Research (CBER) (2007) Guidance for industry: clinical trial endpoints for the approval of cancer drugs and biologics. http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm071590.pdf.3/132013
27. Schemper M, Smith TL (1996) A note on quantifying follow-up in studies of failure time. Control Clin Trials 17(4):343–346
28. Stoeckli SJ, Schuknecht B, Alkadhi H, Fisch U (2002) Evaluation of paragangliomas presenting as a cervical mass on color-coded Doppler sonography. Laryngoscope 112(1):143–146. doi:10.1097/00005537-200201000-00025
29. Mendenhall WM, Amdur RJ, Vaysberg M, Mendenhall CM, Werning JW (2011) Head and neck paragangliomas. Head Neck 33(10):1530–1534. doi:10.1002/hed.21524
30. Parry DM, Li FP, Strong LC, Carney JA, Carney JA, Schottenfeld D, Reimer RR, Grufferman S (1982) Carotid body tumors in humans: genetics and epidemiology. J Natl Cancer Inst 68(4):573–578
31. 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(3):171–176. doi:10.1055/s-0031-1275251
32. Lack EE, Cubilla AL, Woodruff JM (1979) Paragangliomas of the head and neck region: a pathologic study of tumors from 71 patients. Hum Pathol 10(2):191–218
33. Power AH, Bower TC, Kasperbauer J, Link MJ, Oderich G, Cloft H, Young WF Jr, Gloviczki P (2012) Impact of preoperative embolization on outcomes of carotid body tumor resections. J Vasc Surg 56(4):979–989. doi:10.1016/j.jvs.2012.03.037
34. Duffis EJ, Gandhi CD, Prestigiacomo CJ et al (2012) Head, neck, and brain tumor embolization guidelines. J Neurointerv Surg 4(4):251–255. doi:10.1136/neurintsurg-2012-010350
35. Li G, Chang S, Adler JR Jr, Lim M (2007) Irradiation of glomus jugulare tumors: a historical perspective. Neurosurg Focus 23(6):E13. doi:10.3171/FOC-07/12/E13
36. 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 Oncol 41(1):56–61. doi:10.1016/j.oraloncology.2004.06.006
37. Kasper GC, Welling RE, Wladis AR, CaJacob DE, Grisham AD, Tomsick TA, Gluckman JL, Muck PE (2006) A multidisciplinary approach to carotid paragangliomas. Vasc Endovascular Surg 40(6):467–474. doi:10.1177/1538574406290254
38. 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. J Vasc Surg 31(4):806–810. doi:10.1067/mva.2000.103789
39. Burnichon N, Abermil N, Buffet A, Favier J, Gimenez-Roqueplo AP (2012) The genetics of paragangliomas. Eur Ann Otorhinolaryngol Head Neck Dis 129(6):315–318. doi:10.1016/j.anorl.2012.04.007
40. Hermsen MA, Sevilla MA, Llorente JL et al (2010) Relevance of germline mutation screening in both familial and sporadic head and neck paraganglioma for early diagnosis and clinical management. Cell Oncol 32(4):275–283
41. Lima J, Feijao T, Ferreira da Silva A et al (2007) High frequency of germline succinate dehydrogenase mutations in sporadic cervical paragangliomas in northern Spain: mitochondrial succinate dehydrogenase structure–function relationships and clinical–pathological correlations. J Clin Endocrinol Metab 92(12):4853–4864. doi:10.1210/jc.2007-0640
42. Timmers HJ, Taieb D, Pacak K (2012) Current and future anatomical and functional imaging approaches to pheochromocytoma and paraganglioma. Horm Metab Res 44(5):367–372. doi:10.1055/s-0031-1299712
43. Hallett JW Jr, Nora JD, Hollier LH, Cherry KJ Jr, Pairolero PC (1988) Trends in neurovascular complications of surgical management for carotid body and cervical paragangliomas: a fifty-year experience with 153 tumors. J Vasc Surg 7(2):284–291
44. Schick B, Draf W, Kahle G (1998) Jugulotympanic paraganglioma: therapy concepts under development. Laryngorhinootologie 77(8):434–443. doi:10.1055/s-2007-997004
45. Rattenberry E, Vialard L, Yeung A et al (2013) A comprehensive next generation sequencing-based genetic testing strategy to improve diagnosis of inherited pheochromocytoma and paraganglioma. J Clin Endocrinol Metab 98(7):E1248–E1256. doi:10.1210/jc.2013-1319