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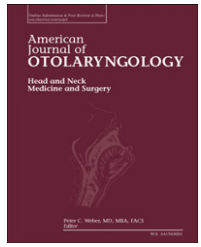

Experiences in the treatment of patients with multiple head and neck paragangliomas☆

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ABSTRACT

Purpose: To analyze treatment results in the multidisciplinary management of patients with multiple head and neck paragangliomas (HNPs).

Methods: Retrospective analysis including all patients with multiple HNPs (VP, vagal paraganglioma; JTP, jugulotympanic paraganglioma; CBT, carotid body tumor) treated between 2000 and 2013 at a tertiary referral center.

Results: Ten patients (three men, seven women) had 25 HNPs (two VPs, eight JTPs, and 15 CBTs). The age range at diagnosis was 31–71 years (mean 40.9 years, median 37 years). Nine tumors (four CBTs, three JTPs, two VPs) were treated only with stereotactic radiotherapy (SRT; 50.4–56 Gy, mean 55.3 Gy) or in one case intensity-modulated radiotherapy (60 Gy). Nine tumors were treated with surgery alone (eight CBTs, one JTP) and three JTPs with subtotal surgery combined with adjuvant SRT. A "wait and scan" strategy was used in three cases (two CBTs, one JTP). The mean follow-up period was 4.3 years (range 0.1–13 years, median 4 years). The rate of tumor control with surgery and/or SRT was 100% (21/21). One patient with a wait-and-scan strategy for CBT had slow asymptomatic progression during a 13-year follow-up.

Conclusions: 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. All of the different treatment strategies available should be discussed with the patient. In particular, the treatment should involve a multidisciplinary team of experts in the fields of nuclear medicine, genetics, pathology, radiology, radio-oncology, and surgery.

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

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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.