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Treatment of cervical paragangliomas: Is surgery the only way?

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1. Introduction

Head and neck paragangliomas (HNPs) are highly vascularized tumors, in which histopathological signs of malignancy are only seen in approximately 3% of cases [1]. HNPs show a mean growth rate of only approximately 0.2 cm per year [2]. They originate in paraganglionic tissue in the area of the carotid bifurcation (carotid body tumors, CBTs), the jugular foramen

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and tympanic plexus (jugulotympanic paragangliomas, JTPs), the vagal nerve (vagal paragangliomas, VPs), and the facial nerve [3,4]. 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* [5]. The internationally accepted clinical classification of CBTs is the Shamblin system, with classes I–III corresponding to permanent postoperative side effects (Table 1) [6,7]. There is no internationally accepted classification system for VPs.

The paradigm used in the treatment of patients with cervical paragangliomas is apparently changing at present, with an increasing trend toward individualized therapeutic strategies. The literature provides good evidence for the effectiveness of a tailored and function-preserving surgical approach in the treatment of CBTs and VPs, as well as for primary or staged stereotactic radiotherapy (SRT) [8–12]. In selected patients, clinical observation appears to be an adequate strategy as well [2].

The purpose of the present study was to analyze the results in relation to long-term tumor control and integrity of the cranial nerves in patients receiving surgery or SRT in the treatment of cervical paragangliomas. Against this background, the decision-making algorithm used in our institution was reevaluated in relation to the existing literature on the topic.

2. Materials and methods

A total of 27 CBTs and nine VPs in 32 patients were treated between 2000 and 2012. The patients consisted of 10 men (31.3%) and 24 women (75%), with a mean age of 54.8 years (range 30–86 years).

2.1. *Algorithm for diagnostic work-up*

All patients with a cervical mass undergo ultrasonography of the neck as the initial diagnostic procedure at our institution, regardless of any imaging findings from external sources that may be available. Ultrasound is also carried out when patients have been admitted with an asymptomatic incidental imaging finding. To distinguish CBTs from VPs, particularly on ultrasonography, it is helpful to recall that CBTs typically displace the external carotid artery anteromedially and the internal carotid artery posterolaterally, while VPs displace both arteries anteriorly. Magnetic resonance imaging (MRI) was used for further diagnosis, particularly in cases of suspected VP, in order to delineate the cranial extension to the skull base. MRI angiography or computed-tomographic angiography was additionally carried out preoperatively. Digital subtraction angiography (DSA), with embolization of the afferent vessels, was performed only in a few patients, particularly in cases of suspected VP [13]. Germline mutations (*SDHx*) have been investigated routinely in our department since 2009 in patients with multiple presentations of HNPs, young patients, and patients with a positive family history, and fluorodihydroxyphenylalanine F 18 (^{18}F-FDOPA) positron-emission tomography (PET) or metaiodobenzylguanidine (MIBG) scintigraphy was carried out [5,14].

Table 1 – The Shamblin classification for carotid body tumors (CBTs).

Class	Characteristics
I	Tumors with splaying of the carotid bifurcation but little attachment to the carotid vessels
II	Tumors that partially surround the carotid vessels
III	Tumors that intimately surround the carotids

2.2. *Algorithm for treatment and decision-making*

Surgery is 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 or subtotal resection. However, if cranial nerve deficits (CNDs) were evident preoperatively or the vagal nerve in particular showed complete tumor infiltration, the surgical procedure was more radical and the nerve was sacrificed. An indication for primary radiotherapy was only established rarely, but this was carried out particularly if a surgical procedure was likely to involve a high risk of damage to several intact cranial nerves. In addition, the indication for surgery or SRT depended on the patient's preferences and concomitant diseases. In patients with multiple HNPs, an individualized treatment strategy combining both surgical and nonsurgical methods was planned.

Ultrasound examinations and MRI were carried out at the annual check-ups. In addition to freedom from recurrences, criteria for successful tumor control following surgical procedures included a postoperatively stable residual tumor or a progression-free primary lesion following SRT.

2.3. *Planning and implementation of radiotherapy*

SRT was performed using a Novalis shaped-beam surgery center (Brainlab Ltd., Feldkirchen, Germany). The dosage was standardized to the reference point; individual doses of 1.8–2.0 Gy, conventionally fractionated, were administered up to 50–56 Gy [3].

The study was approved by the institutional review board at the University of Erlangen–Nuremberg.

3. Results

3.1. *Carotid body tumors*

The 27 CBTs in 24 patients (mean age 54.5 years) were categorized in accordance with the Shamblin classification as: class I: 59.3% (n = 16); class II: 29.6% (n = 8); and class III: 11.1% (n = 3). The most frequent symptom was a neck mass in 75% of cases (n = 18). Paresis of the vagal nerve and irritation of the cervical plexus were present in one case each (4.7%). In five cases (20.8%), the CBT was an incidental finding.

^{18}F-FDOPA PET was performed in six cases and MIBG scintigraphy in one patient. DSA was carried out in two cases, but embolization was possible only in one case.

3.1.1. *Primary surgical therapy for CBTs (n = 21)*
Surgery was carried out in 21 CBTs in 20 patients (Shamblin class I, n = 11; class II, n = 8; class III, n = 2) with a mean age of 51.1 years, with complete tumor removal in 20 cases (95.2%). None of the patients had any CNDs at the initial presentation. Analyses of the *SDHx* gene family identified six patients with germline mutations; detailed information is given in Table 2.

The treatment of three patients who had multiple HNPs, including CBTs, is described in detail below:

- *Patient 1*. A 33-year-old male patient had a class II CBT, and computed tomography (CT) revealed bilateral JTPs. The CBT was completely removed surgically, and the left-sided JTP was subtotally removed in a second procedure. Adjuvant SRT up to 56 Gy was administered. The contralateral JTP has since been receiving close follow-up observation, with no evidence of progression.
- *Patient 2*. In a 31-year-old male patient, MRI and ^{18}F-FDOPA PET revealed bilateral JTPs and CBTs. Both CBTs (class I on the left and class II on the right) were completely removed surgically; the patient developed temporary paresis of the right vagal and hypoglossal nerves. The JTP on the left side was treated using subtotal removal and adjuvant SRT, and the right-sided JTP underwent SRT. None of the tumors in this patient showed any signs of progression or recurrence during a follow-up of 2.15 years.
- *Patient 3*. A 35-year-old female patient was found to have bilateral CBTs and a unilateral VP on ^{18}F-FDOPA PET, as well as paragangliomas in the mediastinum and abdomen. The CBT on the left side was resected, and the left-sided VP was irradiated up to a total dose of 56 Gy. At the time of writing, the second CBT had been receiving clinical observation with no evidence of progression for 2.5 years.

Tumor infiltration into the vagal nerve was noted intraoperatively in three cases; although the integrity of the nerve was preserved in one of these patients, permanent vagal paresis resulted. Postoperatively, eight patients had 19 CNDs, including 12 that were temporary, with complete recovery, and seven that were permanent in five patients (20%). Isolated injury to the superior laryngeal nerve, with a restricted singing voice, was noted in one case. Table 3 provides detailed information on the course in patients with CNDs. The mean follow-up period for this group was 4.23 years (range 0.5–12.91 years). All of the patients with surgically removed CBTs remained free of recurrences up to the time of data collection.

3.1.2. *Primary stereotactic radiotherapy for CBTs (n = 3)*
Primary SRT was performed in two patients with three CBTs. One 71-year-old woman had bilateral CBTs (both class I) and surgery was declined. SRT up to 56 Gy was administered, and the tumors showed partial regression during a follow-up period of 4.18 years. An 84-year-old woman had a suspected Shamblin class III tumor with irritation of the cervical plexus. In view of her age and comorbidity (Parkinson's disease, brainstem stroke, chronic heart failure), SRT was carried out, but it had to be abandoned at 39.6 Gy due the patient's reduced general health. However, the tumor remained stable for 4.15 years until the patient died of chronic lung failure. Overall, no CNDs, dysphagia, or aspiration was observed during or after SRT.

3.1.3. *Clinical observation of CBTs (n = 3)*
One 59-year-old woman with a history of resection of a JTP at a different hospital in 1976, resulting in postoperative vagal and facial paresis, presented with a class I CBT contralaterally. Any treatment was declined, and minimal tumor progression was noted during a follow-up period of 14.42 years. A 38-year-old woman had a history of surgical removal of a left-sided CBT at a different hospital in 2009, with postoperative bilateral paresis of the vagal nerve. ^{18}F-DOPA PET identified a JTP and a CBT (class I) on the right side. Due to progression of the JTP, a course of primary SRT was administered, and the CBT had not so far shown any evidence of progression over a 3-year period at the time of writing. A 35-year-old woman was found to have bilateral CBTs and a unilateral VP on ^{18}F-FDOPA PET. One CBT was resected, the VP was irradiated, and the second CBT is receiving clinical observation, with no evidence of progression for 2.5 years.

3.2. *Vagal paragangliomas*

Among the nine vagal paragangliomas, the symptoms were a neck mass in 66.6% of cases (n = 6), dysphonia due to vagal paresis in 11.1% (n = 1), and a foreign-body sensation in 11.1% (n = 1). Two (22.2%) were incidental findings. One of these patients had multiple HNPs, with positive germline mutations

Table 2 – Patients with germline mutations in the *SDHx* gene family.

Age of patient	Location of tumor	Imaging	*SDHx*	Family history
64	Single CBT	MRI	*SDHB*c.735T>A; exon 6	Positive
57	Single CBT	MRI	*SDHB*c.675 dupG; exon 6	Positive
33	CBT, left JTP	MIBG scintigraphy	*SDHB*c.239T>G, exon 3	Negative
38	Bilateral CBT, bilateral JTP	^{18}F-FDOPA- PET	*SDHB*c.209G>T, exon 3	Negative
31	Bilateral CBT, bilateral JTP	^{18}F- FDOPA- PET	*SDHD*c.209G>T, exon 3	Positive
35	Bilateral CBT, single VP, paraganglioma in mediastinum and abdomen	^{18}F- FDOPA- PET	*SDHD*c.64 C<T, exon 2	Negative

Abbreviations: CBT, carotid body tumor; ^{18}F-FDOPA-PET, ^{18}F-fluorodihydroxyphenylalanine positron-emission tomography; JTP, jugulotympanic paraganglioma; MIBG,^{123}I-metaiodobenzylguanidine; MRI, magnetic resonance imaging; VP, vagal paraganglioma.

Table 3 – Postoperative outcome in patients with cranial nerve deficits after primary surgery for carotid body tumors.

Shamblin class	Age of patient	Intraoperative situation	CND	Function	Follow-up (years)
I	51	No infiltration of CN	Temporary CN X, XII	Complete rehabilitation	3.69
II	76	CN X infiltrated, but preserved due to microscopic dissection	Temporary CN IX, XI, XII; permanent CN X	Temporary dysphagia, no aspiration	2.41
II	31	No infiltration of CN	Temporary CN X, XII	Complete rehabilitation	2.15
II	64	CN X infiltrated and sacrificed	Permanent CN X, XII	Permanent aspiration and temporary dysphagia	3.16
II	57	CN X infiltrated and sacrificed; 5% residual tumor tissue in the foramen magnum	Temporary CN VII (House II), IX, XII; permanent CN XI, X	Complete rehabilitation	3.01
II	47	No infiltration of CN	Temporary CN VII (House II), XII	Complete rehabilitation	9.75
II	44	No infiltration of CN	Permanent CN X	Temporary aspiration	12.91
III	63	No infiltration of CN	Permanent CN X	Temporary dysphagia	1.05

Abbreviations: CN, cranial nerve; CND, cranial nerve deficit; CN VII, facial nerve; CN IX, glossopharyngeal nerve; CN X, vagus nerve; CN XI, accessory nerve; CN XII, hypoglossal nerve.

(Table 2). DSA with embolization of the afferent tumor vessels was performed in three cases.

3.2.1. *Primary surgical therapy for VPs (n = 7)*

A total of seven patients with VPs, with a mean age of 57.5 years, underwent primary surgery, with complete tumor removal in six cases (85.7%). One 70-year-old woman had a large VP, and the tumor was resected subtotally with the aim of preserving vagal function. A residual tumor representing 5% of the lesion remained. Postoperatively, however, the patient suffered from permanent vagal nerve and temporary hypoglossal nerve paresis, and a temporary percutaneous endoscopic gastrostomy (PEG) tube was placed for 18 months. Swallowing function recovered after intense rehabilitation therapy. No signs of tumor progression were observed during close follow-up over 7 years. A 66-year-old woman had postoperative permanent paresis in cranial nerves X, XI, and XII, with temporary aspiration, but function was regained after intense rehabilitation and medialization of the vocal cord. A 38-year-old woman suffered permanent dysphagia due to permanent paresis of cranial nerves IX, X, and XII after radical tumor resection. Injury to the axillary nerve, with weakness in the deltoid muscle, was also observed postoperatively. In a 56-year-old patient, it was possible to preserve the vagal nerve with fine microscopic dissection, and function remained postoperatively intact except for injury to the glossopharyngeal and superior laryngeal nerves. A 65-year-old woman with a 9-month follow-up period showed postoperative permanent vagal and temporary hypoglossal paresis. Due to permanent dysphagia with mild aspiration, a PEG had to be placed, and intense swallowing rehabilitation was initiated. A 54-year-old woman had dysphonia due to preoperative vagal paresis and showed no other deficits postoperatively. An 81-year-old woman with a follow-up period of 1.5 years suffered permanent dysphagia with mild aspiration due to permanent vagal paresis.

Surgery for VPs caused 13 CNDs in seven patients (100%), and 11 of the resulting pareses remained permanent. Table 4 provides detailed information on the course in patients with CNDs. The mean follow-up period was 4.17 years (range 0.75–9.92 years). All of the patients remained free of recurrences up to the time of data collection.

3.2.2. *Primary stereotactic radiotherapy for VPs (n = 2)*

In a 52-year-old woman with a large VP, surgery was initially indicated after embolization, but intraoperatively there was found to be clear tumor infiltration into the vagal and hypoglossal nerves. Because of the high risk for permanent paresis of the caudal cranial nerves, surgery was abandoned and only a biopsy was taken. Subsequently, primary SRT was administered, with a radiation dose of 50 Gy. There has been no evidence of CND or tumor progression during a follow-up period of 7.7 years. As mentioned above, another VP in a 35-year-old female patient with bilateral CBTs was irradiated up to 56 Gy, with no evidence of CNDs or progression for 2.5 years.

Table 4 – Postoperative outcome in patients with cranial nerve deficits after primary surgery of vagal paragangliomas.

Age of patient	CND	Function	Follow-up (years)
70	Temporary CN XII, permanent CN X	PEG for 18 months, complete rehabilitation	7.03
66	Permanent CN X, XI, XII	Temporary aspiration, complete rehabilitation and vocal cord medialization	9.92
38	Permanent CN IX, X, XII	Permanent dysphagia	2.68
56	Permanent CN IX, X preserved and intact	Complete rehabilitation	5.57
65	Permanent CN X, temporary CN XII	Permanent dysphagia with mild aspiration, PEG	0.75
54	Permanent CN X	Dysphonia	1.75
81	Permanent CN X	Permanent dysphagia and mild aspiration	1.50

CN IX, glossopharyngeal nerve; CN X, vagus nerve; CN XI, accessory nerve; CN XII, hypoglossal nerve; CND, cranial nerve deficit.

3.3. *Tumor control rate*

The tumor control rate of CBTs and VPs treated either with surgery or SRT was 100%. One CBT that received clinical observation showed slow progression. The median follow-up period was 4.67 years (range 0.5–13 years).

4. Discussion

It should be emphasized that the present study was carried out in order to reevaluate the decision-making algorithm used in the treatment of cervical paragangliomas at our institution, taking the results and the existing literature on the topic into consideration. The study is of course limited by its retrospective nature.

The present series confirms that CBTs remain clinically silent before presenting in 60–70% of cases as a painless, slowly growing mass in the lateral neck [15,16]. In the remainder of cases, initial symptoms may include cranial nerve dysfunction [1,15]. In fewer than 50% of cases (one patient in the present study), cranial nerve deficits are the initial findings with VPs [17].

HNPs have traditionally been considered to be highly aggressive tumors, but our understanding of the natural history of cervical paragangliomas has improved in recent years, and the literature suggests that a change is taking place in the treatment paradigm. 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 [1,9,10,16]. 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 [3,11,18]. 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) [18,20,21]. According to Langerman et al., observation of cervical paragangliomas is an option in selected patients [2].

Tumor control rates of 89–100% after complete surgical resection of CBTs have been reported [1,11], and these figures are consistent with the data in the present study. The risk of permanent postoperative CNDs has been reported as 17% or 22% [7,15], and complication rates are directly related to the tumor size as estimated using the Shamblin classification [6,15]. In the present study, 20% of the patients had permanent CNDs after surgery for 21 CBTs, but no tracheostomies or PEGs were necessary. None of these patients had CNDs at the initial presentation. This figure is comparable with the data in the literature and underlines the need for rapid and intense swallowing rehabilitation [7]. In summary surgery of class I CBTs caused no CNDs and no functional impairment. In larger CBTs seven permanent paresis were observed with permanent aspiration in one patient. 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 [6,7,12]. Several authors have recommended that these severe complications should be minimized by preoperative tumor embolization and with vascular reconstruction using vascular shunts intraoperatively [14,15,22]. In the present series, including surgery for two Shamblin class III tumors, no vascular interventions were necessary.

As confirmed in the present small group of VPs, rates of local tumor control for VPs may be up to 100% if complete tumor resection can be achieved [11]. In the vast majority of cases, however, the vagal nerve has to be sacrificed, and the rates of additional CNDs increase along with the size of the glomus [8,23]. As in the results reported by Thabet and Kotob, all of the patients in the present group in whom VPs were surgically removed developed vagal paresis and/or other CNDs, with swallowing problems of various degrees [23]. A promising study by Miller et al. described higher rates of preservation of the vagal nerve when microsurgical techniques were used, and this finding was also confirmed in one of the present patients [8]. In contrast, the two patients with VPs who received SRT showed no evidence of CNDs or tumor progression over follow-up periods of 2.5 and 7.7 years.

In 2001, Hinerman et al. published their 35-year experience in the treatment of HNPs, including 24 CBTs and 17 VPs. They recommended resection of small cervical paragangliomas if the surgery did not require the sacrifice of major neural and/or vascular structures. SRT was recommended for all other patients. In their series, the rate of local tumor control with multimodal treatment strategy was 96% for CBTs and 100% for VPs [11]. The local tumor control rate of 100% for surgery and SRT in the present study is well comparable with these data and thus confirms the treatment strategy recommended.

Various authors [24,25] have reported tumor control rates of 76–100% after SRT, as recently confirmed in a meta-analysis by Guss et al. [26]. However, the degree of long-term tumor control achieved with radiotherapy has often been questioned, on the assumption that it causes tumor necrosis not by directly destroying tumor cells, but rather through fibrosis and occlusion of the tumor's vessels [27,28]. Vital tumor cells can lead to recurrences even 10 years after the completion of radiotherapy, and there is a risk of rare but severe radiation-induced long-term sequelae such as osteoradionecrosis and radiogenic secondary malignancies [29,30]. A strategy of observation is a possible option in selected patients, in the absence of worrisome symptoms [2]. In principle, surgical removal is the only therapeutic option that potentially offers a cure for the patient, and it has the further advantage that tissue for histological analysis is obtained [20,24]. Although the metastatic potential of HNPs is low, it represents a limitation for nonsurgical treatment [15]. In patients with multiple HNPs, an individual multimodal treatment strategy is required in order to provide long-term tumor control and an acceptable quality of life.

5. Conclusions

As a consequence of the results obtained in this study, and after a comprehensive review of the literature, the decision-making algorithm used at our institution in the treatment of

patients with cervical paragangliomas was reevaluated. Treatment of carotid and vagal paragangliomas causes different morbidity and should therefore be considered separately. A surgical procedure should be regarded as the treatment of choice in patients with class I CBTs. In 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 recognized in the decision making process. The literature provides good evidence that in large CBTs, tailored surgery while preserving function represents an adequate treatment option, and staged SRT may be considered postoperatively or in case of progression. As surgery for VPs caused regularly impairment of cranial nerves with functional disturbances of various degrees a comprehensive consultation with the patient is mandatory and nonsurgical strategies should be discussed.

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