Paragangliomas and paraganglioma syndromes

Abstract

Paragangliomas are rare tumors of neural crest origin. They are benign in the majority of cases and are characterized by a strong vascularisation.

In the head and neck region they most commonly occur as carotid body tumors. Jugulotympanic and especially vagal paragangliomas are seen less frequently. Complete surgical resection represents the only curative treatment option even though resection of locally advanced tumors regularly results in lesions of the lower cranial nerves and major vessels. Appoximately 30% of all head and neck paragangliomas (HNPs) are hereditary and associated with different tumor syndromes. The paraganglioma syndromes 1, 3 and 4 (PGL 1, 3 and 4) make up the majority of those familial cases. PGL 1 is associated with mutations of the succinate dehydrogenase subunit D (SDHD) gene, PGL 3 is caused by SDHC and PGL 4 by SDHB gene mutations. Multiple HNPs and the occurance of HNPs together with pheochromocytomas are seen in SDHD as well as SDHB mutation carriers. In patients with SDHB mutations the risk for the development of malignant paraganglial tumors is significantly higher compared to SDHC and SDHD patients as well as patients with sporadic tumors. SDHC mutation carriers almost exclusively present with benign HNP that are unifocal in the majority of cases. The role of transmission is autosomal dominant for all three symptoms. Interestingly, there is a "parent-of-origin-dependent-inheritance" in subjects with SDHD gene mutations. This means that the disease phenotype may only become present if the mutation is inherited through the paternal line. We recommend screening for mutations of the genes SDHB, SDHC and SDHD in patients with HNPs. Certain clinical parameters can help to set up the order in which the three genes should be tested.

Keywords: paraganglioma, glomus tumor, pheochromocytoma, paraganglioma syndrome, rare diseases

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1. Introduction

Head and neck paragangliomas (HNPs) represent rare tumors of neural crest origin [1], [2]. They are highly vascular neoplasms that are benign in the majority of cases [1], [2], [3]. They may occur along the paraganglia's pathway of embryologic migration extending from the skull base to the pelvic floor [1], [2], [4], [5], [6]. Paraganglia play an importatnt role in organismic homeostasis by acting as chemoreceptors or by secretion of catecholamines in response to stress [4]. Paraganglial tumors in the thorax and the abdomen are referred to as pheochromocytomas [1], [7], [8].

Terminology

Terminology in science and clinical practice regarding tumors of the paraganglial system is divergent [9], [10], [11]. According to the suggestions of Neumann and coworkers we will use the term pheochromocytoma for all tumors in the thorax and the abdomen whereas the term head and neck paraganglioma (HNP) is only used for tumors in the head and neck region [9]. The vast majority of all pheochromocytomas are endocrinologically active. HNP on the other hand are almost exclusively nonfunctioning [9].

The terms glomus tumor and chemodectoma are often used for HNP [12], [13]. The term glomus tumor is somewhat confusing though, since it may easily be mixed up with a benign tumor of the subcutaneous skin, the so called glomangioma [2], [14], [15]. The term chemodectoma has first been used by Mulligan in 1950 [16]. Strictly speaking it is not correct either, since regarding paraganglia in the head and neck only the carotid body paraganglia act as chemoreceptors [17]. The terms glomus tumor and chemodectoma should therefore not be used any more [17], [18].

Incidence and localisation

HNP are rare neoplasms comprising about 0.03% of all human tumors [2], [6]. The yearly incidence is estimated to be at around 0.001% [2].

The site of origin defines the name given to paragangliomas in the head and neck. The CBT represents the most common tumor type [1], [19], [20], [21]. Other paragangliomas (PGs) that are frequently detected in the head and neck include jugular PGs, tympanic PGs and, although less common vagal PG [2], [22], [23]. PGs in the nose [24], the paranasal sinuses [25], parotid gland [26], cervical sympathic chain [27], [28], larynx [29], [30], [31], thyroid gland [32], parathyroid gland [33], esophagus [34] or the orbit [35] are exceedingly rare.

Function of paraganglia in the head and neck

Paraganglia in the carotid body work as chemoreceptors measuring hypoxia, hypercapnia and ph value in arterial blood. Via the glossopharyngeal nerve they are directly connected to the respiratory centers in the central nervous system. Carotid body paraganglia are involved in regulation of respiration and blood pH value, blood pressure and heart rate [36], [37], [38], [39]. The function of the other head and neck paraganglia remains less clear [40].

Etiology

Many etiologic aspects of HNP development remain unclear [36], [41]. Sporadic CBTs have been demonstrated to be more frequent in people living at high altitudes [42] and in patients with chronic obstructive lung disease [42]. Therefore, a chronic hypoxic stimulation probably plays an important role in the occurance of those unusual neoplasms [36], [42], [43].

Age at diagnosis and sex distribution

HNPs may occur at any age [36], [44]. Most patients become symptomatic between their 30th and their 60th birthday [36], [45]. Concerning sex distribution, there is a clear female predominance by a factor of approximately 3:1 until 4:1 [1], [10], [17], [46], [47], [48], [49].

2. Discussion

2.1 Symptoms

CBTs often remain clinically silent before they present as a painless, slowly enlarging mass in the lateral neck [1], [4], [21], [36], [45], [48]. In later stages of tumor development dysphagia, deficits of the cranial nerves VII, IX, X, XI and XII as well as Horner's syndrome may be seen [4], [48].
Physical examination typically reveals a rubbery, nontender mass in the lateral neck. The lesion is more freely moveable in a horizontal plane than vertically, which is referred to as a positive Fontaine's sign. The finding of a carotid bruit or a pulsatile character of the tumor strenthens the tentative diagnosis of a CBT. A careful examination for deficits of the lower cranial nerves as well as the cervical sympathetic chain is mandatory [4], [48].
Tympanic PGs usually become symptomatic as a pulsatile tinnitus that might be accompanied by a conductive hearing loss. In patients with jugular PGs there may be lower cranial nerve deficits in addition [2], [3], [46], [49], [50]. Tympanic as well as jugular PGs usually present to the otorhinolaryngologist by means of a bluish, pulsating mass behind the ear drum [2].
Vagal PGs most commonly arise from the inferior nodose ganglion but they may occur at any point along the course of the cervical vagal nerve [4]. Therefore, there is a wide variety of possible symptoms ranging from a painless mass in the lateral neck to dysphagia, cranial nerve deficits and Horner´s syndrome [17].
The rate of functioning HNPs is low. About 1-3% of HNPs present with elevated catecholamines and subsequent tachycardia, tremor and hypertension [18], [48], [51], [52]. Secretion of dopamine with resulting hypotension is very infrequently seen in HNP patients [52].

2.2 Diagnosis

2.2.1 Radiology

After taking the patient´s history and a thorough examination of the head and neck region an evaluation by imaging procedures is absolutely necessary to establish the diagnosis of a HNP.
In cervical HNPs, B-mode sonography with color-coded Doppler sonography represents an inexpensive, non-invasive diagnostic tool frequently used as the first imaging step [1], [2], [53], [54]. A CBT will typically present as a solid, well-defined, hypoechoic tumor with a splaying of the carotid bifurcation [1], [54]. The external carotid artery (ECA) is usually displaced anteriorly and medially whereas the internal carotid artery (ICA) is typically displaced posteriorly and laterally [54], [55].
Vagal PGs often displace both the ECA and the ICA anteriorly. The internal jugular vein is typically compressed and displaced posteriorly [55], [56]. In large vagal PGs there may also be a splaying of the carotid bifurcation [56].
In color-coded duplex sonography, cervical HNPs typically present as hypervascular masses. It is important to mention though that the absence of hypervascularity does not exclude a cervical HNP [54].
Magnetic resonance imaging (MRI) today plays the most important role in the pretherapeutic evaluation of HNPs. HNPs typically show a hyperintense signal on T2-weighted images and a distinct contrast enhancement on the T1-weighted images [57]. MRI also presents the exact extension of the tumor and its exact relationship to the carotid vessels. The classification of CBTs is according to criteria set forth by Shamblin [58]. Class I tumors are localized tumors with splaying of the carotid bifurcation but little attachment to the carotid vessels. Class II tumors partially surround the carotid vessels and Shamblin class III CBTs
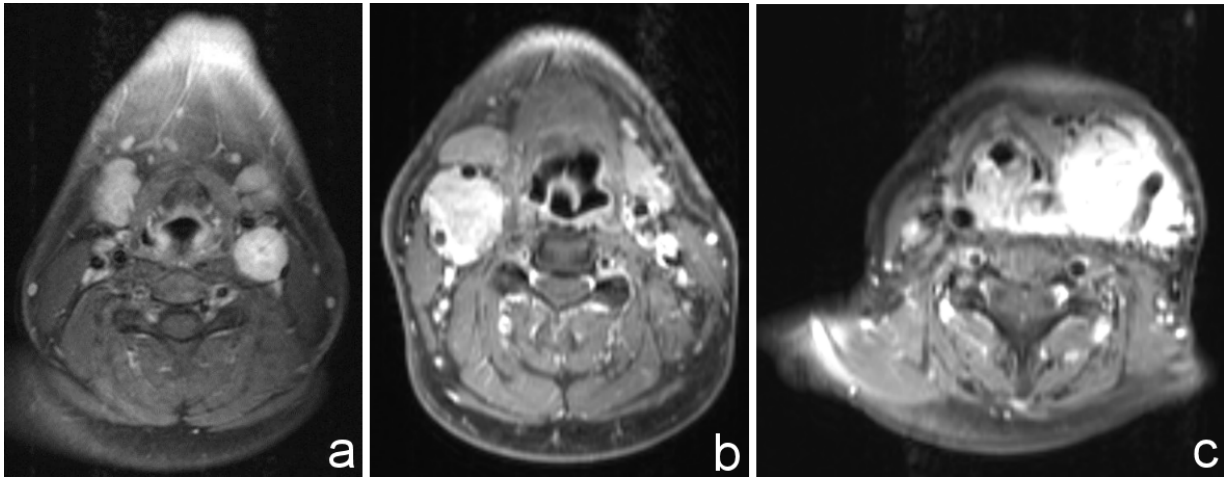
Figure 1a: CBT (class I): The axial T1-weighted MRI with contrast medium shows a CBT in typical location. Splaying of the left carotid bifurcation without any surrounding of the carotid vessels.

Figure 1b: CBT (class II): Axial T1-weighted MRI with contrast showing a right-sided CBT partially surrounding the internal and external carotid artery.

Figure 1c: CBT (class III): A large left-sided CBT intimately surrounding the carotid vessels (axial T1 weighted MRI with contrast).

intimately surround the carotids [58]. Figure 1 demonstrates those three classes of CBTs.
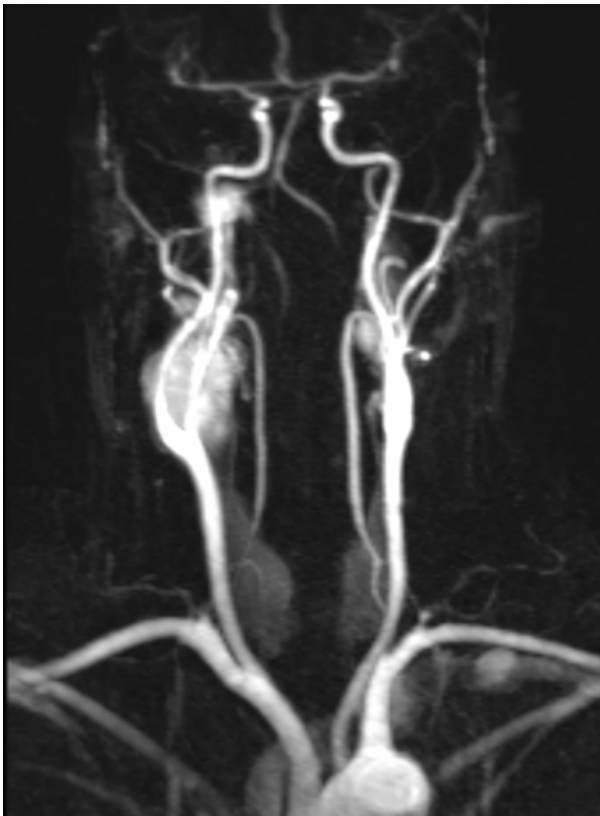

Figure 2: Dynamic contrast-enhanced magnetic resonance angiography (MRA) of a 44 year old male SDHD mutation carrier. Note bilateral CBTs and a jugular paraganglioma on the right in the early arterial phase.

In jugulotympanic HNPs the MRI is helpful to detect dura infiltration and intradural tumor growth. It is also needed to exclude other tumor entities occuring in the area such as neurinomas and endolymphatic sac tumors (ELST) [59]. Today, the MRI will be performed in combination with a dynamic contrast-enhanced magnetic resonance angiography (MRA). The MRA helps to diagnose or rule out additional paragangliomas in the head and neck (Figure 2) [59].

Computed tomography (CT) is needed to evaluate jugulotympanic HNPs. The extend of temporal bone destruction is important to classify those tumors according to the Fisch classification (Table 1) [60]. This preoperative classification is essential, since the surgeon will choose the operative approach depending on tumor stage [59]. Digital substraction angiography (DSA) provides an arterial „map" and identifies the blood supply and flow dynamics of the tumor. It also provides endovascular access for tumor embolisation [1], [2], [3], [48], [54]. As an invasive imaging procedure, DSA is not free of side affects. Today, it should only be performed when there is the need for pre-operative tumor embilisation. In all other cases, an MRA should be performed [59], [61].

2.2.2 Nuclear medicine

The role of metabolic imaging procedures in the diagnosis of HNPs as well as pheochromocytomas has greatly increased within the last 10 years [13], [57], [62], [63], [64], [65].

The 123I-Metaiodobenzylguanidin-szintigraphy (MIBG szintigraphy) has often been used as a metabolic imaging tool in the diagnosis of neuroendocrine tumors [62], [63], [64]. The tracer needed, [123I]MIBG, is readily availeable in all nuclear medicine centers in Germany. MIBG szintigraphy also has some clear disadvantages though. The images are made two and 24 hours after intraveneous application of the tracer which means that patients do have to come in twice. The tracer also interferes with many common drugs such as heart medication, blood pressure medication and antidepressants. Moreover, [123I]MIBG is often accumulated in the salivary glands

Table 1: Classification of jugulotympanic paragangliomas according to Fisch & Mattox [60]

class	location and extension of tumor
A	tumors that arise along the tympanic plexus on promontory
B	tumors with invasion of hypotympanon; cortical bone over jugular bulb intact
C_1	tumors with arrosion of carotid foramen
C_2	tumors with destruction of carotid canal
C_3	tumors with invasion of carotid canal; foramen lacerum intact
C_4	tumors with invasion of foramen lacerum and cavernous sinus
$De_{1/2}$	tumors with intracranial but extradural extension; $De_{1/2}$ according to displacement of dura (De_1 = less than 2 cm, De_2 = more than 2 cm)
$Di_{1/2/3}$	tumors with intracranial and intraduraler extension; $Di_{1/2/3}$ according to depth of invasion into posterior cranial fossa (Di_1 = less than 2 cm, Di_2 = between 2 and 4 cm, Di_3 = more than 4 cm)

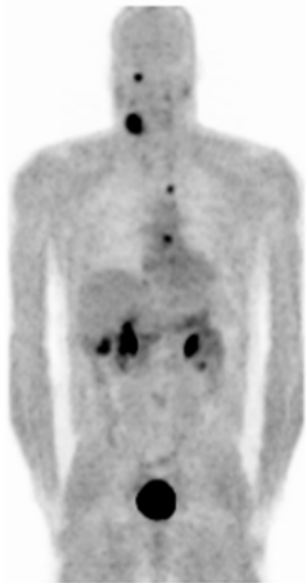which complicates proper diagnosis [57]. In addition, sensitivity is not very high [57].

Figure 3: ^{18}F-DOPA-PET presenting a right CBT, a right jugular paraganglioma, a remnant of a left CBT as well as pheochromocytomas in the left atrium and in projection to the aortic arch. This 41 year old male SDHD patient had already undergone surgery for bilateral abdominal pheochromocytomas. Physiologic tracer uptake is seen in the gallbladder, the renal pelvis and the urinary bladder.

At the University of Freiburg Medical Center the 18F-Fluorodihydroxyphenylalanin positron emission tomography (18F-DOPA-PET) has been used for more than ten years in the diagnosis of paraganglial tumors. Hoegerle et al. could demonstrate as early as 2002 that the 18F-DOPA-PET is an excellent tool for the detection of pheochromocytomas which is superior to MIBG szintigraphy [13]. The following year, the same could be shown for HNPs [57]. 18F-DOPA-PET is capable to detect even very small paraganglial tumors and metastatic disease. The tracer is not accumulated in the head and neck. With a single procedure, paraganglial tumors in the head and neck, the thorax as well as the abdomen may be detected (Figure 3). On the downhand side, the tracer is only available at selected nuclear medicine centers [57].

Other nuclear medicine procedures frequently used for the diagnosis of paraganglial tumors include 18F-fluoro-dopamin-PET (18F-FDA-PET), 18F-fluoro-2-deoxy-D-glucose-PET (18F-FDG-PET) [64] and the 68Ga-DOTA-D-Phe1-Tyr3-octreotate-PET (68Ga-DOTATATE-PET) (Figure 4) [66], [67].

The PET examinations mentioned are often combined with a CT scan. Those fusions between PET and CT (Figure 5) lead to an increased specifity and sensitifity [65]. Luster et al. recently examined 25 paraganglioma and pheochromocytoma patients with 18F-DOPA-PET/CT fusions. Sensitivity in this study was 100%, specifity was 88% with a positive predictive value of 100% and a negative predictive value of 88% [65].

Figure 4: ^{68}Ga-DOTATATE-PET with multiple bone metastases in the spine, the rips and at the skull base (marked by arrows). Physiologic tracer uptake in the liver, the kidneys, the adrenals, the stomach, pancreas, spleen and the small bowel. This 41 year old female SDHB mutation carrier had first undergone resection of a malignant carotid body tumor with regional lymph node metastases seven years earlier.

Figure 5: Frontal fusion between computed tomography and PET affirms the spinal metastasis in the SDHB mutation carrier from Figure 4.

2.2.3 Histopathology and immunhistochemistry:

HNPs as well as pheochromocytomas are basically composed of two cell types: chief cells and sustentacular cells [6], [68], [69], [70], [71]. The histological aspect of the tumor is the typical „Zellballen" pattern where nests or cords of chief cells are surrounded by sustentacular cells (Figure 6). Paraganglial tumors derive from the chief cells and are benign neoplasms in the majority of cases [4], [20], [72], [73]. Overall less than 10% of HNPs are cited to be malignant [1], [3], [6], [48]. Interestingly, there are no histopathological or immunohistochemical criteria for the diagnosis of a malignant paraganglial tumor. Therefore, a malignant HNP or pheochromocytoma may only be diagnosed when there is metastasis to non neuroendocrine tissue [1], [3], [4], [6], [18], [48]. In HNPs, metastases are most frequently found in cervical lymph nodes. Distant metastases are most common in bone, liver and lung [44], [74], [75], [76], [77], [78], [79].
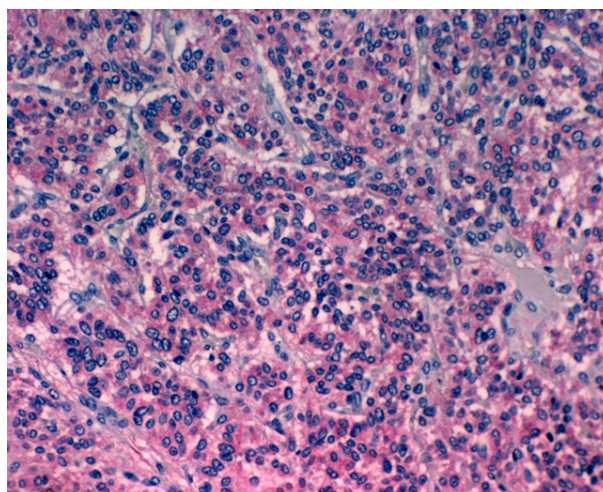

Figure 6: The hematoxiline-eosine staining reveals chief cells in a classical "Zellballen" pattern surrounded by ectatic blood vessels and sustentacular cells (original magnification x100).

Immunohistochemically, chief cells express neuroendocrine markers such as CD56, synaptophsin, chromogranin (Figure 7), and neuron specific enolase (Figure 8) [68], [69], [74], [80]. Sustentacular cells are positive for the S-100 protein (Figure 9) [68], [69], [74], [81].
Whether fine needle aspiration biopsy (FNA) should be used as a means of confirming a clinical diagnosis of HNP is controversial. Monatabi and coworkers report on their results regarding FNA in 13 patients with CBT [82]. The authors state that the correct diagnosis of a CBT with FNA is „extremely difficult". Nevertheless they regard FNA as an important tool for the pre-therapeutic diagnosis of HNPs. On the other hand, aspirates from CBTs have been mistaken for many different neoplasms including neurofibroma, neurofibrosarcoma, malignant melanoma, different forms of thyroid cancer as well as metastases from a carcinoma [68]. In addition to the questionable diagnostic value of a FNA in HNPs one has to consider potential side effects such as heavy bleeding [68].

We think, that FNA does not deserve any role in pre-operative diagnosis of HNPs. It is a potentially dangerous examination with a very low sensitivity and specifity.
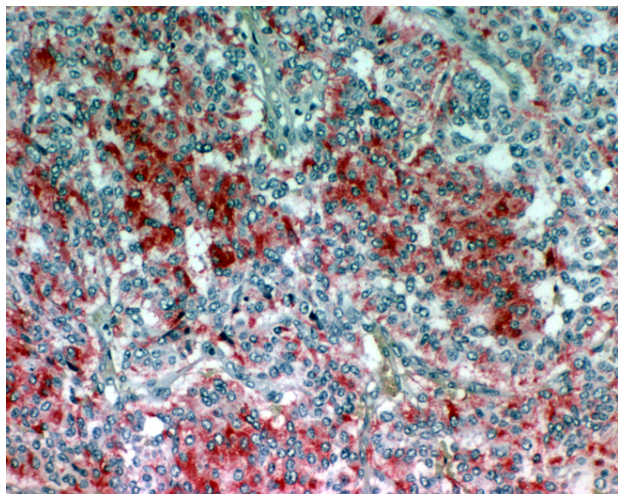

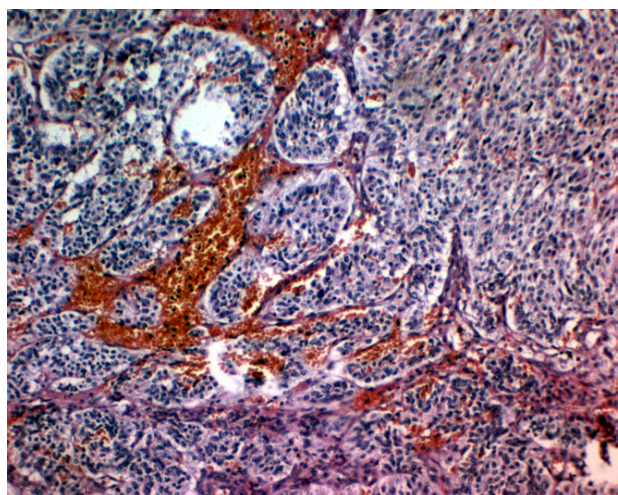**Figure 7: On immunhistochemistry the chief cells are positive for chromogranin (original magnification x200).**

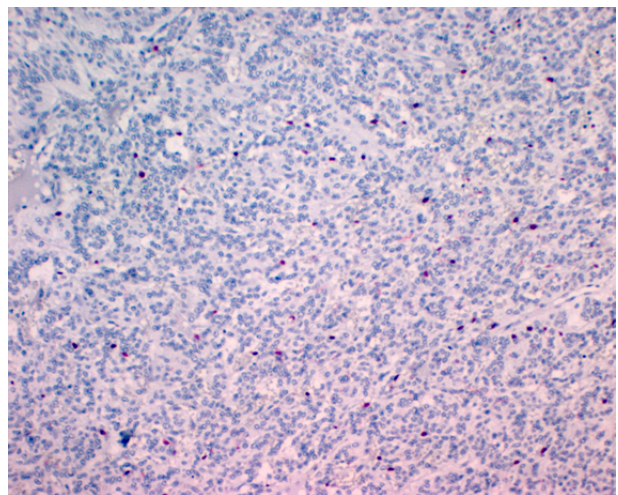**Figure 8: Positive staining of the chief cells for NSE (original magnification x100).**

Figure 9: S-100 positive sustentacular cells surrounding the chief cells (original magnification x100).

2.3 Differential diagnosis

Cervical HNPs often become symptomatic by means of a painless, slowly enlarging lateral neck mass [1], [4], [21], [36], [45], [48]. The differential diagnosis of a non-tender lateral neck mass includes lymphadenopathies, branchial cleft cysts, salivary gland tumors, neurogenic tumors, aneurysms of the carotid artery as well as HNPs [36], [45]. Differentiation between a HNP and the other masses mentioned can usually easily be made by means of the radiologic as well as functional imaging modalities mentioned above.

Jugulotympanic HNPs often present with pulsatile tinnitus [2], [3], [46], [49], [50]. Gehrking et al. reviewed possible causes of pulse synchronous tinnitus [50]. Jahnke and Klingbeil reported on a patient with pulsatile tinnitus caused by an intratympanic encephalocele [83]. Schikschneit and coworkers added an amputation neuroma of the middle ear as another unusual cause for pulsatile tinnitus [84].

Table 2 features possible causes for the symptom „pulsatile tinnitus".

Differentiation between a jugulotympanic PG and the other causes mentioned can be obtained by a thorough examination of the ear in combination with the radiologic examinations above.

2.4 Therapy

The management of HNPs remains controversial [1], [3], [4], [37], [48], [85], [86], [87]. The current treatment options include surgical resection [1], [2], [3], [19], [48], [59], [88], [89], conventional radiation therapy [47], [90], [91], [92], stereotactic radiosurgery (for jugulotympanic PGs only) [85], [86], [93], permanent embolisation [20], [37] and a combination of those modalities.

Due to the fact that HNPs are usually slow-growing tumors it may be appropriate under certain circumstances to withhold any kind of invasive therapy and to observe tumor growth with serial MRI studies („wait and scan") [1], [2], [3], [45].

The tentative diagnosis of a HNP has to be made pre-operatively in any case, so that the surgeon does not face the tumor unprepared. Matthews wrote all the way back in the year 1915: "...this rare tumor presents with unusual difficulties to the surgeon, and should one encounter it without having suspected the diagnosis, the experience will not soon be forgotten" [94].

2.4.1 Therapy of cervical paragangliomas

Therapeutic options for the treatment of cervical HNPs include complete surgical resection [1], [2], [3], [4], [19], [48], [88], [95], conventional radiotherapy [47], [90], [91], [92] and permanent embolisation [20], [37]. Due to generally slow tumor growth, a "wait and scan" policy might be justified in certain cases [1], [2], [3], [45].

In every case, benefits and potential risks of all the treatment options mentioned have to be taken into con-

Table 2: Differential diagnosis of pulsatile tinnitus (modified according to Gehrking [50])

general	hypervascular/ hyperamic	arterial	venous
hyperthyroidism anemia pregnancy cardiac murmur	Acute otitis media otosklerosis Paget's disease cholesteatoma tympanic PG jugular PG hemangioma amputation neuroma	stenosis of ICA fibromuscular dysplasia of A. vertebralis arterio-venous fistulas aneurysms arterial ectasias aberrant ICA persistant A. stapedia persistant A. trigeminalis	anomalies of jugular bulb varikous Vv. emissariae BIH intracranial tumor hydrocephalus

ICA: internal carotid artery; A.: arteria; Vv.: venae; BIH: benigne intracranial hypertension;

sideration for every individual patient. Factors that play an important role in the search for optimal therapy include size, classification and exact localisation of the tumor(s), age and general health of the patient as well as pre-therapeutic cranial nerve deficits [1], [3], [48].

Surgical resection

Complete surgical resection represents the only curative treatment option for HNPs [1], [4], [19], [49], [88]. The first successful resection of a CBT dates back to 1889 (cited in [36]). Before the development of vascular surgical reconstructive techniques in the 1960s and 1970s the results of sugical resection were miserable [37]. Mortality rates of 5-30 % have been reported in those days (cited in [37]). Today, complete surgical resection of cervical HNPs is considered the treatment of choice for the vast majority of patients by most authors around the world [1], [2], [3], [4], [19], [48], [56], [88], [89], [95], [96], [97], [98].

The resection of CBTs is performed via a transcervical approach [36], [59], [95], [98]. Special care is taken to avoid injury to the cranial nerves. Proximal and distal control of the large vessels is then optained [36], [59]. Especially in Shamblin class III tumors, there might be injury to the common or internal carotid artery. Therefore the surgeon should be familiar with the use of intraluminal vascular shunts as well as vascular reconstructive techniques [59].

When we resect a cervical HNP, we also perform a selective neck dissection in the regions IIA, IIB and III [99] to exclude or varify lymph node metastases [1], [59].

Cure rates after complete surgical resection of CBTs are generally reported to be as high as 89-100% [1], [19], [47], [88], [95]. The major morbidity associated with surgery is related to post-operative cranial nerve dysfunction [1], [3], [17], [48], [100]. Patetsios et al. described their experiences with the resection of CBTs. Permanent post-operative cranial nerve deficits were seen in five out of 29 patients (17.2%) [48]. Wang and coworkers detected cranial nerve deficits in seven out of 29 patients (24.1%) after tumor resection [36]. Anand and coworkers reviewed the post-surgical results of 1181 patients with CBTs. Permanent cranial nerve deficits were seen in 21.8% of patients [100].

In patients with vagal PG, the affected vagal nerve usually has to be sacrificed during surgery [3], [19].

Primary radiation

The aim of conventional radiotherapy in HNPs is to achieve long term tumor control. One has to keep in mind that radiotherapy of HNPs is not a curative treatment option [47], [49].

Histopathologic studies could demonstrate that radiation therapy does not have any effect on the chief cells but leads to structural changes of the vascular connective tissue [19], [48], [91].

Radiation of cervical HNPs is reported to achieve long term tumor control in up to 96% of cases [47]. The dose commonly recommended is 45 to 56 Gy. When doses of less than 40 Gy are applied, failure rates have been shown to be as high as 22% [101].

Permanent cranial nerve deficits seem to be less common after radiation therapy of cervical HNPs when compared to surgical resection [3], [47], [86]. Nevertheless, the potential risk for radiation induced malignancies has to be taken into serious account not only in young patients [86], [102]. This potential risk has been estimated to be as high as 3-5% [102].

In our opinion, radiation therapy of cervical HNPs should be considered as a treatment option when a tumor is clearly not resectable without reasonable risk, when the

patient is in poor health or does not want any surgical procedure or in the setting of multiple HNPs [1], [3].

Alternative therapeutic options

Due to slow tumor growth, a "wait and scan" policy may be an option in selected cases [1], [3], [45], [59]. Tumor doubling time has been estimated to be between 4.2 and 13.8 years for HNPs [3], [86].

Persky and coworkers suggest a "wait and scan" policy in old patients with multiple medical problems [3]. Westerband et al. report on an asymptomatic 77 year old patient with a small CBT (diameter of 0.9 x 0.5 cm). Due to the very small size, the authors decided to follow up the patient in yearly intervals.

A so called permanent embolisation may have the potential to slow down tumor growth for a short period of time [20], [37]. In our opinion, this option should only be considered in a clearly palliative setting.

2.4.2 Therapy of jugulotympanic paragangliomas

The different treatment options have been a matter of discussion in international medical literature when it comes to treatment of jugulotympanic PGs. The current treatment options include surgical resection [2], [19], [46], [59], [103], [104], [105], [106], [107], conventional radiation therapy [47], [90], [91], [92], stereotactic radiosurgery [85], [86], [93], permanent embolisation [20], [37] and a "wait and scan" policy [3], [59].

As in patients with cervical HNPs, benefits and potential risks of all the treatment options mentioned have to be taken into account for every individual patient. Factors that play an important role in the search for optimal therapy include size, classification and exact localisation of the tumor(s), age and general health of the patient and, especially in patients with jugular PGs, pre-therapeutic cranial nerve deficits [1], [3], [48].

Surgical resection

The first (partial) resection of a jugular paraganglioma was described by Rosenwasser in 1945 [cited in 49]. Until the development of microsurgical techniques, new approaches to the skull base as well as modern interventional neuroradiology is was not possible to completely resect jugular PGs [49]. Potentially life-threatening vascular complications were frequently seen, the rate of post-operative cranial nerve deficits was extremely high and, due to incomplete resection, patients faced recurrent tumor growth in the vast majority of cases [49].

Today local tumor control is achieved even in extensive jugular PGs in 80-90% in most surgical series [3], [17], [108], [109], [110], [111].

Compared to all other treatment options, surgical resection bears two major advantages. First of all, it is the only curative treatment option [1], [3], [59]. In addition, it is the only way to obtain material for histopathologic examination, since taking an open biopsy as well as FNA is obsolete in those neoplasms [59].

For patients with tympanic PGs (Fisch class A and B) complete surgical resection clearly represents the therapy of choice whenever there are no contraindications against a general anesthesia [3], [17], [46], [49], [59], [112]. Those tumors become symptomatic by means of pulsatile tinnitus and conductive hearing loss at an early stage in the majority of cases. Complete surgical resection can be optained in almost every case with a low risk for damaging of the lower cranial nerves [46], [49], [59], [112]. Schick and coworkers report on their results in surgical resection of tympanic PGs [49]. Ten tympanic PGs were resected in that study. There were no post-operative cranial nerve deficits and the rate of tumor recurrance was 0% [49]. Gstoettner et al. did not detect any cranial nerve deficits after resection of six class B tympanic PGs [46].

When it comes to optimal treatment of jugular PGs the discussion in international medical literature is much more controversial [3], [4], [47], [49], [90]. Fisch class C and D jugular PGs are resected via an infratemporal approach in the majority of cases. In classes C1, C2 und De,i1/2 the juxtacondylar approach represents an alternative. An intra-operative neuromonitoring of the cranial nerves VII, IX, X, XI and XII has been shown to be of benefit in patients with class C and D jugular PGs [59]. When it comes to class Di3 tumors, the attempt of a surgical resection does not make any sense. Those patients should be send for palliative radiation therapy [59].

The downside of surgical resection of jugular PGs is the large percentage of post-operative cranial nerve deficits. As jugular PGs are intimately involved with the lower cranial nerves, patients frequently suffer from post-operative facial palsy as well as voice, swallowing, articulation and shoulder weakness problems [3], [19], [49], [108], [109], [110].

Persky et al. detected post-operative cranial nerve deficits in 10 out of 14 patients with jugular PGs (71.4%) [3]. Schick et al. described new cranial nerve deficits after resection of 32 class C and D jugular PGs as often as: N. VII in 37.9%, N. IX in 31%, N. X in 45.8%, N. XI in 7.1% and N. XII in 36% of cases [49]. Additional surgical procedures such as vocal cord medialization and others were required in 15 out of 32 patients in this study (46.9%) [49].

Due to the fact that older patients find it more difficult to cope with post-operative cranial nerve deficits, Glasscock and coworkers suggested a maximum age of 60 years for the surgical resection of jugular PGs [113]. In our opinion though, the age of a patient alone should not be the only reason whether surgical resection should be suggested to the patient or not.

Primary radiation

One advantage of conventional radiation therapy has been said to avoid the morbidity of surgery while offering a high probability of local tumor control [47], [90], [91],

[92]. Powell and coworkers achieved a local tumor control rate of 90% after radiation of 46 patients with jugulotympanic PGs. Median follow-up in this study was nine years [92]. Chino et al. reported on long-term follow-up in a group of 31 patients with jugulotympanic PGs. Local control rates 5 years, 10 years and 15 years after surgery where 96%, 90% and 90% respectively [114]. Boyle even reported a tumor control rate of 100%. Unfortunately, there are only nine patients in this study and follow-up time was very heterogenous, ranging from one to 12 years [90].

Lower cranial nerve deficits after radiation therapy do occur less frequently after radiation compared to surgery [3], [47], [86]. In the study by Powell et al. a facial nerve palsy was detected in 2/46 patients (4.7%) after radiation of a jugulotympanic PG [92]. In a group of 53 patients reported by Hinerman and coworkers, there was a facial palsy in just one patient (1.9%) [47].

Nevertheless, a number of serious complications have been reported after radiation of jugular PGs including temporal bone osteomyelitis, necrosis of the temporal lobe as well as insufficiency of the pituitary gland [47], [49], [86]. More frequently seen but less dramatic side affects of temporal bone radiation include chronic otitis media, chronic stenosis of the external ear canal as well as chronic problems in the maxillary joint. Those kind of „minor" complications were seen in 5/53 patients (9.4%) reported by Hinerman [47].

In addition to the fact that radiation therapy of jugulotympanic PGs represents no curative but only a palliative treatment option, the potential risk for radiation induced malignancies has to be taken into serious account not only in young patients [86], [102].

In addition, surgical resection is more difficult in cases where local tumor control is not achieved by radiation therapy [49].

Stereotactic radiosurgery

Stereotactic radiosurgery („gamma knife") represents a rather new treatment option for patients with jugulotympanic PGs [85], [86], [93]. In contrast to conventional radiotherapy, the whole radiation dose of 12-18 Gy may be applied within a single day [85]. Foote et al. report on their experiences with stereotactic radiosurgery in the treatment of 25 patients with jugulotympanic PGs [86]. During a median follow-up time of 37 months the authors did not detect any tumor growth in those patients. Additionally, there were no cranial nerve deficits due to therapy. Feigenberg and coworkers on the other hand report on two out of five patients that presented with growing jugulotympanic paragangliomas after stereotactic radiosurgery [85]. One patient in that study also developed a deficit of the trigeminal nerve.

Concerning stereotactic radiosurgery, we agree with Hinerman that larger studies with a longer follow up are needed to judge the oppertunities of this treatment option in the therapy of jugulotympanic paragangliomas [93].

Alternative therapeutic options

As in patients with cervical PGs, tumor growth is also slow in the majority of jugulotympanic PGs [49], [59]. There are reports of patients in the literature that survived without any kind of treatment for more than 40 years [115].

A „wait and scan" policy is always to be considered in elderly patients with underlying medical conditions or very small tumors as well as in patients with small recurrent tumors after therapy [59].

A permanent embolisation only has a palliative character [20], [37].

In the last few years, there have been promising results of heavy ion therapy in the treatment of benign and malignant neoplasms of the skull base [116], [117], [118]. Heavy ion therapy is a treatment option that may play a future role in patients with recurrent and extensive jugular PGs.

2.4.3 Recommendations for therapy

Our therapy recommendations for patients with HNPs are listed in Table 3.

In our opinion, the majority of patients with HNPs should undergo complete tumor resection. One has to keep in mind, that complete resection represent the only curative treatment option for those unusual neuroendocrine neoplasms.

The recommendations in Table 3 are only valid for patients that may be operated in general anesthesia without any major risks. Especially in large vagal PGs, class III CBTs as well as class C and D jugular PGs a number of additional factors have to be considered when therapy is planned on an individual basis for every patient. Those factors include the age and general health of the patient, size, class and localisation of the tumor(s) as well as preoperative cranial nerve deficits.

2.4.4 Therapy of multifocal paragangliomas

Patients with multifocal HNPs represent a special challenge [1], [18], [20], [59], [119], [120]. A one step surgery in subjects with bilateral HNPs is usually obsolete since it is bearing the risk of bilateral cranial nerve palsies resulting in severe disabilities [1], [18], [20], [59], [119], [120]. Velegrakis et al. recommend to always resect the largest tumor first. The remaining HNP(s) can be observed or, if needed, treated by radiation therapy or permanent embolisation [119]. Sobol and coworkers think that a one step surgical procedure may be an option in patients with multiple unilateral HNPs. They report on a 27 year old patient with a CBT and a vagal PG on the right side. During the resection of the vagal PG, the vagal nerve had to be sacrificed. The class I ipsilateral CBT could be resected without problems during the same surgery [18].

Based on our experiences in the treatment of multifocal HNPs we recommend to resect the largest tumor first whenever possible [20], [59], [120]. Depending on the

Table 3: Recommendations for therapy of head and neck paragangliomas

location of tumor and class	therapy	approach	neuro-monitoring
CBT class I	resection	transcervical	no
CBT class II	resection	transcervical	no
CBT class III	resection	transcervical	Nn. X, XII
vagal PG	resection	depending on localisation and extend	depending on localisation and extend
tympanic PG (class A)	resection	transtympanic	no
tympanic PG (class B)	resection	modified mastoidectomy alternative: juxtakondylar	optional N. VII
jugular PG (class C)	resection	infratemporal juxtacondylär (class $C_{1/2}$)	Nn. VII, IX, X, XI, XII
jugular PG (class Di/e $_{1/2}$)	resection	infratemporal transcranial juxtakondylär	Nn. VII, IX, X, XI, XII
jugular PG (class Di$_3$)	radiation	does not apply	does not apply

CBT: Carotid body tumor; PG: paraganglioma; N.: nervus; Nn.: nervi

post-operative cranial nerve status, therapy of the remaining tumor(s) may be individually planned. In the case of a 45 year old patient with bilateral jugular PGs, we could completely resect both tumors without the occurance of cranial nerve deficits within one year [120]. The same was true for a 34 year old patient with bilateral CBTs [1]. A 38 year old patient presented with a palsy of the vagal and hypoglossal nerve after resection of a class III CBT. The two remaining contralateral HNPs therefore underwent radiation therapy [20].

Patients with bilateral vagal PGs are somewhat of a special issue. Since it is usually not possible to resect those tumors without sacrificing the vagal nerve, we suggest resection of the larger tumor followed be radiation of the remaining paraganglioma.

2.4.5 Follow-up

No matter what kind of therapy has been applied, patients with HNPs need long time follow-up. Forrest et al. recommend yearly intervals within the first five years after therapy. Thereafter intervals may be stretched to three to five years [112]. At our department, patients are seen every six months during the first five years. After that, patients come in once a year. All patients undergo a thorough examination of the head and neck during those follow-ups. In patients with cervical HNPs be perform a bilateral B-mode sonography with color-coded duplex sonography. Whenever needed, an MRA is performed in addition. Patients with jugulotympanic HNPs undergo an MRI and an MRA.

Especially patients with jugular PGs need life long follow-up. Recurrent tumors have been seen in those patients decades after initial treatment.

2.5 Preoperative embolisation

The primary goals of pre-operative embolisation of HNPs are to reduce blood loss in the surgical field, minimize the risk of intraoperative complications, prevent recurrence by contributing to complete resection as well as minimizing the need for blood transfusions [4], [37], [121].

Since embolisation is an invasive and potentially dangerous procedure, the risk of potential complications from embolisation always have to be weighed against the advantages. An experienced vascular neuroradiology team has to be absolutely familiar with the complexities and possible variations in head and neck vascular anatomy. At the Department of Neuroradiology of Freiburg Medical School different polyvinyl alcohol (PVA) particles with

diameters between 50 and 600 µm are routinely used for embolisation of HNPs. Occasionally, coils may be useful in addition. Proper timing of pre-operative embolisation is needed. In our opinion, embolisation should be performed between two and four days before surgery [1], [4].

Possible minor side effects of embolisation include fever as well as local pain and hematomas in the groin. Severe side effects include skin necrosis, blindness, cranial nerve deficits and a large number of neurological deficits including unilateral palsy and death [3], [20], [36], [122], [123], [124]. Miller et al. did not observe any neurological deficits after embolisation of five vagal PGs [17]. The same was true for a group of six HNP patients reported by Frühwirt and coworkers [37]. Persky and coworkers report on 47 patients with 53 HNPs. All tumors in that study underwent pre-operative embolisation. Complications were seen in six patients (12.8%). Those complications included two vagal verve palsies, one jugular foramen syndrome, one facial nerve palsy, one temporary unilateral palsy and one asymptomatic dissection of the vertebral artery [3].

Pre-operative embolisation of cervical paragangliomas

The embolisation of a CBT was first described by Schick in 1980 [125]. The arterial supply of CBTs and vagal PGs typically derives from the external carotid artery. Branches from the ascending pharyngeal artery, the posterior auricular artery as well as the occipital artery usually form the main arterial feeding vessels [37]. It is of great importance to be aware that there may be a great variety of blood supply in cervical HNPs though [3]. The question, whether cervical HNPs should be routinely embolised is a matter of controversial discussion [1], [4], [36], [37], [48], [87], [126], [127]. Many authors are in favor of embolisation of CBTs and vagal PGs [1], [4], [36], [37], [59], [126], [127]. Miller et al. report on a group of 19 patients with vagal PGs. 16 of those tumors were resected and five tumors underwent embolisation before resection. In those five patients intra-operative blood loss was much smaller and time in the operating theatre was shorter. There was also a smaller incidence of post-operative cranial nerve deficits in this group of patients [17]. Wang et al compared a group of 17 CBTs that underwent embolisation with a group of 12 CBTs that were not embolised. The intra-operative blood loss was significantly smaller in the group of CBTs that had undergone embolisation [36]. Based on own experiences with pre-operative embolisation of 28 CBTs, Persky and coworkers also strongly recommend this approach [3].

Pre-operative embolisation of jugulotympanic paragangliomas

The first embolisation of a jugular PG was described by Hekster in 1973 [128]. The arterial tumor supply in jugulotympanic PGs depends on the tumor stage. Class A tympanic PGs are usually supplied via the inferior tympan-

ic artery. Class B tympanic PGs usually get their blood supply via branches of the ascending pharyngeal artery. In class C jugular PGs the main blood supply is via the ascending pharyngeal artery as well as the maxillary, occipital and temporal arteries. Class D jugular PGs usually have a very individual blood supply [59]. It is of great importance to be aware that there may be a great variety of blood supply in patients with jugulotympanic HNPs though.

The pre-operative angiographic embolisation represents the international gold standard in treatment of class C and D jugular PGs [3], [46], [49], [59], [129], [121]. Without embolisation, it would not be possible to completely resect those tumors in the vast majority of cases [46].

Recommendations for pre-operative embolisation of paragangliomas

Our recommendations regarding embolisation of HNPs are summarized in Table 4.

Table 4: Recommendations regarding preoperative embolisation

location of tumor and class	embolisation
CBT (Shamblin class I)	optional
CBT (Shamblin class II)	optional
CBT (Shamblin class III)	yes
vagal PG	optional
tympanic PG (class A)	no
tympanic PG (class B)	optional
jugular PG (class C)	yes
jugular PG (class D)	yes

CBT: carotid body tumor; PG: paraganglioma

In class I and II CBTs a pre-operative embolisation is not mandatory. Those patients should be clearly informed about potential benefits and risks of embolisation. We strongly do recommend embolisation in Shamblin class III tumors though.

For vagal paragangliomas the question concerning the need for embolisation may only be answered on an individual basis.

Class A tympanic PGs must not be embolised whereas embolisation may be useful in selected cases of class B tympanic paragangliomas.

Class C and D jugular paragangliomas on the other hand must undergo pre-operative embolisation whenever surgical resection is performed.

2.6 Malignant paragangliomas

Interestingly, there are no histopathological or immuno-histochemical criteria for the diagnosis of a malignant paraganglial tumor. Therefore, a malignant HNP or pheochromocytoma may only be diagnosed when there is metastasis to non neuroendocrine tissue [1], [3], [4], [6], [18], [48]. In HNPs, metastases are most frequently found in cervical lymph nodes. Distant metastases are most common in bone, liver and lung [44], [74], [75], [76], [77], [78], [79].

Overall, less than 10% of all HNPs have been cited to be malignant [1], [3], [6], [48]. Malignancy seems to be most common in vagal PGs (16-19%) when compared to CBTs (6%) and jugulotympanic PGs (2-4%) [6].

Malignant HNPs are often reported as single case reports in the literature [44], [52], [74], [75], [77], [78], [130], [131]. Concerning the incidence of malignancy in HNPs, the publication of large groups of PG patients is more interesting [3], [17], [19], [48], [95]. Miller et al. detected three malignant tumors in a group of 19 patients with vagal PGs (15.8%). Two patients presented with regional lymph node metastases, one patient had systemic disease to the sacrum [17]. Patetsios et al. reported on three malignant HNPs in a group of 29 CBT patients (10.3%) [48]. Two patients had cervical lymph node metastases, one presented with intrahepatic metastatic disease. Grotemeyer et al. diagnosed four malignant tumors in a group of 39 HNP patients (10.3%) [95]. In the large series (n=79 HNP patients) reported by Kollert et al. there were no signs of metastatic disease in any patient [19].

The largest study to date dealing with malignant HNPs was published by Lee in 2002 [6]. For this study, the data of the "National Cancer Data Base" from 1985 until 1996 was studied. There were 59 malignant paragangliomas in a group of 355019 patients (0.017%). There were 30 female (50.9%) and 29 male patients (49.1%). Median age at the time of diagnosis was 44 years. 68.7% of patients presented with cervical lymph node metastases, 31.3% of patients had systemic metastases. Five year survival was 59.5%. There was a significant difference between patients with local metastases and patients with systemic disease though. 76.8% of patients with regional lymph node metastases were alive after five years compared to only 11.8% in the group with systemic metastases. Therapy of choice in patients with malignant HNPs is complete tumor resection with resection of all metastases whenever possible [6]. Radiation therapy is a sufficient tool to significantly prolong survival whenever complete resection is not achieved. Median survival time in patients who underwent radiation was 45 months versus 12 months in the group of patients without radiation [6].

Benefits of chemotherapy in the treatment of malignant HNPs are a matter of controversial discussion in the literature. Many authors do not see any benefit for this kind of treatment [6], [44], [74], [76]. Argiris and coworkers reported on their experience with a 33 year old female patient suffering from a CBT with pulmonary and osseous metastases. The patient underwent chemotherapy with cyclophosphamide, adriamycin and dacarbazin leading to partial remission of disease [8]. One has to keep in mind though, that the course of disease is indolent and hard to predict in patients with metastatic HNPs. There are reports of patients with malignant HNPs in the literature who survived for decades without any kind of treatment [132].

There have been promising initial results in the therapy of patients with widespread metastatic disease from paraganglial tumors using radiolabeled somatostatin analogs such as 111In-octreotid, 131I-metaiodobenzyl-guanidin (131I-MIBG) and 177LU-DOTATATE [133], [134], [135]. Nervertheless, prognosis remains poor for HNP patients with systemic metastases.

Recommendations regarding lymphadenectomy in HNP patients

Cervical lymph node metastases are not an uncommon feature in patients with cervical HNPs. Therefore we perform an ipsilateral selective neck dissection in levels II and III in patients undergoing resection of a cervical HNP. When we resect a jugular paraganglioma we do a lymphadenectomy in the upper region of the ipsilateral jugular vein. In patients with tympanic PGs we usually do not perform any kind of lymph node resection. The risk for lymph node metastases is considered very low for those tumors of the middle ear [4].

2.7 Hereditary paragangliomas and pheochromocytomas

HNPs as well as pheochromocytomas may occur as sporadic or familial entities [136], [137], [138], [139], [140], [141], [142].

It has been well known for decades that familial pheochromocytomas are part of different tumor syndromes [132], [139], [143], [144], [145], [146]. Pheochromocytomas do occur in 30 to 50% of patients with multiple endocrine neoplasia type 2 (MEN2) [132], [146], [147], [148], [149]. 10-20% of patients with von Hippel-Lindau syndrome present with pheochromocytomas [132], [146], [149], [150] and the risk to develop pheochromocytomas is estimated to be 1-5% for patients with neurofibromatosis type 1 (NF 1) and around 1% for subjects with multiple endocrine neoplasia type 1 (MEN1) [146], [149].

The familial clustering of HNPs has also been described in international medical literature for decades. In 1933, Chase first described two sisters who both presented with CBTs [151]. Goekopp mentioned the occurance of jugulotympanic paragangliomas in three sistern the same year [152]. The first description of familial vagal paragangliomas dates back to 1956 [153].

Although so called „paraganglioma syndromes" (PGL) have been described for many years, they have not been classified based on molecular genetics until the beginning of this century. In 2000, Baysal et al. first identified

germline mutations of the succinate dehydrogenase subunit D gene (SDHD gene) as the underlying cause of PGL 1 [139]. PGL 3 is associated with SDHC and PGL 4 with SDHB gene mutations [154], [155]. The genes SDHB, SDHC and SDHD are all tumor suppressor genes [155], [156], [157], [158], [159]. PGL 2 is caused by mutations of the succinate dehydrogenase complex assembly factor 2 gene (SDHAF2 gene) which is also known as SDH5 [160], [161]. PGL 2 has only been characterized on a molecular genetic basis in 2009 [160].

Succinatedehydrogenase, consisting of the subunits SDHA, SDHB, SDHC and SDHD, forms the mitochondrial complex II. It plays an important role in the mitochondrial respiratory chain as well as the tricarboxylic acid cycle [41], [144], [156], [162], [163], [164], [165].

The molecular genetic screening for mutations of the genes SDHB, SDHC and SDHD require 10ml of EDTA anticoagulated blood as well as a written informed consent [9]. The screening for all three genes, SDHB, SDHC and SDHD, costs approximately 2700 US$ per patient. The Dutch group around van Nederveen developed an elegant and cheap immunohistochemical examination for the detection of SDHx mutations. Sensitivity and specifity of the SDHB immunohistochemistry is 100% and 84% respectively [166]. Obviously, this method can only be applied after surgery. It is only possible to predict whether there is an SDHx mutation or not. The method can not tell which kind of SDHx mutation there is.

Table 5 shows all tumor syndromes characterized on a molecular genetic basis until October 2010 that are associated with HNPs and/or pheochromocytomas.

2.7.1 MEN1

Multiple endocrine neoplasia type 1 (MEN1) is an autosomal dominant disease caused by mutations of the MEN1 gene. MEN1 consists of 10 exons and it encodes the 610 amino acid protein menin [174]. Disease penetrance is nearly complete and patients with MEN1 typically develop tumors of the parathyroid glands, the pancreatic islet cells and the anterior pituitary gland. Less prevalent neoplasms associated with MEN1 are carcinoid tumors, facial angiofibromas, lipomas and collagenomas. Pheochromocytomas are only seen in about 1% of patients with MEN1 [146], [149]. HNPs have not been described in association with MEN1 yet.

2.7.2 MEN2

MEN2 is an autosomal dominant syndrome associated with mutations of the RET gene. The RET gene consists of 21 exons [167]. All RET mutations described in the literature to date may be found on http://arup.utah.edu/database/MEN2/MEN2_display.php?sort=1. There are a total of three subtypes. The most common subtype, MEN2A, is characterized by medullary thyroid carcinomas (MTC), pheochromocytomas and parathyroid neoplasia. Patients with MEN2B present with early onset aggressive MTC, pheochromocytomas and characteristic physical features such as a marfanoid habitus as well as neurinomas of the tongue, conjunctivas and the colon. FMTC (familial medullary thyroid cancer) is the third subtype in which MTC is the sole manifestation [167], [168].

About 30 to 50% of MEN2 patients develop pheochromocytomas [132], [146], [147], [148], [149]. HNPs have only been described in the three subjects with MEN2 so far [20], [169], [170].

2.7.3 NF1

Neurofibromatosis type 1 (NF1) is an autosomal dominant tumor syndrome caused by mutations of the NF1 gene [171]. The NF1 gene, consisting of 57 exons, is one of the largest human genes. The disease phenotype is dominated by multiple neurofibromas of the skin, café-au-lait spots, axillary freckling and so called Lisch nodules of the iris. NF1 patients are also at risk for the development of multiple tumors deriving from nerve tissue and endocrine tissues. 1-5% of NF1 mutations carriers present with pheochromocytomas [132], [146], [149], [172], [171]. A HNP in association with NF1 has only been described in one caes yet [173].

2.7.4 VHL

Von Hippel-Lindau syndrome (VHL) is a multisystemic autosomal dominant disease due to mutations of the VHL gene [169], [174], [175], [176], [177]. The VHL gene consists of three exons. The encoded protein has got 213 amino acids. All VHL mutations described up to date may be found at http://www.umd.be/VHL/. VHL displays full penetrance by age 65 although the individual disease phenotype is highly variable. The tumors most commonly seen in VHL mutation carriers are hemangioblastomas, retinal angiomas, renal cell cysts and renal cell carcinomas, pancreatic cysts as well as pheochromocytomas [174]. Occasionally endolymphatic sac tumors (ELST), among others, may also be observed [178].

Between 10 and 20% of all VHL patients present with pheochromocytomas [132], [146], [149], [150]. The fact, that VHL mutation carriers are also at risk for the development of HNPs has found little attention in international medical literature for many years. Until the year 2009 there were only five single case reports of patients with a HNP and VHL syndrome [179], [180], [181], [182], [183]. In 2009, our group conducted a large international multicenter study including a total of 2084 registered VHL patients. Eleven of those patients (0.53%) had a HNP [169]. In a later work, Gaal et al. could demontrate that HNPs are part of VHL and are due to VHL gene inactivation in those patients [175].

2.7.5 Paraganglioma syndromes (PGL)

Since the description of SDHD gene mutations as the cause of PGL 1 by Baysal et al. in the year 2000 [139], the paraganglioma syndromes (PGL) have attracted a lot of scientific attention.

Table 5: Tumor syndromes associated with HNPs and pheochromocytomas

tumor syndrome	gene mutation	locus	paraganglionic tumor(s)
MEN 1	MEN 1	11q13	pheochromocytomas
MEN 2	RET	10q11.2	pheochromocytomas (paragangliome)
NF 1	NF 1	17q11.2	pheochromocytomas (paragangliomas)
VHL	VHL	3p25-26	pheochromocytomas paragangliomas
PGL 1	SDHD	11q23	paragangliomas pheochromocytomas
PGL 2	SDHAF2	11q13.1	paragangliomas
PGL 3	SDHC	1q21	paragangliomas pheochromocytomas
PGL 4	SDHB	1p36	pheochromocytomas paragangliomas

MEN: multiple endocrine neoplasia; NF 1: neurofibromatosis type 1; VHL: von Hippel-Lindau; PGL: paraganglioma syndrome; SDH: succinatedehydrogenase; q: short arm of a chromosome; p: long arm of a chromosome

In the meantime, several large international studies could demonstrate that approximately 30% of all seemingly sporadic HNPs are due to genetic mutations [9], [10], [143], [184], [185], [186], [187]. The large majority of those hereditary HNPs is due to the paraganglioma syndromes 1, 3 and 4. HNPs in association with PGL 2 and VHL are less common [160], [161], [169] and in patients with MEN2 and NF1 head and neck paragangliomas are only very rarely seen [169], [173].

The PGL are characterized by distinct clinical features [9], [10], [143], [184], [185], [186], [187], which will be briefly shown.

PGL 1

Paraganglioma syndrome 1 (PGL 1) is caused by SDHD gene mutations [139]. In the SDHD gene, there are 4 exons and the encoded protein has 160 amino acids. All different SDHD gene mutations described in the literature so far may be found at http://chromium.liacs.nl/lovd_sdh/variants.php?action=search_unique&select_db=SDHD.

PGL 1 is the most common paraganglioma syndrome. SDHD mutation carriers are at risk for the development of both HNPs and pheochromocytomas, although HNPs are much more commonly seen. Pasini and Stratakis reviewed a total of 95 international manuscripts dealing with SDHx mutations [142]. There were a total of 395 SDHD patients in this review. 91% of those patients displayed at least one HNP and 79% even presented with multiple HNPs. Malignant paraganglial tumors are seen on a regular basis in SDHD mutation carriers although malignancy is significantly more common in SDHB patients [142]. Neumann et al. presented the results of a large multicenter study in 2009 [10]. A total of 598 patients with apparently sporadic HNPs were screened for mutations of the genes SDHB, SDHC and SDHD. Mutations were detected in a total of 183 subjects (30.6%). There were 94 SDHD mutations carriers as well as 63 SDHB and 26 SDHC patients, respectively. SDHD patients presented with multiple HNPs in 56 out of 94 cases (59.6%). HNPs and pheochromocytomas were seen in 17 cases (18.1%) whereas malignant paraganglial tumors had to be diagnosed in 9 SDHD mutation carriers (9.6%). The family history was positive in 45 patients which is 47.9% of cases.

Tumor penetrance in SDHD mutation carriers is high. Neumann et al. first published data on age related penetrance in SDHD mutation carriers in 2004 [9]. SDHD mutations conferred 50% penetrance by age 31 rising to 86% by the age of 50 in that study. In a 2010 study by Hensen and coworkers, age related penetrance in SDHD patients was 54% by age 40 and 87% by age 70 [186].

The trait of inheritance in SDHD mutation carriers is autosomal dominant with a „parent-of-origin-dependent-inheritance" [9], [132], [139], [164], [188]. This means

that patients with an SDHD mutation are only at risk for the development of paraganglial tumors if they inherited the mutation from their father. Though not at risk for tumor development themselves, SDHD mutation carriers who inherited the mutation through the maternal line will still pass the mutation to their children in 50% of cases.

PGL 2

PGL 2 is associated with mutations of the SDHAF2 gene [160], [161]. SDHAF2, also known as SDH5, consists of 4 exons. It plays an important role in flavination of succinate dehydrogenase subunit A [161].

In 1982, van Baars et al. described a large Dutch family (295 living family members) with familial HNPs [189]. The PGL in this family has later been referred to as PGL 2 [7], [161]. It was not until the year 2009 though, that Hao et al. identified a mutation of the SDHAF2 gene as the underlying cause of PGL 2 [189].

Bayley and coworkers detected another family with PGL 2, this time in Spain [161]. The authors also looked for SDHAF2 mutations in 443 additional HNPs and pheochromocytoma patients without finding another case of PGL 2.

In both families with PGL 2 only HNPs but no pheochromocytomas have been described [161], [189]. As in PGL 1 there is also a "parent-of-origin-dependent-inheritance" in SDHAF2 mutation carriers [161]. Tumor penetrance has been described to be very high in both the Dutch as well as the Spanish family [161], [189].

PGL 3

PGL 3 is caused by SDHC gene mutations [154]. The SDHC gene consists of 6 exons and encodes a 169 amino acid protein [142]. The SDHC mutations described so far are listed at http://chromium.liacs.nl/lovd_sdh/variants.php?action=search_unique&select_db=SDHC. Nieman et Müller first identified an SDHC mutation as the underlying cause of PGL 3 [154]. Until October 2005, only four patients with SDHC mutations had been described [154], [159], [190], [191]. Many authors concluded that SDHC mutations must be exceedingly rare and therefore, HNP patients were not routinely tested for mutations of the SDHC gene. This only changed when Schiavi et al. reported on a total of 22 SDHC mutation carriers in October 2005 [184]. Due to the following increased rate of SDHC testing, many SDHC mutations could be detected in the years following 2005. Nevertheless, SDHC mutations are still less common than SDHD and SDHB mutations.

In sharp contrast to patients with PGL 1 and PGL 4, SDHC mutation carriers almost exclusively develop benign, single HNPs [10], [184]. Malignant paragangliomas [159] and pheochromocytomas [192], [193], are only very rarely seen in SDHC patients.

In a 2009 study by Neumann and coworkers, there were 26 subjects with SDHC mutations in a total of 598 HNP patients [10]. There were no pheochromocytomas and no malignant HNPs in that SDHC group of patients. 21 out of 26 patients (80.8%) presented with a single HNP, five patients had two HNPs.

SDHC mutations follow an autosomal dominant trait of inheritance [5], [156], [159], [184]. Penetrance is probably rather low. In the study by Neumann et al., family history has only been positive in three out of 26 SDHC patients (11.5%) [10].

PGL 4

PGL 4 is caused by mutations of the SDHB gene [155]. The SDHB gene consists of 8 exons and the protein encoded has 280 amino acids [142]. The site http://chromium.liacs.nl/lovd_sdh/variants.php?action=search_unique&select_db=SDHB lists all SDHB mutations that have been published so far.

The first description of the SDHB mutation as the cause of PGL 4 dates back to 2001 [155].

Patients with PGL 4 frequently develop HNPs and pheochromocytomas. In contrast to SDHD mutation carriers, patients with SDHB mutations develop pheochromocytomas significantly more often than HNPs [142], [185], [193], [194]. Multiple HNPs are significantly less frequent when compared to SDHD patients [10], [142].

The most striking clinical feature of PGL 4 is the very high percentage of malignant pheochromocytomas and malignant HNPs [9], [10], [137], [142], [185]. In the study by Neumann et al. there were malignant paraganglial tumors in 13 out of 63 SDHB mutation carriers (20.6%) [10]. Ricketts et al. reported on 40 SDHB patients with malignant paragangliomas and pheochromocytomas in a group of 163 SDHB mutation carriers (25.2%) [185]. In a literature review by Pasini and Stratakis, malignant paraganglial tumors were diagnosed in 105 out of 256 SDHB mutation carriers (41%) [142]. In addition, PGL 4 patients are at an incresed risk for the development of kidney cancers. In 2004, Vanharanta described two SDHB patients who developed malignant kidney tumors at age 24 and 26 [195]. Ricketts et al. estimate the risk for subjects with PGL 4 to develop a malignant renal tumor by age 70 to be as high as 14%.

SDHB mutations follow an autosomal dominant trait of inheritance [5], [9], [10], [155]. Tumor penetrance is somewhat lower than that seen in SDHD mutation carriers. Recent studies estimated the age related tumor penetrance in SDHB mutation carriers to be at 29% at age 30 rising to 45% at age 40 [196].

Differences between PGL and sporadic HNPs

Patients with paraganglioma syndromes develop paraganglial tumors at a significantly younger age than patients with sporadic HNPs and sporadic pheochromocytomas [5], [142], [197]. Burnichon et al. compared 242 tumor patients with SDHB, SDHC and SDHD mutations with a group of 203 subjects with sporadic paraganglial tumors [197]. The age at first manifestation of a paraganglial tumor was 36.2 years in the PGL group

compared to 50.2 years in the group with sporadic tumors (p<0.0001). Multiple paraganglial tumors were also significantly more frequent in SDHx mutation carriers (n=112 versus n=10; p<0.0001). PGL patients also had a significantly higher risk for the development of malignant paraganglial tumors (n=40 versus n=9; p<0.0001), although this difference was greatly due to the very large percentage of malignant tumors in the SDHB subgroup [197].

Tumor development in PGL

Development of sporadic CBTs has been linked to chronic hypoxic stimulation of the glomus caroticum as it can be seen in patients living at high altitudes and in subjects with chronic obstructive lung disease [36], [42], [43].

The role of SDHB, SDHC and SDHD as tumor suppressor genes has been clearly defined. Mutations in one of the three genes lead to complete loss of function of SDH [142], [158]. Thus inactivation of SDHB, SDHC or SDHD with subsequent loss of SDH function results in a pseudohypoxic state. The resulting activation of hypoxia-inducible factors (HIF) pathways has been linked to accumulation of succinate and resulting inhibition of prolyl hydroxyase enzymes that are needed for proteosomal degradation of HIF-alpha subunits. This is believed to lead towards cell proliferation, angiogenesis and tumorgenesis in paraganglial tissue [185].

2.7.6 Additional genes of interest

The majority of familial HNPs is associated with PGL 1, 3 and 4. Pasini and Stratakis reviewed the studies concerning SDHx mutations and paraganglial tumors that were available in 2009 [142]. 87.8% of familial HNPs described in the literature up to then had been due to mutations in the genes SDHB, SDHC and SDHD. The fact, that a certain percantage of clearly familial HNPs does not seem to be associated with PGL 1, 3 and 4, VHL or PGL 2 makes it very likely that other genes probably play a role in the development of HNPs and pheochromocytomas [142], [157].

In this context, two promising genes of interest have been described in 2010.

SDHA

The SDHA gene consists of 15 exons and encodes a 664 amino acid protein that forms the SDHA subunit of SDH [142], [163]. SDHA mutations follow an autosomal recessive trait of inheritance [163]. Interestingly, as the only subunit of SDH, SDHA mutations had not been linked to paraganglial tumors but to a familial neurologic disorder called the Leigh syndrome [161], [198]. Burnichon and coworkers first described a 32 year old SDHA mutation carrier who developed a pheochromocytoma in 2010 [157]. Right now, it is too early to predict what kind of

role SDHA mutations with play in the future of hereditary paraganglial tumors though.

TMEM127

Qin et al. described mutations of the TMEM127 gene in patients with hereditary pheochromocytomas in 2010 [199]. Again, it is not possible yet to predict how many patients with paraganglial tumors really do suffer from a TMEM127 mutation.

2.7.7 Carney triad

In 1977, Carney et al. reported on two patients with sarcomas of the stomach (today referred to as gastrointestinal stromal tumor or GIST), extraadrenal pheochromocytomas and pulmonary chondromas [200]. Since the year 1981, this tumor complex is known as the Carney triad [201]. Patients with the triad are also at risk for the development of paragangliomas and esophageal leiomyomas [200].

In 1999, Carney reviewed the literature and found a total of 79 patients who were diagnosed with the Carney triad. Two of those 79 subjects were later outsourced from this group of patients by Carney and Stratakis and were diagnosed with the Carney-Stratakis syndrome [202][. Interestingly, none of the remaining 77 patients had a positive family history for the Carney triad or even for one of its associated tumors. Moreover, none of the 355 first degree relatives had the triad or even one of its tumors [203], [202]. Therefore the potentially hereditary status of the Carney triad remains at best unclear.

2.7.8 "Carney-Stratakis syndrome"

Carney and Stratakis reported on five families in 2002 presenting with GIST, paragangliomas as well as pheochromocytomas [202]. This association of tumors is also referred to as the „Carney-Stratakis syndrome" in the literature [142], [204]. In the meantime, it could be demonstrated that the majority of patients who had been diagnosed with „Carney-Stratakis syndrome" really suffer from mutations in one of the genes SDHB, SDHC or SDHD [142]. Therefore, we do not consider the „Carney-Stratakis syndrome" to be a real syndrome. It is more likely that patients with PGL 1, 3 and 4 also develop GIST occasionally.

2.7.9 Molecular genetic screening

According to the 2003 policy statement from the American Society of Clinical Oncology for cancer genetic testing all patients who are at a risk of more than 10% to harbour a genetic mutation should undergo molecular genetic testing [205].

After the molecular genetic characterization of the paraganglioma syndromes 1, 3 and 4 in the years 2000 and 2001 there was a lack of international standards regarding the question who should be tested for SDHx mutations. In 2002, Young and coworkers suggested a
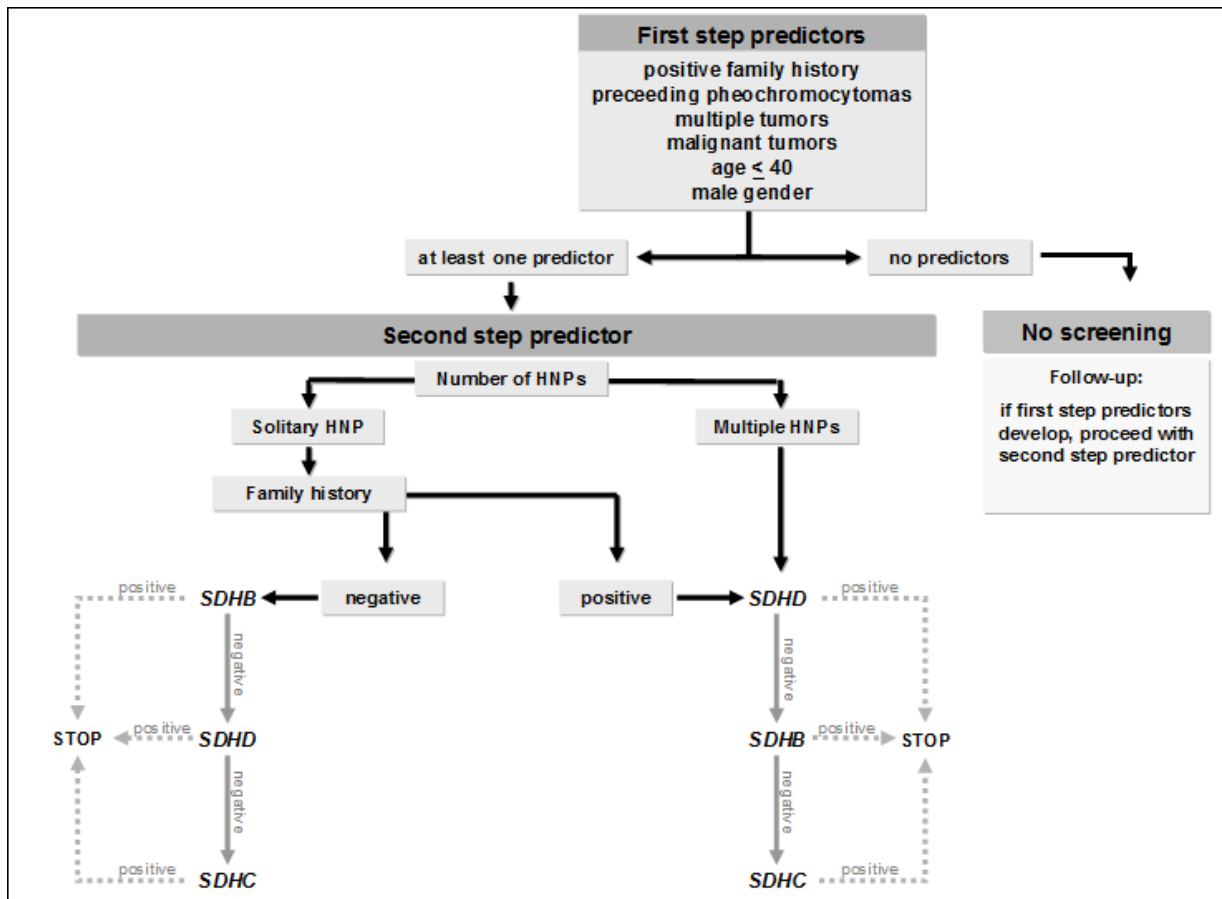
Figure 10: General algorithm for cost-effective mutation screening in patients with head and neck paragangliomas (HNPs) according to Neumann et al. [10].

screening for all HNP and pheochromocytoma patients with a positive family history [132]. Neumann et al. published the molecular genetic screening results of 271 patients with apparently sporadic pheochromocytomas in 2002 [143]. In 24% of cases there was a mutation in one of the genes SDHB, SDHD, VHL and RET. Therefore, Neumann strongly recommended a screening of all pheochromocytoma patients for mutations of the genes SDHB, SDHD, VHL and RET [143]. Based on own results, Gimenez-Roqueplo et al. came to the same conclusion in 2003 [158]. Since then it could be demonstrated that up to 30% of all patients with apparently sporadic HNPs suffer from mutations in the genes SDHB, SDHC and SDHD [9], [10], [142], [184], [194], [196]. The molecular genetic screening of all HNP patients is therefore regarded as international standard by the majority of authors.

On the other hand, screening for intragenetic mutations as well as large deletions in all three genes costs approximately 2700 US$ per patient [10]. In many cases, those expenses are not paid for by health insurance companies. Therefore, an algorithm for a cost effective screening would be very helpful. Neumann et al. screened 598 patients with apparently sporadic HNPs for mutations of the genes SDHB, SDHC and SDHD [10]. All patients were screened for mutations in all three genes. Mutations were detected in 183 subjects (30.6%). There were 94 SDHD, 63 SDHB and 26 SDHC gene mutations, respectively. No

patient presented with more than one mutation. In the next step, Neumann et al. looked for clinical predictors that were associated with a high probability of an SDHx mutation. A total of six first step predictors could be identified: positive family history, previous pheochromocytomas, multiple HNPs, manifestation of first tumor before age 40, male gender as well as malignant HNPs. Based on those first step predictors, Neumann and coworkers developed an algorithm (Figure 10). Using the approach of testing only patients with first step predictors would have resulted in a cost reduction of approximately 60% in this group of 598 patients. On the other hand, a total of 15 patients with SDHx mutations would not have been detected [10].

Therefore, we recommend molecular genetic screening of all HNP patients. In order to do this testing in a cost effective way without having the risk of missing a mutation we recommend a step by step approach. Clinical parameters will help to decide which gene should be tested first. Only if this test is negative, the second gene would be testet and so on.

We recommend the following approach for patients with HNPs:

- multiple HNPs:
  1) SDHD 2) SDHB 3) SDHC
- solitary HNP, positive family history:
  1) SDHD 2) SDHB 3) SDHC

- HNP(s) and pheochromocytoma(s):
  1) SDHD 2) SDHB 3) SDHC
- solitary HNP, negative family history:
  1) SDHB 2) SDHD 3) SDHC
- malignant HNP(s):
  1) SDHB 2) SDHD 3) SDHC

This approach should be modified under certain circumstances. If family pedigree confirms a disease transmission from mother to child, showing lack of the parent-of-origin effect seen in SDHD mutations, the SDHB gene should be tested first, followed by the SDHC gene if necessary [10].

A routine screening of HNP patients for mutations of the genes SDHAF2 (PGL 2), VHL (VHL syndrome) und RET (MEN2) is not necessary.

PGL 2 has only been described in two families yet [160], [161]. A screening for SDHAF2 gene mutations would only be useful in an patient with hereditary HNPs in the absence of an SDHB, SDHC and SDHD gene mutation.

HNPs are a part of the VHL tumor syndrome. Nevertheless, they are extremely uncommon compared to hemangioblastomas, retinal angiomas, renal cysts, renal cell cancer, pancreatic cysts and pheochromocytomas [174]. Before developing a HNP, patients with VHL syndrome have usually developed one or multiple of the other neoplasms mentioned [169].

HNPs are exceedingly rare in MEN2 with only three single cases published in the literature [20], [169], [170].

In pheochromocytoma patients without HNPs, the possibility of an RET or VHL mutation have to be kept in mind though. In patients with solitary extraadrenal pheochromocytomas Erlic et al. recommend a screening in the order SDHB, VHL, SDHD and RET [193]. Whenever there is an adrenal pheochromocytoma or in cases with multiple pheochromocytomas the order of choice would be: VHL, RET, SDHB and SDHD [169].

A thorough genetic counselling in combination with molecular genetic screening is essential. Patients and their families have to be familiar of the clinical features of the different hereditary HNP and pheochromocytoma syndromes. Of special interest is the trait of inheritance and here especially the parent-of-origin effect in PGL 1 and PGL 2.

2.7.10 Follow-up for PGL patients

The life-time risk for patients with SDHB and SDHD mutations to develop HNPs and/or pheochromocytomas is very high. Whereas tumor penetrance in SDHB mutation carriers seems to be slightly lower, one has to consider the high risk of PGL 4 patients for the development of malignant paraganglial tumors and malignant renal cell tumors [9], [10], [137], [142], [185], [195].

Those aspects have to be taken into consideration when it comes to follow-up of PGL patients. All mutation carriers should undergo a clinical and radiologic screening after the molecular genetic diagnosis has been established. The only exception is children of female SDHD mutation carriers. In addition to a thorough physical examination the following procedures should be considered a standard program:

- MRI with contrast medium of the head and neck, the thorax and the abdomen
- Catecholamines or metanephrines in plasma or 24h urine

Additional procedures such as an 18F-DOPA-PET may be of great benefit in selected cases.

In our opinion, patients with SDHC mutations should only undergo MRI of the thorax and abdomen once. Thereafter, MRI follow up of the head and neck region together with a physical examination should be sufficient, since PGL 3 harbours only a very low risk for the development of pheochromocytomas.

SDHD patients who have already developed a paraganglial tumor should undergo the whole standard program once a year. For SDHD patients without any signs of tumor, stretching of intervals to three years seems to be justified.

Due to the high risk for malignant tumors, we suggest the standard examination in SDHB patients once a year. Whenever malignancy is expected, the 18F-DOPA-PET has been an excellent tool in our hands.

SDHC patients with paraganglial tumors should undergo yearly MRI of the head and neck as well as a thorough physical examination. In SDHC patients who have not developed any tumor yet, an MRI of the head and neck together with a physical exam every three to five years should be sufficient.

The percentage of SDHB and SDHD patients who develop a tumor during the first two decades of life is rather high. In the study by Burnichon et al., 21 out of 242 (8.7%) SDHB and SDHD mutation carriers developed a tumor before age 18 [197]. The authors therefore suggest to start examinations in SDHB and SDHD patients at age 6. Whenever a paraganglial tumor is detected in a PGL patient an individual therapy regimen should be developed. When it comes to HNPs, our general therapy suggestions also apply to PGL patients. Pheochromocytomas of the thorax should be completely resected whenever possible. The same is true for adrenal and extraadrenal abdominal pheochromocytomas. In recent years, a cortical sparing laparoscopic partial adrenalectomy has become the gold standard of surgery [206], [207], [208]. Neumann and coworkers could demonstrate that even in cases of bilateral adrenal tumors enough tissue can be left in place to avoid the need for post-operative hormone therapy. The risk for local recurrences has been shown to be very low for this approach [206], [207].

3. Conclusion

Head and neck paragangliomas (HNPs) are rare, neuroendocrine neoplasms with a strong vascularisation. They are most commonly found as carotid body tumors. Jugulotympanic and especially vagal paragangliomas are less

common. Paraganglial tumors in the thorax and the abdomen are referred to as pheochromocytomas.

Post-operative deficits of the lower cranial nerves are the main risk of morbidity after surgical resection. Nevertheless, we recommend surgery as the therapy of choice for the majority of all HNPs since complete tumor resection represents the only curative treatment option. Depending on tumor size, number and localisation, the patients age and general status and pretherapeutic cranial nerve status other treatment options always have to be taken into account. Those alternative options include conventional radiotherapy, stereotactic radiosurgery and a "wait and scan" policy.

Shamblin III CBTs as well as Fisch C and Fisch D jugulotympanic paragangliomas should always undergo pre-operative embolisation whenever a resection is planned. Fisch A jugulotympanic paragangliomas must not be embolised. In all other cases, the need for embolisation should be individually decided.

Both HNPs and pheochromocytomas may occur as sporadic as well as hereditary entities. Up to 30% of apparently sporadic HNPs are associated with different tumor syndroms. Approximately 90% of all hereditary HNPs are related to the paraganglioma syndromes (PGL) 1, 3 and 4. PGL 1 is associated with mutations in the gene encoding succinate dehydrogenase subunit D (SDHD), whereas PGL 3 ist due to SDHC and PGL 4 to SDHB gene mutations. Trait of transmission is generally autosomal dominant for all PGL. In PGL 1 there is a so called "parent-of-origin-dependant-inheritance". This means that mutation carriers only suffer an increased risk for tumor development if the mutation has been transmitted through the paternal line.

Patients with PGL 1, 3 and 4 develop paraganglial tumors at a significantly younger age when compared to patients with sporadic HNPs and pheochromocytomas. SDHC patients develop benign, single HNPs in the great majority of cases. SDHD mutation carriers frequently suffer from multiple HNPs, whereas SDHB patients do have a significantly increased risk for the development of malignant paraganglial tumors. Malignant renal cell tumors are also detected in SDHB patients on a regular basis.

We recommend a molecular genetic screening of all HNP patients for mutations of the genes SDHB, SDHC and SDHD. The order of testing is performed according to individual clinical features. Whenever a mutation is detected, the affected patient should undergo a thorough clinical examination, an MRI with contrast medium of the head and neck, the thorax and the abdomen as well as catecholamines or metanephrines in plasma or 24h urine. The identification of patients with PGL will, in addition with follow up examinations, lead to early detection of HNPs and pheochromocytomas in the future. In turn, carriers identified early in the course of their disease can be brought to surgical attention before their disease becomes extensive and potentially life-threatening.

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