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Angaben zur Veröffentlichung / Publication details:

Künzel, Julian, Julie de Tristan, Konstantinos Mantsopoulos, Michael Koch, Marcela Baussmerth, Johannes Zenk, and Heinrich Iro. 2014. "Experiences in the treatment of patients with multiple head and neck paragangliomas." American Journal of Otolaryngology 35 (3): 294–99.
https://doi.org/10.1016/j.amjoto.2014.02.012.

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Experiences in the treatment of patients with multiple head and neck paragangliomas

Julian Künzel, MD [a,*,1], *Julie de Tristan, MD* [a,1], *Konstantinos Mantsopoulos, MD* [a], *Michael Koch, MD* [a], *Marcela Baussmerth, MD* [b], *Johannes Zenk, MD* [a], *Heinrich Iro, MD* [a]

[a] *Department of Otorhinolaryngology, Head and Neck Surgery, University of Erlangen–Nuremberg Medical School, Erlangen, Germany*
[b] *Department of Radiotherapy, University of Erlangen–Nuremberg Medical School, Erlangen, Germany*

1. Introduction

Head and neck paragangliomas (HNPs) are rare tumors, representing less than 0.5% of all head and neck tumors. Approximately 3% of all paragangliomas occur in the head and neck area [1,2]. Paragangliomas in the head and neck region are highly vascularized tumors, which in the majority of cases are benign. The incidence is two to five times higher in women. The age at manifestation is between 40 and 60 [3,4]. Paragangliomas only show histopathological signs of malignancy or metastases to nonendocrine tissue in approximately 3% of cases. The mean tumor doubling rate is 4.2 years [5], and the

☆ Conflict of interest statement and financial disclosure: The authors hereby declare that there are no conflicts of interest and no financial relationships to disclose.

* *Corresponding author at:* Department of Otorhinolaryngology, Head and Neck Surgery, University of Erlangen–Nuremberg, Waldstrasse 1, 91054 Erlangen, Germany. Tel.: +49 9131 8533156.
E-mail address: julian.kuenzel@gmx.net (J. Künzel).

[1] These authors contributed equally to the present study.

mean growth rate is only approximately 0.2 cm per year [6]. They originate in paraganglionic tissue in the area of the carotid bifurcation (carotid body tumors, CBTs), the jugular foramen and tympanic plexus (jugulotympanic paragangliomas, JTPs), the vagal nerve (vagal paragangliomas, VPs), and the facial nerve [7,8]. HNPs may occur either sporadically or in the context of a hereditary familial tumor syndrome. Multilocular presentations of glomus tumors are observed in 10–20% of sporadic cases and up to 80% of hereditary cases. Hereditary HNPs are mostly caused by mutations in the succinate dehydrogenase complex (*SDHx*) genes, in particular *SDHD* [2].

Currently, there is no standard therapeutic protocol in patients with multiple paragangliomas and some patients thus end up with overtreatment, while others are undertreated. The aim of the present study was to analyze and provide treatment results in the multidisciplinary management of patients with multiple HNPs.

2. Materials and methods

A retrospective analysis was carried out including all patients with multiple HNPs who were treated between 2000 and 2013 in the Department of Otolaryngology, Head and Neck Surgery and the Department of Radio-oncology at the University Hospital in Erlangen–Nuremberg, Germany.

The JTPs were categorized in accordance with the Fisch classification [9] and the CBTs in accordance with the Shamblin classification [2].

Clinical examinations of the cranial nerves were carried out both before and after treatment, in addition to endoscopic examinations. Before the start of treatment, all of the patients with JTPs underwent audiometry and detailed vestibular nerve diagnosis. Facial nerve function was classified in accordance with the House–Brackmann system [10]. For further diagnosis, computed tomography (CT), magnetic resonance imaging (MRI) of the head and neck region, or CT/MRI angiography were carried out. Ultrasonography was additionally performed in patients with carotid body tumors. Preoperative catecholamine analyses were not part of the routine diagnostic program.

Germline mutations (*SDHx*) have been investigated routinely since 2009 in patients with multiple presentations of HNPs, young patients, and patients with a positive family history. 18-Fluorodihydroxyphenylalanine (^{18}F-DOPA) positron-emission tomography (PET) or metaiodobenzylguanidine (MIBG) scintigraphy was also carried out in these cases [2,11].

MRI was carried out if JTPs were found at annual check-ups, and ultrasonography was carried out in patients with carotid body tumors. Criteria for successful tumor control following primary surgical procedures, with or without adjuvant radiotherapy, included — in addition to an absence of recurrences — a postoperatively stable residual tumor or a progression-free primary lesion following primary stereotactic radiotherapy (SRT).

2.1. *Surgical access routes*

Three different access routes were basically used for the surgical treatment of JTPs. Depending on the location and size of the JTP, a classic tympanic access route was used for type B, with additional mastoidectomy and tympanotomy if necessary. In types C and D, or when cranial nerve pareses were already present preoperatively, the standard approach used was a transmastoid–transcervical (TMTC) route [7].

For cervical paragangliomas, surgery was generally indicated as the treatment of choice, with the aim of achieving complete macroscopic resection of the tumor. When the caudal cranial nerves were found to be free of tumor or only partly infiltrated intraoperatively, every effort was made to preserve the neural structures — e.g., with microscopic Dissection.

2.2. *Planning and implementation of radiotherapy*

The radiotherapy methods used involved either fractionated SRT or radiosurgery. The patients received radiotherapy in a Novalis Shaped-Beam Surgery center (Brainlab Ltd., Feldkirchen, Germany). For radiotherapy planning, all of the patients underwent contrast MRI (with a slice thickness of 1–3 mm) as well as receiving individually prepared thermoplastic stereotactic masks and a planning CT with a slice thickness of 1–2 mm. Using the Novalis Brain Scan planning system, MRI and CT data were fused for contouring of the target volume (a macroscopic tumor with a safety margin of 2–3 mm). The dosage was standardized to the reference point (in accordance with International Commission on Radiation Units and Measurements Report No. 50); individual doses of 1.8–2.0 Gy, conventionally fractionated, were administered up to a final dosage of 50–56 Gy. Dosages of 12–18 Gy were administered in radiosurgery. One patient was treated with intensity-modulated radiotherapy (IMRT) with 54 Gy and a boost to 60 Gy in a different radiotherapy department.

3. Results

Ten patients with multiple HNPs (n = 25) were treated between 2000 and 2013. The patients presented with two VPs, eight JTPs, and 15 CBTs (Table 1). Three of the patients were men and seven women. The age range at the time of diagnosis was 31–71 years (mean 40.9 years, median 37 years).

The paragangliomas were exclusively located in the head and neck region in eight patients (80%). Two patients (20%) had disease both in the head and neck region and below the neck (patient 7, mediastinal; patient 10, adrenal gland).

Five patients (50%) had a family history of paragangliomas. One family consisted of seven siblings, four of whom had multicentric paragangliomas (patient 5, patient 6, patient 8, and one patient treated elsewhere). Details of the study population, including results of genomic testing for *SDHx* mutations and the patients' family histories, are given in Table 2.

The clinical presentations were diverse (Table 1). The most frequent symptoms were tinnitus (28%), a palpable neck mass (28%), and cranial nerve paralysis (12%). The tumors were discovered incidentally during an imaging study in asymptomatic patients in 28% of cases. Table 1 lists all of the patients and different tumor locations, including the Fisch or Shamblin tumor classifications and the different treatment strategies used. No clinical signs of increased secretion of neuropeptides or vasoactive amines were present in any of the patients.

Table 1 – All head and neck paragangliomas and their locations, tumor classification, and treatment strategy.

Patient	HNP	Age	Type	Side	Fisch	Shamblin	Primary symptom	Treatment	Persistent symptoms	Temporary symptoms	Follow-up (y)	Course
1	1-1	71	CBT	L		1	Neck mass	SRT			5.25	Stable
	1-2	71	CBT	R		1	Neck mass	SRT			5.25	Stable
2	2-1	44	CBT	R		3	Neck mass	SRT			4.75	Stable
	2-2	44	CBT	L		3	Neck mass	SRT			4.75	Stable
3	3-1	32	CBT	L		2	Tinnitus	Surgery			4.25	Stable
	3-2	33	JTP	L	C		Tinnitus, hearing loss	Subtotal resection + adjuvant SRT			4.25	Stable
	3-3	33	JTP	R	D		Dysphonia, CNP (X, XII, right)	Wait and scan	Dysphonia, CNP (X, XII, right)		4.25	Stable
4	4-1	37	JTP	L	C		Tinnitus, hearing loss	Surgery	**CNP (VII, X, left), dysphagia**		13	Stable
	4-2	59	CBT	R		2	Neck mass	Wait and scan			13	Progression
5	5-1	37	CBT	L		3	Neck mass	Surgery	Dysphagia	**CNP (X, left), aspiration, TS, PEG**	4	Stable
	5-2	40	VP	R			Incidentaloma, CNP (X, right)	SRT	CNP (X, right), dysphagia		1	Stable
	5-3	40	JTP	R	D		Tinnitus, CNP (X, right)	SRT	CNP (X, right), dysphagia		1	Stable
6	6-1	31	CBT	R		2	Incidentaloma	Surgery		**CNP (X, XII, right), dysphagia**	3.5	Stable
	6-2	31	CBT	L		1	Incidentaloma	Surgery			3.4	Stable
	6-3	31	JTP	L	C		Tinnitus, hearing loss	Embolization + subtotal resection + adjuvant SRT			2.6	Stable
	6-4	31	JTP	R	B		Incidentaloma	SRT			1.25	Stable
7	7-1	35	CBT	R		3	Neck mass	Surgery			2.5	Stable
	7-2	35	VP	R			Incidentaloma	SRT			2	Stable
	7-3	35	CBT	L		1	Incidentaloma	Wait and scan			2.5	Stable
8	8-1	36	CBT	L		2	Globus sensation	Surgery			0.5	Stable
	8-2	36	CBT	R			Globus sensation	Surgery planned			–	–
9	9-1	48	CBT	R		2	Hypertonia, visual impairment	Surgery			10	Stable
	9-2	54	JTP	R	B		Tinnitus	Embolization + subtotal resection + adjuvant SRT			4.5	Stable
10	10-1	38	JTP	R	D		Tinnitus	IMRT	**CN VI paresis, right), hearing loss**		5.5	Stable
	10-2	38	CBT	L		2	Incidentaloma	Surgery			0.1	Stable

CBT, carotid body tumors; CNP, cranial nerve paralysis; HNP, head and neck paraganglioma; IMRT, intensity-modulated radiotherapy; JTP, jugulotympanic paragangliomas; L, left; R, right; SRT, stereotactic radiotherapy; VP, vagal paragangliomas; y, year. **Bold type**: CNP due to treatment.

Table 2 – Study population.

Patient	Sex	Age at diagnosis	HNPs (n)	Gene mutation	Family history
1	F	71	2	Not tested	Positive
2	F	44	2	None	Positive
3	M	32	3	SDHBc239T > G	Negative
4	F	37	2	Not tested	Negative
5	F	37	3	SDHDc.209G > T	Positive
6	M	31	4	SDHDc.209G > T	Positive
7	F	35	3	SDHDc64C < T	Negative
8	F	36	2	Testing declined	Positive
9	M	48	2	None	Negative
10	F	38	2	Test in progress	Negative

MRI of the head and neck region was performed in 18 tumors (72%) and CT imaging in 15 tumors (60%). Angio-CT was performed in five tumors, angio-MRI in seven tumors, and angiography of the head and neck region in one tumor. Ultrasound examinations were also carried out in eight patients with 12 tumors (48%) and in 13 of the 15 CBTs (86%). Six patients received ^{18}F-DOPA PET (Fig. 1) and one patient underwent metaiodobenzylguanidine (MIBG) scintigraphy.

Nine tumors (CBT, n = 4; JTP, n = 3; VP, n = 2) were treated only with stereotactic radiotherapy (50.4–56 Gy, mean 55.3 Gy) or intensity-modulated radiotherapy in one case (60 Gy). Nine tumors were treated with surgery alone (CBT, n = 8; JTP, n = 1) and three JTPs with subtotal surgery after embolization in two cases combined with adjuvant stereotactic radiotherapy. A "wait and scan" strategy was used in three cases (CBT, n = 2; JTP, n = 1). Surgery is planned in one patient with a CBT.

New cases of cranial nerve paralysis were detected after the completion of treatment in four patients (16%). The postoperative cranial nerve paralysis was permanent in one patient, and a slight CN VI paresis persisted after IMRT in another patient (Table 1).

The mean follow-up period was 4.3 years (range 0.1–13 years, median 4 years). One patient died of an unrelated disease during the follow-up period (patient 2). Tumor control with surgery and/or SRT was 100% (21/21). Among three patients in whom a wait-and-scan strategy was used, one patient with a CBT showed asymptomatic slow progression during a follow-up period of 13 years (Table 1, Fig. 2).

4. Discussion

HNPs have traditionally been considered to be highly aggressive tumors, but our understanding of them has improved in recent years. The literature suggests that a change is taking place in the treatment paradigm, with an increasing trend toward individualized therapeutic strategies. In principle, surgical removal is still the only therapeutic option that potentially offers a cure for the patient, and the goal of any form of surgery should be complete tumor resection [5,12–15]. Evidently, however, views regarding the treatment of choice are generally moving away from radical resection toward surgical tumor reduction in order to preserve function and reduce morbidity [7,16–18]. Staged SRT may be considered immediately postoperatively or in case of tumor progression [19]. Alternative treatment options, depending on the individual situation (e.g., in relation to age, comorbidity, multifocal lesions, and risk of injury to the cranial nerves) include SRT (50–60 Gy) or radiosurgical procedures such as the GammaKnife or CyberKnife (12–18 Gy) [19,20]. According to Langerman et al., observation of cervical paragangliomas is an option in selected patients [6]. This is illustrated in one of our patients, in whom slow progression of a CBT was observed over 14 years of follow-up (Table 1).

A surgical procedure should be regarded as the treatment of choice in patients with small CBTs. With larger CBTs, particularly in elderly patients with unimpaired cranial nerves, radical surgery should be regarded critically. The patient's symptoms, age, comorbidities, and environment should be taken into account in the decision-making process. For large CBTs, tailored surgery while preserving function represents an adequate treatment option, and staged SRT may be considered postoperatively or in case of progression [21]. The risk of permanent postoperative cranial nerve deficits has been reported as 17% or 22%, and complication rates are directly related to the tumor size as estimated using the Shamblin classification [22,23]. These figures are almost consistent with the those in the present report, in which four patients (16%) had new cranial nerve paralyses after the completion of treatment. However, the postoperative cranial nerve paralysis was only permanent in one patient (Table 1). As reported in the literature in relation to Shamblin class III CBTs, there is a significant increase in permanent vascular or neural deficits after surgery, due to intraoperative interruption of the carotid vessels and cerebral circulation [22]. These severe complications should be minimized by carrying out tumor embolization preoperatively and with vascular reconstruction using vascular shunts intraoperatively [23]. In the present series, including surgery for two Shamblin class III tumors, no vascular interventions were necessary.

It is possible almost without exception to completely resect smaller JTPs of sizes A and B, using a diversified surgical approach. Larger JTPs of sizes C and D can be treated either with primary surgery or stereotactic radiotherapy with function-preserving intent and with a comparable degree of tumor control. Particularly in older patients with normal cranial nerve function and acceptable auditory function, radical surgery should be regarded particularly critically, as a loss of function in the major cranial nerves is usually followed by a difficult and stressful rehabilitation process. The extent of the surgery should therefore be based on the intraoperative findings. In many situations, reducing the size of the tumor while preserving function represents an adequate treatment option [7]. In the present series, eight JTPs were locally controlled using a multimodal approach combining surgery and radiotherapy.

A recently published review by Suárez et al. provides evidence that radiotherapy offers a similar chance of tumor control with lower risks of morbidity compared with surgery in patients with JTPs. Although the evidence is based on retrospective studies, these results suggest that surgery should be considered only for selected cases, but the decision should be individual for every patient [24].

Offergeld et al. described six susceptibility genes and associated syndromes that are relevant for patients with HNPs (*SDHx* complex, von Hippel–Lindau, *TMEM127*) [2]. Rarely, mutations of the well-known genes causing multiple endocrine neoplasia type

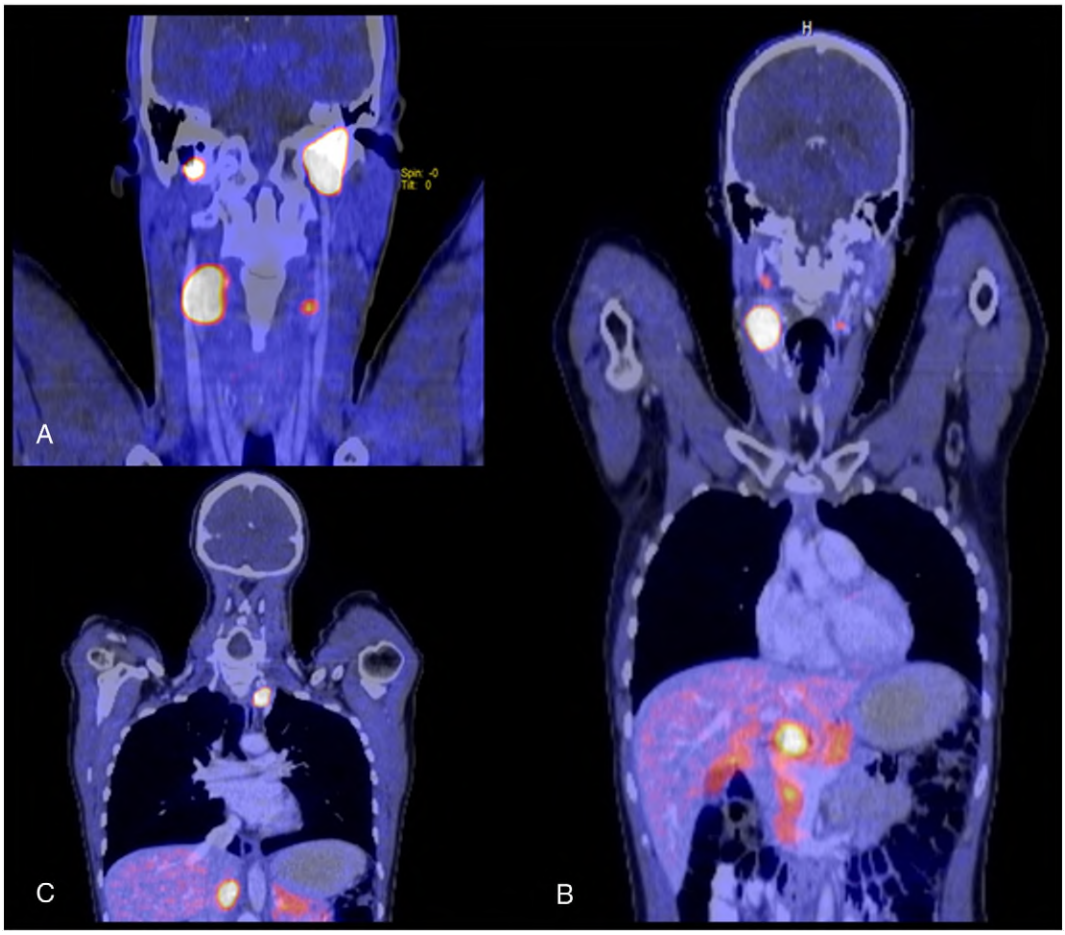

Fig. 1 – (A) Patient 6: ^{18}F-DOPA PET/CT, showing bilateral jugulotympanic and carotid paragangliomas with contrast enhancement and ^{18}F-DOPA uptake. °(B) Patient 7: ^{18}F-DOPA PET/CT, showing bilateral carotid paragangliomas (right > left) and one vagal paraganglioma on the right side with contrast enhancement and ^{18}F-DOPA uptake. °(C) Patient 7: ^{18}F-DOPA PET/CT, showing a paraganglioma in the left upper mediastinum and in the hilum of the liver.

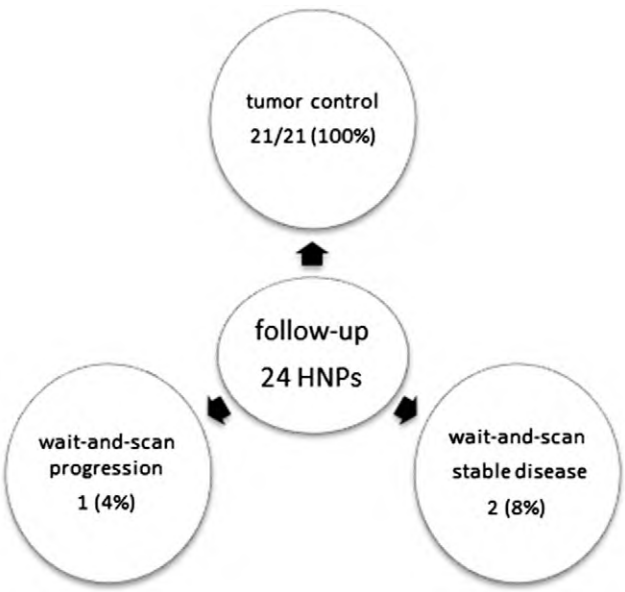

Fig. 2 – Outcome for patients at follow-up.

2 (*MEN2*), von Hippel–Lindau disease, and neurofibromatosis type 1 (*VHL*, *RET*, and *NF1*) may also predispose to HNPs [25]. According to Boedeker et al., about one-third of all patients with HNPs are carriers of germline mutations. All patients with HNPs should be offered molecular genetic screening, usually restricted to mutations of the genes *SDHD*, *SDHB*, and *SDHC* [26]. Burnichon et al. compared 242 patients who had tumors with *SDH* mutations with a group of 203 patients with sporadic paragangliomas. The age at first manifestation of a paraganglial tumor was 36.2 years in the PGL group, in comparison with 50.2 years in the group with sporadic tumors. Multiple paraganglial tumors were also significantly more frequent in *SDHx* mutation carriers (n = 112 vs. n = 10; $P < 0.0001$) [27].

Three of four patients with a positive *SDHx* mutation had a positive family history in the present series, but negative genomic testing should also lead to a detailed history being taken (Table 2). Predictive factors for a positive mutation test include family history, previous adrenal or extra-adrenal pheochromocytoma, multiple HNPs, age ≤ 40 years, and male gender [25]. These predictive factors should also lead to early nuclear imaging in order to detect multiple paragangliomas. HNPs typically show avid uptake with different functional imaging techniques.

5. Conclusion

The treatment results in this series of patients with multiple HNPs show that a very high rate of long-term tumor control with low morbidity can be achieved using tailored and individualized approaches. Treatment decision-making should involve a multidisciplinary team of experts in the fields of nuclear medicine, genetics, pathology, radiology, radio-oncology, and surgery. A complete diagnostic check-up, including genetic testing, should be part of the routine diagnostic program. This is particularly important in patients with multifocal paragangliomas. In the present authors' experience, some patients may become frightened of the morbidity of surgery following surgical treatment for a first paraganglioma, leading them to decline subsequent treatment options for a second or third paraganglioma. This shows the importance of discussing all of the available different treatment strategies with the patient.

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