Head and Neck Paragangliomas: The Experience of a Southern European Cancer Center

Paragangliomas da Cabeça e Pescoço: A Experiência de um Centro Oncológico do Sul da Europa

ARTIGO ORIGINAL

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ABSTRACT

Introduction: Paragangliomas are usually benign slow-growing tumors, but they are locally invasive and can cause significant morbidity. The aim of this study was to characterize the presenting symptoms, secretory status, genetics, imaging features, treatment modalities, post-treatment complications and survival of patients with head and neck paragangliomas treated at a single institution.

Material and Methods: We retrospectively reviewed the clinical records of patients managed at our center between 1997 and 2020.

Results: Seventy-three patients were included in the study, encompassing 89 head and neck paragangliomas. Forty-eight patients (65.8%) were female and 15 (20.5%) had multiple tumor sites (including 10 patients with multicentric benign paragangliomas and five with disseminated malignant disease). Regarding location, our series encompassed 40 temporal bone paragangliomas (44.9%), 24 carotid body paragangliomas (27%), 22 vagal paragangliomas (24.7%), two laryngeal paragangliomas (2.2%) and one sinonasal paraganglioma (1.1%). Excessive catecholamine secretion was detected in 11 patients (15.1%). Sixty-four patients (87.7%) underwent genetic testing. Of those, 24 (37.5%) exhibited pathogenic succinate dehydrogenase complex germline mutations. Regarding patients who presented with untreated disease, 45 patients (66.2%), encompassing 55 tumors, underwent surgery as primary treatment modality, 20 (29.4%; 23 tumors) were initially treated with radiotherapy and three patients (4.4%, encompassing three solitary tumors) were kept solely under watchful waiting. Five-year overall survival was 94.9% and disease-free survival was 31.9%.

Conclusion: Head and neck paragangliomas are rare, slow-growing but locally aggressive tumors resulting in high morbidity but low mortality rates.

Keywords: Carotid Body Tumor; Cranial Nerve Neoplasms; Extra-Adrenal Paraganglioma; Head and Neck Neoplasms; Paraganglioma

RESUMO

Introdução: Os paragangliomas apresentam frequentemente um comportamento benigno e um crescimento indolente. Apesar disso, são localmente invasivos, podendo causar morbilidade significativa. O objetivo deste trabalho foi descrever as manifestações clínicas, atividade secretora, estudos genéticos e imagiológicos, modalidades terapêuticas, complicações e sobrevivência dos doentes com paragangliomas da cabeça e pescoço.

Material e Métodos: Estudo retrospetivo dos doentes com paragangliomas da cabeça e pescoço observados num centro hospitalar terciário entre 1997 e 2020.

Resultados: Foram incluídos no estudo 73 doentes, englobando 89 paragangliomas. Quarenta e oito doentes (65,8%) eram do sexo feminino e 15 (20,5%) apresentavam múltiplos focos tumorais (10 por multicentricidade e cinco por doença maligna disseminada). Foram incluídos 40 paragangliomas do osso temporal (44,9%), 24 tumores do corpo carotídeo (27%), 22 vagais (24,7%), dois laríngeos (2,2%) e um nasossinusal (1,1%). A secreção excessiva de catecolaminas foi detetada em 11 doentes (15,1%). Sessenta e quatro doentes (87,7%) foram alvo de teste genético. Desses, 24 (37,5%) exibiram mutações patogénicas do complexo succinato desidrogenase. Dos doentes com doença primária, 45 (66,2%; 55 tumores) foram submetidos a tratamento cirúrgico, 20 (29,4%; 23 tumores) a radioterapia e três (4,4%) ficaram sob vigilância. Aos cinco anos, a sobrevida global foi de 94,9% e a sobrevida livre de doença foi de 31,9%.

Conclusão: Os paragangliomas da cabeça e pescoço são tumores raros, de crescimento lento, mas localmente agressivos que resultam em elevadas taxas de morbilidade, mas baixas taxas de mortalidade.

Palavras-chave: Neoplasias de Cabeça e Pescoço; Neoplasias dos Nervos Cranianos; Paraganglioma; Paraganglioma Extrassuprarrenal; Tumor do Corpo Carotídeo

INTRODUCTION

Paragangliomas are tumors that arise from the paraganglionic system, which are aggregations of cells found throughout the body and are associated with vascular and neuronal adventitia.[1] Although they are usually benign slow-growing tumors, they are locally invasive and can cause significant morbidity.[2] In the head and neck these lesions can be classified as temporal bone paragangliomas (TBP); which include tympanomastoid and tympanojugular paragangliomas) and cervicocarotid tumors [comprising vagal paragangliomas (VP) and carotid body paragangliomas (CBP)]. Tympanomastoid paragangliomas arise within the inferior tympanic or mastoid canaliculi, while tympanojugular paragangliomas arise from the paraganglia of the adventitia of the jugular bulb.[3] CBPs arise from the carotid

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body, which is located in the carotid bifurcation, and VPs arise from the paraganglia along the vagus nerve.[4] While paragangliomas have been identified in up to 20 sites in the head and neck, they are extremely rare in locations other than the ones mentioned above.[2]

These tumors represent only about 0.6% of all head and neck tumors, with an estimated incidence ranging from 1 in 30 000 to 1 in 100 000.[3,5-7] CBPs and VPs usually present as a painless neck mass, in contrast with pulsatile tinnitus or hearing loss for TBPs.[8]

Paragangliomas can be sporadic or familial. It is now known that at least 30% of patients with a paraganglioma harbor a genetic mutation that increases their risk of developing these tumors and other neoplasia.[9] As nearly all germline mutations that lead to hereditary HNPs are attributable to succinate dehydrogenase complex (*SDHx*) genes, these tumors are extremely rare in neurofibromatosis type 1, Von-Hippel Lindau disease and multiple endocrine neoplasia type 2.[10-11]

The surgical management of these lesions is also associated with the possibility of cranial nerve palsies and risk of injury to vital vascular structures, especially in advanced cases, resulting in transient ischemic attacks or major cerebrovascular accidents, leading to permanent neurologic deficits.[2,12] These cardiovascular events may have long-standing cosmetic and/or functional implications.[12] Accordingly, the patient's expected lifespan and quality of life must be balanced against the tumor's predicted biological behavior.[2] Factors such as multicentricity, endocrine activity, malignancy and genetic predisposition further complicate an ever-changing algorithm, which trends towards individualized management.[2,12-14]

The aim of this study was to characterize the presenting symptoms, secretory status, genetics, imaging features, treatment modalities, post-treatment complications and survival of patients with head and neck paragangliomas (HNPs) treated at a single institution.

MATERIAL AND METHODS

Our study was conducted at the Department of Otolaryngology of the Instituto Português de Oncologia de Lisboa Francisco Gentil, a Portuguese tertiary cancer center, from May to December 2020. Considering this is a non-interventional study where data was retrospectively obtained, analyzed and anonymized, the need for ethics committee approval and informed consent was waived.

Study protocol

We retrospectively reviewed the clinical records of patients with HNP managed at our center between 1997 and 2020. We collected data regarding demographics (gender, age at presentation), presenting symptoms and physical examination findings, audiometric, secretory, genetic and imaging studies, pathology reports, treatment modality, post-treatment complications and functional outcomes, recurrence and survival.

The current protocol at our institution for patients with a possible HNP includes biochemical testing (24-hour urine fractionated metanephrines and vanillylmandelic acid; plasma free chromogranin A; 3-methoxytyramine is not available at our center), genetic testing, audiometric testing (pure-tone audiogram and tympanogram), site-specific imaging [computed tomography (CT) scan and magnetic resonance imaging (MRI) of the head and neck] and functional imaging [^{111}indium-octreoscan (^{111}In-Octreoscan), ^{18}fluorodeoxyglucose (^{18}FDG) positron emission tomography (PET)/CT, ^{68}gallium-DOTANOC (^{68}Ga-DOTANOC) PET/CT, or ^{123}metaiodobenzylguanidine (^{123}MIBG) scan].

Various classification systems were used, depending on tumor location. The Fisch and Mattox classification modified by Sanna was used for tympanomastoid and tympanojugular paragangliomas.[15] The Shamblin classification modified by Luna-Ortiz was used for CBP.[16] The Netterville classification was used for VP.[17] Other tumor locations are rare and lack staging systems.

Excessive catecholamine secretion was assumed when more than two-fold of fractioned urinary metanephrines and/or urinary vanillylmandelic acid and/or plasma free chromogranin A were observed. Values between the upper normal limit and two-fold elevation may represent false-positives and were considered doubtful.

Malignancy was assumed when metastatic lymph nodes, distant metastasis or a locally infiltrative pattern with gross invasion of adjacent tissues occurred. Multifocality was assumed when all tumors were located in the usual sites for paragangliomas.

Genetic tests were performed using Sanger sequencing or next-generation sequencing (NGS) for the detection of missense and indel mutations, and multiplex ligation-probe amplification (MLPA) for the detection of large deletions and insertions of the following genes: *SDHA*, *SDHB*, *SDHC*, *SDHD*, *VHL*, *RET*, *TMEM127*, *MAX*, *SDHAF2* and *EPAS 1*.

As for patients who presented with multiple, functioning, advanced and/or malignant lesions, a multidisciplinary meeting with the presence of Otolaryngologists, Oncologists, Radiologists, Radiotherapists and Endocrinologists was held to make decisions regarding the management of these patients.

Follow-up

For overall survival (OS) measurements, follow-up time was defined as the time between initial presentation at this institution for the tumor of interest and the date of the last medical appointment or death. For disease-free survival (DFS), follow-up time was measured from the conclusion of tumor treatment until the date of first recurrence, death or last contact. In cases where there was residual disease after primary treatment, DFS was considered zero.

Statistical analysis

Quantitative variables were expressed as mean ± standard deviations or as median ± interquartile range for data not normally distributed. Qualitative variables were expressed as absolute values and percentages. Kolmogorov-

Smirnov and Shapiro-Wilk normality tests were used to access the distribution pattern in quantitative variables. Student's *t*-test and one-way ANOVA were used to relate normally distributed continuous variables with primary outcomes (death and recurrence). Non-parametric tests (Mann-Whitney and Kruskal-Wallis) were used for ordinal and continuous variables with a non-normal distribution. χ^2/ Fisher's exact test was used for qualitative variables. Kaplan-Meier curves were determined for 5-year OS and DFS; qualitative variables were compared regarding survival. A *p* value < 0.05 was considered statistically significant. Statistical analysis was performed using SPSS 24.0 for Windows (SPSS Inc., Chicago, IL, USA).

RESULTS

Demographical & clinical characteristics

Seventy-three patients were included in the study, encompassing 89 HNP. Mean age at diagnosis was 56.5 years (range, 28 – 90 years). Forty-eight patients (65.8%) were female. Sixty-eight patients (93.2%) presented with untreated disease. Fifteen patients (20.5%) had multiple tumor sites (including 10 patients with multicentric benign HNPs and five with disseminated malignant disease).

Clinical manifestations varied greatly with tumor location (Table 1). Hearing loss (46.6%), neck mass (39.7%) and tinnitus (27.4%) dominated a wide list of presenting symptoms. In five patients (6.8%) the lesions were an incidental finding. In the analysis of preoperative cranial nerve deficits, the vestibulocochlear nerve was not taken into account because it would be difficult to differentiate the symptoms induced by the tumor from those induced by presbycusis. Vagal nerve palsy was the most frequent cranial nerve deficit at presentation (26%), followed by the hypoglossal (13.7%) and the glossopharyngeal nerves (12.3%). When analyzed

Table 1 – Clinical manifestations and tumor location

Characteristics		TBP n (%)	CBP n (%)	VP n (%)	Overall n (%)	Other n (%)	Multiple n (%)	*p*-value*
Patients	n (%)	29 (39.7)	14 (19.2)	12 (16.4)	73 (100.0)	3 (4.1)	15 (20.5)	
Symptoms	Hearing loss	22 (75.9)	1 (7.1)	1 (8.3)	34 (46.6)	0	9 (60.0)	**< 0.001**
	Neck mass	0	12 (85.7)	10 (83.3)	28 (38.4)	0	6 (40.0)	**< 0.001**
	Tinnitus	14 (48.3)	1 (7.1)	2 (15.4)	20 (27.4)	0	3 (20.0)	**0.004**
	Dysphonia	6 (20.7)	1 (7.1)	2 (16.7)	13 (17.8)	1 (33.3)	3 (20.0)	0.708
	Vertigo	5 (17.2)	0	0	7 (9.6)	0	2 (13.3)	0.146
	Dysphagia	2 (6.9)	2 (14.3)	2 (16.7)	7 (9.6)	0	1 (6.7)	0.290
	Otalgia	1 (3.4)	0	0	3 (4.1)	0	2 (13.3)	0.488
	Aspiration	2 (6.9)	0	0	2 (2.7)	0	0	0.547
	Headache	1 (3.4)	0	0	2 (2.7)	0	1 (6.7)	0.547
	Otorrhagia	1 (3.4)	0	0	1 (1.4)	0	0	1.000
	Epistaxis	0	0	0	1 (1.4)	1 (33.3)	0	**0.030**
	Incidental	0	2 (14.3)	1 (8.3)	5 (6.8)	1 (33.3)	1 (6.7)	0.082
Cranial nerve deficits	VII	4 (13.8)	0	0	6 (8.2)	0	2 (13.3)	0.218
	IX	7 (24.1)	0	1 (8.3)	9 (12.3)	0	1 (6.7)	0.456
	X	8 (27.6)	2 (14.3)	5 (41.7)	19 (26.0)	0	4 (26.7)	0.433
	XI	5 (17.2)	0	2 (16.7)	8 (11.0)	0	1 (6.7)	0.443
	XII	7 (24.1)	0	3 (25.0)	10 (13.7)	0	0	0.399
Catecholamine secretion	High	3 (10.3)	2 (14.3)	2 (16.7)	11 (15.1)	0	4 (26.7)	0.470
	Doubtful	4 (13.8)	3 (21.4)	3 (33.3)	12 (16.4)	0	1 (6.7)	
	Normal	20 (69.0)	4 (28.6)	5 (41.7)	39 (53.4)	2 (66.7)	8 (53.3)	
	Undetermined	2 (6.9)	5 (35.7)	1 (8.3)	11 (15.1)	1 (33.3)	2 (13.3)	
Malignant	Locally infiltrative	0	0	0	1 (1.4)	1 (33.3)	0	**0.017**
	Lymph nodes	0	0	0	2 (2.7)	0	2 (13.3)	
	Distant metastasis	0	0	0	3 (4.1)	0	3 (20.0)	
	Subtotal	-	-	-	6 (8.2)	-	-	
Genetic testing	*SDHB*	3 (10.0)	3 (30.0)	4 (28.6)	10 (15.2)	0	0	**0.005**
	SDHC	2 (6.7)	0	2 (14.3)	6 (9.1)	0	2 (22.2)	
	SDHD		1 (10.0)	2 (14.3)	8 (12.1)	0	5 (55.6)	

*: All *p*-values were obtained using the Monte-Carlo test, which compares the frequency of a given nominal variable considering the different tumor locations A statistically significant difference (**bold**) was found between the prevalence of hearing loss, neck mass, tinnitus and epistaxis at presentation. Multiple tumors were associated with malignancy and genetic mutations involving the *SDHx*.

by location, only two patients in the CBP group and none in the other locations group (non- TBP, non-CBP and non-VP) presented with cranial nerve deficits.

Thirty-one patients with TBP (77.5%) presented with suggestive otoscopic changes: the classically described blanching of the tympanic membrane, Brown's sign, was present in two patients, the 'rising sun' sign (tumor extension through the tympanic bone) was described in 16, a retrotympanic red mass with uncontrollable margins in six, a mass bulging the tympanic membrane in four and polyps/otorrhea in three. The remaining nine patients (22.5%) had an unsuspicious otoscopy.

Tumor characteristics

Location and classification

Our series included 40 TBP (44.9%), 24 CBP (27%), 22 VP (24.7%), two laryngeal paragangliomas (2.2%) and one sinonasal paraganglioma (1.1%). Tumor classification is summarized in Table 2.

Catecholamine secretion

Excessive catecholamine secretion was detected in 11 patients (15.1%). Endocrine activity is summarized in Table 1.

Imaging and other tumors

Most patients (n = 65, 89%) underwent both CT scan and MRI of the head and neck, with the remaining patients undergoing just one modality. ^{111}In-Octreoscan was performed in 56.1% (n = 41) of patients, ^{123}MIBG in 5.5% (n = 4), ^{18}FDG-PET/CT in 4.1% (n = 3) and ^{68}Ga-DOTANOC PET/CT in 2.7% (n = 2). Sensitivity for primary lesions varied: 100% for ^{18}FDG-PET/CT (3/3) and ^{68}Ga-DOTANOC PET/CT (2/2), 95.1% (39/41) for ^{111}In-Octreoscan and 50% for ^{123}MIBG scan (2/4). Six patients (8.2%) had at least another paraganglionic tumor outside the head and neck region: three due to distant metastasis and three due to multicentric tumors (two mediastinal and one mediastinal and mesenteric).

Table 2 – Tumor location and classification

	No. of patients (%)
Temporal bone	**40 (44.9)**
Class A	3 (3.4)
Class B	6 (6.7)
Class C	17 (19.1)
Class D	14 (15.7)
Carotid body	**24 (27.0)**
Stage I	11 (12.4)
Stage II	8 (9.0)
Stage IIIa	3 (3.4)
Stage IIIb	2 (2.2)
Vagal	**21 (23.6)**
Group A	7 (7.9)
Group B	10 (11.2)
Group C	5 (5.6)
Other	**3 (3.3)**
Larynx	2 (2.2)
Sinonasal	1 (1.1)

Note: The Fisch and Mattox classification modified by Sanna was used for tympanomastoid and tympanojugular paragangliomas.[8] The Shamblin classification modified by Luna-Ortiz was used for CBP.[9] The Netterville classification was used for VP.[10] Other tumor locations are rare and lack staging systems.

Malignancy

Six patients (8.2%) had a malignant HNP - three developed distant metastasis (two were VP and the other was multicentric HNP), two showed regional nodal disease (two TBP with neck and intraparotideal metastatic lymph nodes) and one (sinonasal) had a gross invasion of adjacent structures with highly suggestive histological findings after primary tumor resection. Malignancy rates and patterns are summarized in Table 1.

Genetic testing

At presentation, only three patients (4.1%) reported a known family history of paraganglioma.

Sixty-four patients (87.7%) underwent genetic testing. Of those, 24 (37.5%) exhibited likely pathogenic and pathogenic *SDHx* germline mutations – in 10 patients (41.7%) involving the subunit B (*SDHB*), in six (25%) the subunit C (*SDHC*) and in eight (33.3%) the subunit D (*SDHD*).

Genetic testing of direct relatives revealed similar mutations in five cases, two of which had a CBP in the presymptomatic phase.

Clinical characteristics according to genetic mutation are shown in Table 3. In patients with *SDH* germinal mutations, HNPs were diagnosed at an earlier age [t(59) = 3.804; p = 0.001], while *SDHC* cases did not show the typical female predominance [$\chi^2_{MC}(4) = 1.775$; p = 0.809].

Treatment and follow-up

The primary treatment characteristics are summarized in Table 4.

As for patients who presented with untreated disease (68/73), 45 patients (66.2%), encompassing 55 tumors, underwent surgery as primary treatment modality, 20 (29.4%; 23 tumors) were initially treated with radiotherapy and three (4.4%, encompassing three solitary tumors) were kept solely under watchful waiting. In two patients with multiple HNP who underwent surgery, two tumors were not addressed and kept under wait and scan. Preoperative embolization was performed in 64.4% (29/45) of patients who underwent surgical treatment.

By stratifying the treatment options throughout the years, we observed an increase in the number of patients treated with radiotherapy or under observation and a decrease in upfront surgery (χ^2_{KW} = 21.005; p = 0.002). The primary treatment modalities through the years are shown in Fig. 1.

The mean follow-up time was 91 months. Patients were usually kept under close surveillance for two years, with

Table 3 – Clinical characteristics according to genetic mutation

Characteristics		*SDHB*	*SDHC*	*SDHD*	Total
Total number of individuals with genetic mutation	n (%)	10 (41.7)	6 (25.0)	8 (33.3)	24 (100.0)
Gender, n (%)	M	4 (40.0)	3 (50.0)	3 (37.5)	10 (41.7)
	F	6 (60.0)	3 (50.0)	5 (62.5)	24 (58.3)
Age at diagnosis (years)	Mean ± SD	48.1 ± 13.6	55.0 ± 10.7	40.8 ± 9.9	47.4 ± 12.6
	Range	28 - 71	42 - 72	32 - 63	28 - 72
Tumor location, n (%)	TBP	3 (30.0)	2 (33.3)	0	5 (20.8)
	CBT	3 (30.0)	0	1 (12.5)	4 (16.7)
	VP	4 (40.0)	2 (33.3)	2 (25.0)	8 (33.3)
	Other	0	0	0	0
	Multicentric	0	2 (33.3)	5 (62.5)	7 (29.1)
Catecholamine secretion, n (%)	High	0	1 (16.7)	2 (25.0)	3 (12.5)
	Doubtful	4 (40.0)	1 (16.7)	2 (25.0)	7 (29.1)
Malignant, n (%)		2 (20.0)	1 (16.7)	1 (12.5)	4 (16.7)
Paraganglioma outside the head and neck	n (%)	0	1 (16.7)	2 (25.0)	3 (12.5)
Affected relatives (n)	Mutation	2	1	2	5
	Tumor	0	0	2	2

M: male; F: female; SD: standard deviation; succinate dehydrogenase complex germline mutations –subunit B (*SDHB*), C (*SDHC*) and D (*SDHD*)

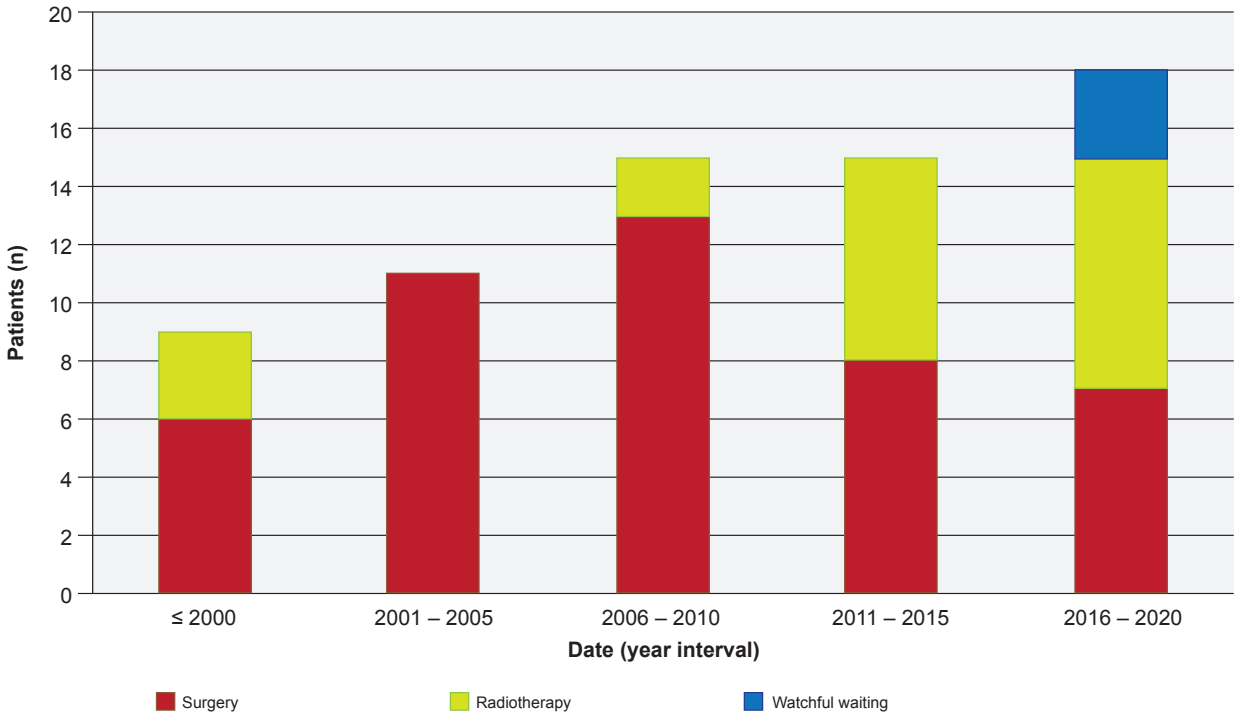

Figure 1 – Primary treatment modalities through the years

follow-up appointments every three months, then every six months until five years and after that once a year.

Surgery

Complete resection with no further evidence of disease was achieved in 47.2% (25/53) of tumors (22 patients). These rates varied according to tumor location: 100% for laryngeal paragangliomas (2/2), 61.5% for CBP (8/13), 57.1% for VP (8/14), 30.4% for TBP (7/23) and 0% for nasal paragangliomas (0/1). Patients with single tumors achieved remission and are currently alive and disease-free (n = 19).

Twenty-four patients, encompassing 28 tumors, had persistent disease after surgery – twenty with residual disease (incomplete initial removal) and four had local recurrence. Nine patients were kept under wait and scan, 14 underwent radiotherapy and one was reoperated. Five of these patients were stable in subsequent scans, one is presently in remission, two died due to unrelated causes and one died due to disease progression associated with multinodular goiter.

Table 4 – Treatment characteristics (primary treatment)

Modality	No. of patients (%)	No. of tumors (%)
Surgery	**45 (66.2)**	**55 (66.3)**
Not evaluable margins	2 (2.9)	2 (2.4)
Complete resection	22 (32.4)	25 (30.1)
Residual/recurrent disease	24 (35.3)	28 (33.7)
+ watchful waiting	9	
+ radiotherapy	14	
+ surgery	1	
Non-surgical	**23 (33.8)**	**28 (33.7)**
Radiotherapy	20 (29.4)	23 (27.7)
Watchful waiting	3 (4.4)	5* (6.0)
Total	**68 (100.0)**	**83 (100.0)**

*: In two patients with multiple HNP who underwent surgery, two tumors were not addressed and kept under surveillance

All lesions treated with surgery and subsequent radiotherapy showed stability or partial response except one – a patient with metastatic bone disease, who underwent further treatment with ^{177}Lutetium peptide receptor radionuclide therapy (^{177}Lu-PRRT) and zoledronic acid.

Two patients were excluded from resection status analysis: one patient with a Class IIIB CBP became comatose following a perioperative cardiac-arrest; another patient with a class IIIA CBP was referred to the vascular surgery department (surgery was performed solely by Vascular Surgeons).

Radiotherapy

Concerning the patients initially treated with radiotherapy, 35% (7/20) showed partial response with tumor size reduction; 40% (8/20) remained stable, 5% (1/20) underwent surgery immediately after and 15% died (3/20 – one due to stroke, one due to aspiration pneumonia and one due to unrelated causes). One patient is yet to undergo comparative imaging.

Observation

Three patients with 76, 63 and 72 years of age, who had solitary tumors (Shamblin stage II and I CBP with no other symptoms except for a neck mass and an asymptomatic Netterville group A VP, respectively), were kept under wait and scan and are awaiting comparative tests. Two patients with multiple HNP underwent surgery for more symptomatic and locally advanced tumors, while small CBPs (Shamblin stage I) were kept under watchful waiting and remained stable.

Secondary treatment

Regarding the five patients who were referred from other institutions, two had progressive metastatic disease and were treated with ^{177}Lu-PRRT – one died (male, 36 years) after a 40-month follow-up and the other (female, 55 years) is alive but with considerable pain due to bone metastasis. One 79-year-old female with a class B TBP had been under surveillance at another institution and was referred for radiotherapy due to the development of facial palsy (no lower cranial nerve deficits). Two other patients underwent surgery at another institution but were referred for radiotherapy due to symptomatic residual disease – one died due to unrelated causes and the other one is stable.

Complications and survival

Surgery-related cranial nerve deficits are presented in Table 5. Patients with multiple HNPs were excluded from this table due to the difficulty in attributing a deficit to a specific surgery. As the surgical management of some class B and all class C TBPs will result in maximal conductive hearing loss (blind sac closure is an integral part of both the subtotal petrosectomy and the type A infratemporal fossa approach), vestibulocochlear nerve function was not taken

Table 5 – Surgery-related cranial nerve deficits and sympathetic trunk injury for solitary tumors

Structure	TBP (16) n (%)	CBP (8) n (%)	VP (7) n (%)	Other (3) n (%)
VII	10 (62.5)	1 (12.5)*	0	0
IX	1 (6.3)	1 (12.5)	2 (28.6)	0
X	2 (12.5)	3 (37.5)	4 (57.1)	0
XI	1 (6.3)	1 (12.5)	1 (14.3)	0
XII	1 (6.3)	1 (12.5)	5 (71.4)	0
Bernard-Horner	0	0	1 (14.3)	0

*: All facial nerve palsies grade III or higher (according to House-Brackman classification) appeared after a type A infratemporal fossa approach except one – patient with a CBP who developed a paralysis compatible with marginal mandibular branch injury

into account.

All facial nerve palsies grade III or higher (according to the House-Brackman classification) appeared after a type A infratemporal fossa approach except for one – patient with a CBP who developed a paralysis compatible with marginal mandibular branch injury.[18]

All the patients with VPs who were treated surgically had their vagal nerve sacrificed intraoperatively (three patients already had a preoperative vagal nerve deficit).

Postoperative aspiration was present in seven patients, in whom VOX® implants were used.

Besides the aforementioned complications, other complications included: a retroauricular cutaneous fistula (in a patient with a TBP who underwent surgery and subsequent radiotherapy), iatrogenic cholesteatoma and a liquor fistula. These were all managed with subsequent surgery.

Five-year OS was 94.9% and DFS was 32.4%. Despite the differences in DFS according to location (laryngeal 100%, CBP 46.2%, TBP 27.5%, VP 25%, sinonasal 0%), no statistically significant differences were found [$\chi^2_{KM}(4) = 5.672$; $p = 0.225$]. Advanced TBPs were associated with postoperative facial nerve palsy (U = 14.500; $p = 0.007$), residual/recurrent disease (U = 73.000; $p = 0.045$) and lower DFS [$\chi^2_{KM}(3) = 10.163$; $p = 0.017$]. DFS was affected by VP classification [$\chi^2_{KM}(2) = 6.364$; $p = 0.042$]. None of these differences were found for CBPs. No statistically significant differences in DFS were found for germline mutation cases [$\chi^2_{KM}(1) = 0.639$; $p = 0.424$].

DISCUSSION

This study is, to the best of our knowledge, the most complete Portuguese cohort regarding HNPs. Although some authors find it illogical to include all HNPs in the same study due to the undeniable different tumor characteristics and management, we feel a lot of information regarding tumor behavior can be retrieved from these series.

In agreement with most series, a female predominance and a peak age of presentation in the sixth decade of life were noted. These assumptions change for germinal mutation cases, which typically present at an earlier age and predominantly in males.[8,12-14]

Multicentricity rates in the literature range from 7% to 58%, with reports of a higher incidence for familial cases.[12] In our series, 20.5% of patients were seen with multiple paragangliomas and it increased to 29.1% in the subset of patients with germinal mutations. As recommended by Cass *et al*, whole-body imaging should be obtained if excessive catecholamine secretion and/or susceptible gene mutations are detected.[19] All patients with multiple tumors (multicentric or metastatic) in our series showed excessive catecholamine secretion or a germline mutation, confirming this premise.

HNPs are classified based on their anatomical location, with CBPs comprising the most common location (≈ 60%) due to a higher mass of normal paraganglionic tissue in this area.[2,12] In our series, TBP was the most common subtype of HNP (44.9% *vs* 27% for CBP). We speculate this may be related with the fact that other surgical specialties in Portugal (such as vascular, maxillofacial and general surgery) may intervene and follow-up a significant quota of the CBPs, while TBPs are exclusively approached by Otorhinolaryngologists (and occasionally in collaboration with neurosurgery).

In the CBP group, only two cranial nerve deficits were reported at presentation, while in both the TBP and VP groups up to 42 cranial nerve deficits were described. Surgery-related cranial nerve deficits were also significantly lower for the CBP group. These findings overlap with other studies.[12,13]

The current literature states that HNPs rarely secrete catecholamines (< 4%) due to their predominantly parasympathetic origin.[19] However, our series showed a higher frequency of functioning tumors (15.1%). This may be due to the fact that, in some series, only a small percentage of patients undergo biochemical testing. Nevertheless, this is a much higher value compared to the previously reported 1%.[20]

Rates of malignancy range between 0% and 19% in the literature.[12-13] Defining malignancy in HNPs is a controversial issue due to the difficulty of distinguishing true metastasis (paraganglionic cells in non-neuroendocrine tissue) from multicentric primary neoplasms, which explain conflicting rates among different studies.[19]

Genetic testing is now recommended in all patients presenting with phaeochromocytoma and paraganglioma.[10,11,19,21-23] The increasingly lower costs of gene panel testing combined with the ineffectiveness of family history screening for predicting syndrome risk (due to overall low penetrance) has led to this recommendation.[19] Although it may help predicting tumor behavior and prognosis, the ultimate goal of genetic testing is to identify those patients who should be screened and to diagnose this condition at a presymptomatic stage. Early intervention can then be considered with the objective of maintaining a normal quality of life.[2,23] The minimum age for which genetic testing should be performed depends on the specific causal gene. Based on current literature, the proposed minimum age for starting genetic testing is five years for SDHB and 10 years for the other *SDHx* genes.[23] Additionally, genomic information is also allowing the identification of specific tumorigenic pathways that are relevant in the development of potential therapeutic targets for metastatic or inoperable paragangliomas.[23]

Complete surgical resection represents the only curative treatment option for HNPs which hinders the comparison of results between treatment modalities. The generally benign slow-growing course of these tumors (reflected in the high OS), the possibility of multiple treatments *per* tumor, cumulative sequalae and unrelated deaths further complicate this comparison. Most of our patients underwent surgical treatment, which is in agreement with other reports.[12,13,24] However, this traditional approach has profoundly changed over the years, mainly due to a better understanding of the behavior of HNPs allied with improvements in the fields of

diagnostic imaging and radiation therapy, which have led to an emphasis on observation and non-surgical treatment in many patients.[14] In our series, primary radiotherapy showed a control rate (size stability or decrease) of at least 75% while surgery with no other active treatment showed satisfactory results (complete resection or partial resection with remission or stability in further scans) in 58.4%. This paradigm shift is well documented in our series and has been noted in other institutions.[12,25]

As we mentioned above and in agreement with other reports, the surgical treatment of non-CBPs (tympanojugular and VPs) is associated with a more significant functional impairment when compared with CBPs (namely speech and swallowing, but also facial nerve function for tympanojugular paragangliomas). This has prompted some institutions to consider non-surgical treatment as an alternative in patients with non-CBP, either with active surveillance or radiotherapy.[12] On the other hand, recent evidence has brought to light several pitfalls concerning primary treatment with radiotherapy. Notch signaling, a fundamental molecular pathway which promotes radioresistance in glioma cells, is commonly activated in HNPs.[26,27] MicroRNAs such as mir-34b/c and miR-200c, known to be significantly down-regulated in these tumors, were shown to enhance radiosensitivity by promoting radiation-induced apoptosis in various cancer types.[26,28-31] Other studies have also shown that the histopathology and vascularization of HNPs remained almost unchanged after radiation.[26,32-34]

Despite conflicting evidence, the more we know about a given patient with HNP, the more we will be able to justify one treatment option over another. Therefore, data such as age, symptoms (particularly lower cranial nerve function), classification, secretory activity, multicentricity and malignancy is crucial to make treatment recommendations based on an algorithm built for each tumor location.[13] TBP and VP staging systems have proven to be essential from a prognostic standpoint. The fact that this does not apply to CBPs may be due to the low number of class III CBPs. In our series we could not establish an association between location and survival, as we mentioned above. Nevertheless, it has shown to clearly influence the risk of sequalae.

Our study has some limitations. First, due to its retrospective nature, it is subject to selection and information bias. Second, some data regarding posttreatment comparative tests was not yet available and it could have been important to compare different treatment modalities. Third, this study concerns the experience of a single department. In the future, a multicenter prospective study should be carried out.

CONCLUSION

Head and neck paragangliomas are rare, slow-growing but locally aggressive tumors resulting in high morbidity but low mortality rates. Current practice demands a thorough evaluation in association with diagnostic tests before recommending a therapeutic option. Genetic testing is now widely recommended in order to diagnose this disease at a pre-symptomatic stage. A lifelong commitment is required as rehabilitation of surgical sequalae and clinical surveillance play a fundamental role in ensuring the provision of appropriate care.

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AUTHORS CONTRIBUTION

LC: Design of the work, data acquisition and analysis, literature research, first draft of the paper.

FC: Statistics analysis.

SD: Critical review of the endocrine and genetic mutation themes.

LF: Design of the work, critical review of the treatment and follow-up themes.

PM: Design of the work, database management.

MM: Database management.

PROTECTION OF HUMANS AND ANIMALS

The material submitted conforms with regulations currently in force regarding research ethics. The work was performed in accordance with the principles of the Declaration of Helsinki updated in 2013.

DATA CONFIDENTIALITY

The authors declare having followed the protocols in use at their working center regarding patients' data publication.

PATIENT CONSENT

Obtained.

COMPETING INTERESTS

The authors have declared that no competing interests exist.

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