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Artículo Original

Head and Neck Paragangliomas: Management of 32 cases including Peptide Receptor Radionuclide Therapy

Paragangliomas da cabeça e pescoço: Apresentação de 32 casos e experiência com Análogos da Somatostatina

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Abstract

Background: Paragangliomas (PG) account for 0.6% of all tumors in the head and neck region. Widely distributed, predilection for carotid body, jugular foramen, tympanic plexus and vagus nerve ganglia is observed. The management of these tumors remains a challenge with three possible options: surgery, radiation therapy and wait-and-see policy. Regardless treatment must be individualized.

Aim: We conducted a revision of all paragangliomas treated in the Otolaryngology Head and Neck Surgery Department of the Portuguese Institute of Oncology, in Porto. The aim of this analysis is to characterize clinical features, investigations until diagnosis, type of treatment and results.

Methods: Retrospective study (Analysis of 40 years).

Results: Our population involved 32 patients aged between 25 to 75 years who had been treated in the last 40 years. Of the 32 PG, 24 were jugulotympanic; 6 were carotid body lesions and 2 vagal paragangliomas. One patient has bilateral and multiple tumors. Just 2 cases were hereditary.

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Conclusion: Clinical presentation and histological diversity makes the management of head and neck paragangliomas a challenge. Although in cases with similar histology, there is no consensus between surgery and radiotherapy as treatment options. Therefore we consider that treatment must be individualized, taking into account patient`s age, tumor localization and size, multicentricity, and preexisting cranial nerve deficits. PRRT (Peptide Receptor Radionuclide Therapy), an investigational option adopted for some of our cases, could be an alternative or instead a complementary treatment modality for paragangliomas in several stages.

Keywords: Paragangliomas, Therapy, Surgical therapy, Radionuclide, Radiotherapy

RESUMO

Introdução: Os tumores glómicos, também denominados por paragangliomas (PG) correspondem a 0,6% dos tumores da região da cabeça e pescoço. Nesta àrea geralmente localizam-se na bifurcação carotídea , no gânglio nodoso do nervo vago ou a nível do osso temporal. A vigilância clínica, a radioterapia e a exérese cirúrgica com ou sem embolização prévia, são consideradas opções terapêuticas válidas, pelo que, cada caso deverá ser individualizado.

Objectivo: Analisar os casos estudados e tratados no Instituto Português de Oncologia do Porto (IPO-Porto). Esta revisão visa descrever as manifestações clínicas, a etiopatogenia, o diagnóstico, o tratamento e o follow-up.

Material e Métodos: Estudo retrospectivo (40 anos de experiência)

Resultado: A nossa amostra é constituída por 32 doentes com diagnostico de paragangliomas da região da cabeça e pescoço, com idades compreendidas entre 25 a 75 anos, que foram submetidos a tratamento no IPO-Porto, tendo em consideração os últimos 40 anos. Dos 32 paragangliomas: 24 são jugulo-timpânicos; 6 localizam-se no corpo carotídeo; e 2 são paragangliomas vagais. Um doente apresentou tumores múltiplos e bilaterais. Em dois casos foi detectada anomalia genetica.

Conclusão: O tratamento dos PG continua a ser foco de discussão na literatura médica. A cirurgia é geralmente o tratamento de eleição, no entanto, em casos particulares outras modalidades de tratamento, primário ou complementar, poderão ser implementadas. A terapêutica com radiofármacos é uma opção promissora no tratamento destes tumores.

Palavras-Chave: Paragangliomas, Tratamento Cirúrgico, Radionuclídeos, Radioterapia

Introduction

Head and neck paragangliomas (HNPs) are neuroendocrine neoplasmas derived of neural crest cells, arising from head and neck paraganglia that are closely aligned along the parasympathetic nervous system[1]. The incidence is estimated at between 1/30000 and 1/100000 inhabitants/year, which represents approximately 0.6% of all head and neck tumours [1] .Widely distributed, these tumors has special predilection for the carotid body at bifurcation of the common carotid artery (CCA) (carotid body tumor - CBT) (60-70%); jugular foramen and/or tympanic plexus(jugulotympanic paraganglioma - JTPG) (30-40%) and vagus nerve ganglia (vagal paragangliomas - VPG) (2-3%)[1]. Laryngeal, orbital or sinonasal PGs very rarely present in this region[2].

Paragangliomas may occur sporadically or as inherited, familial tumors. Published prevalence of the familial forms ranges between 10% and 50%; in approximately 35% of patients with PG, there is a hereditary predisposition, related to known genetic alterations[2]. It is now recognized that several types of these tumors are inherited through mutations of genes that encode for succinate-dehydrogenase (SDH) subunits D and B (SDHD and SDHB). Patients with germline mutations of subunit D almost invariably have multicentric lesions[1]; and are responsible for up to 70% of the familial cases; these genes are also altered in approximately a third of HNPs, apparently sporadic[3]. Multifocal PG are not infrequent, being found in up to 20% of the sporadic forms, and up to 80% in the familial. Among the hereditary forms, The SDH complex subunit D (SDHD) mutations represent the greatest risks of being multifocal and of developing pheochromocytoma. Classic tumor syndromes associated with a high incidence of paragangliomas include multiple endocrine neoplasia type II (MEN II), von Hippel-Lindau disease and neurofibromatosis type I (NF I)[4].

HNPs are classified on the basis of their location and microscopic appearance. Usually they are non secreting tumors, and frequently present as a neck mass or associated to symptoms due to compression or infiltration of adjacent head and neck structures[1].

Most paragangliomas are benign. However some cases of malignancy have been described. Rates of malignancy have been reported as 2 to 19% depending to the location of the tumors: 16 a 19% for VPG; 6% for CBT and 2-4% for JTPG[1]. Prognosis is directly related to the location. Patients with CBT have the best outcome, whereas those with skull base tumors have a less favorable prognosis, because of the increased difficulty in achieving total resection[2].

Wait-and-see policy, radiotherapy (RT) or surgery are recognized treatment options, but treatment selection must be individualized. Of these, surgery is the only curative possibility. However, because surgery may be complicated by significant morbidity, especially in patients with larger tumors, it is considered by some as controversial.

In this article, we describe clinical features, locations and tumors size, treatment options with special emphasis for PRRT (Peptide Receptor Radionuclide Therapy) as a new possible option, complications and follow-up of all cases treated in the ENT Department of Portuguese Institute of Oncology, in Porto.

Material and Methods

This is a retrospective study approved by the Ethics Committee, including 32 patients with HNPs who had been treated over a period of forty years in the ENT Department at Portuguese Institute of Oncology, in Porto.

For this analysis were reviewed the records of all patients, with special emphasis to clinical and imagiological features, location and size of the tumors, treatment options, complications and results. We also review the literature.

In our service, testing for detecting genetic mutations of HNPs has been requested since 2010. The complementary diagnostic tests included CT scan with contrast; MRI, studies of catecholamine and its metabolites in urine, and for some of them somatostatin gammagraphy scanning. Arteriography was not systematically requested for diagnostic purposes; it was performed in only PG cases scheduled for surgery to plan tumour embolisation tumoral in the days before surgery. In follow-up, MRI and Galium DOTA NOC were used.

The CBT were reclassified according to the *Shamblin* classification. For the JTPG cases, we used the *Sanna* classification (modified by *Fish*). There is no generally accepted system for the classification of VPG.

The criteria used in the management of isolated PGs were: for the surgery treatment were choosed patients younger than 65 years old, in a good state of health, capable of compensating for a possible lower cranial nerve deficit or patients older than 65 years with secretory symptoms, malignant tumours, tumours with intracranial mass effect, tumours with prior paralysis of lower cranial nerves, tumours previously submitted to radiotherapy that had experienced significant progression after finishing that radiotherapy; for the radiotherapy were choosed patients aged more than 65 years with tumours that had undergone significant growth.

The management of multifocal PG (in this study there is one case) depended on various factors, that included, in the first place, individual patient factors, such as age and general health state; and , in second place, genetic factors, such as the presence of germinal SDH mutations and the predisposition to develop malignant or metachronous tumours; and lastly, tumour factors, bearing in mind tumour number, size and location, existence or not of intradural extension, bilaterality, initially deficit cranial nerves and the surgical risk of them.

Results

Thirty two patients were included, most female (78%) (n= 25 female; n=7 male), aged between 25 and 75 years (mean: 52.8; median:57).

Twenty four of these patients had a JTPG (75%), 6 a CBT (19%), and 2 a VPG (6%) (table 1). Most of these paragangliomas were solitary, with the exception of a young patient who had multicentric paragangliomas, in atypical locations: pterygopalatine fossa (PPF), paravertebral space and vagus nerve. This patient was the only that had a positive familiar history of paragangliomas and the genetic study showed a germline mutation of subunit D of SDH enzyme. There was other case that germinal mutation was found, in this case, a germinal mutation of SDHB in a CBT. Malignant PG, defined as the presence of distant metastasis, was found in 1 patient. There were no secreting tumors.

Table 1: Clinical cases.

	Number of cases	Clinical Apresentation	Preoperative cranial nerve palsies	Type of treatment	Posoperative cranial nerve palsies	Persistent/ Recurrent disease
CBT	**6:** 2 type I * 4 type II *	Large and no tender neck mass located anterior to the SM	X e XII	**4 patients-** Surgery: cervical approach **2 patients-** PRRT	The same of preoperative, without new complications	**2 patients** (pos – surgery and PRRT, respectively)
VPG	**2**	One case with multiple and bilateral paragangliomas: PPF,on the parapharyngeal and paravertebral spaces.	X	Surgery: 1.Transcervical approach 2.Mixed approach(Caldwell-Luc associated with Wilson approach) + collaboration of other specialties	Without new complications (X)	**1 patient** (residual disease)
JTPG	**24:** 4 type B ** 9 type C **: 4C1; 3C2; 2C3 11 type D **: 8 De;3 Di	Hearing loss + pulsatile tinnitus + middle ear mass in hypotympanum	XII: 5 patients X: 4 patients VIII and VII: 2 cases XI: 1 case	**18 patients**: Surgery: 1. retroauricular transmastoid and cervical extension approach Infratemporal type A approach **2 patients**-RT **4 patients** - PRRT	The same of preoperative more new sequelae: 33%(n=8 patients) facial paralysis ; 16% (n=4) deafness and dizziness; 8% (n=2) hoarseness	**14 patients:** 7 patients with persistent disease pos surgical treatment 7 patients with recurrent disease (5 pos surgical treatment; 1 pos RT and 1 pos PRRT

CBT: carotid body tumor ; **VPG:** vagal paraganglioma; **JTPG:** jugulotympanic paraganglioma; **SM:** sternocleidomastoid muscle; ***** according to the *Shamblin* Classification ; ****** according to the *Sanna* classification (modified by *Fish*); **PPF:** Pterygopalatine fossa; **PRRT:** Peptide receptor radionuclide therapy; **RT:** Radiotherapy

Post treatment all patients were followed as outpatients for 12 to 53 months (mean: 37,2; median:36). Follow-up included clinical and imagiological examinations.

Carotid body tumors (CBT)

Clinically most of patients presents with a large and no tender neck mass, located anterior to the sternocleidomastoid muscle at the level of the hyoid bone. One patient had a concomitant deficit in the XII nerve. Other presented hoarseness with months of evolution. In this patient physical examination showed palsy of vocal cord and, bulging of the lateral pharyngeal wall. One patient presented mutation of SDHB. According to the Shamblin classification, 2 were type I tumors and 4 type II.

Four tumors were removed by cervical approach without previous embolization (figure 1). Preoperative cranial nerve palsies were not resolved with the surgery, but no new postoperative complications were observed. The treatment of one patient with a type II CBT was supplemented with RT and 3 years after with PRRT, due to recurrent disease. In this patient three years after were diagnosed metastases in liver. This patient was that presented mutation of SDHB.

In two patients PRRT was the primary treatment option. Only in one patient was observed a good clinical response to this treatment.
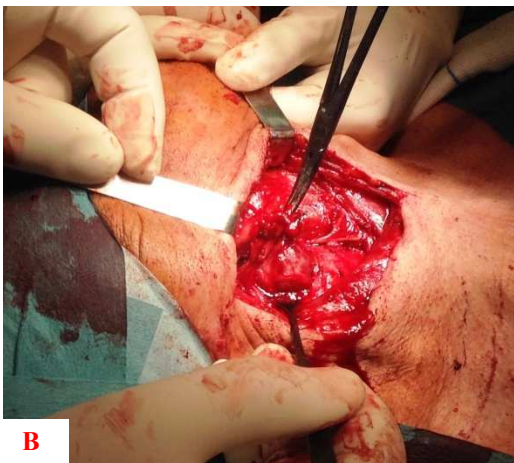

Figure 1: Case of CBT.

A: CBT right with overexpression of somatostatin receptors.

B, C, D: Intraoperative pictures - tumor resection by transcervical approach.

Vagal Paragangliomas (VPG)

Our series include two patients. One of these patients has multicentric and bilateral paragangliomas, with atypical locations (figure 2) and had a positive familiar history of paragangliomas and a germline mutation of subunit D of SDH enzyme. It was a man, 25 years old, presented with nasal obstruction associated with recurrent episodes of epistaxis. CT scan detect a lesion located in the left PPF, and reveal the presence of other lesions compatible with paragangliomas located on the left parapharyngeal and on the right paravertebral spaces. The excision of the paraganglioma located in PPF was performed by a mixed approach (Caldwell-Luc associated with Wilson approach). After surgery, residual disease was observed by PET, and the patient received radiotherapy. Until the present disease remain controlled.

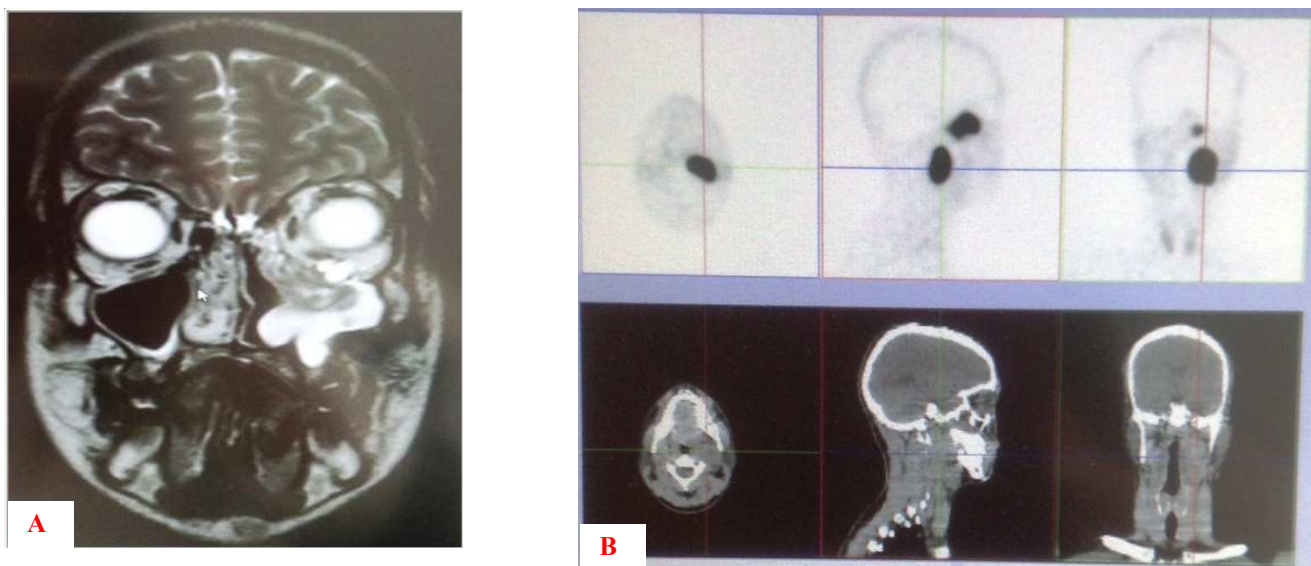All the patients with VPG treated surgically had a postoperative paralysis of the vagal nerve.

Figure 2: One case – multiple and bilateral paragangliomas.

A: MRI maxillofacial revealing lesion on the left PPF , reaching the ipsilateral nasal cavity, the left chamber of the sphenoid sinus, the inferior orbital fissure and the ipsilateral vidian channel; intense vascularization after contrast.

B: PET 68 Ga-SRP : paraganglioma on the left PPF, on the left parapharyngeal space and on the right paravertebral space.

Jugulotympanic Paragangliomas (JTPG)

Our series include 24 JTPG (figure 3). In the majority of patients the most common complaint was hearing loss associated with pulsatile tinnitus. On examination, patients presented a middle ear mass, usually located in hypotympanum.

Based on CT and MRI findings, 4 of the JTPG were classified as Sanna type B, 9 as type C (4 C1; 3 C2; 2 C3) and 11 as type D (8 De; 3 Di). Cranial nerve palsies were seen in patients with more advanced stages (5 cases – 20%): XII nerve was involved in 5 patients; X nerve in 4; VIII and VII nerves in 2 cases and XI nerve in 1 case.

Surgical treatment was first-line in 18 tumors. The approach chosen for resection of these PGs depended on the location and extend of the tumor: for type B JTPG was performed a retroauricular transmastoid (with extended facial recess with intact canal wall) approach ; for types C and D was performed a infratemporal type A approach without facial nerve translocation. Residual tumor was observed in 7 patients, and in these treatment was complemented by RT or PRRT. Recurrences were observed in 5 (27%) patients over a follow-up period between 12 to 56 months.

Radiotherapy was performed in two patients (1 with a type B PG and other with type C). It was effective in one type B PG.

In four patients treatment option was PRRT (all type C tumors) and, three responded effectively to treatment. PRRT was also a treatment option in 8 patients with persistent disease or recurrence, and in six patients there was response to treatment.

No signs of malignancy were observed in any tumor after histologic examination. Cranial nerve palsies detected in the preoperative period remained postoperatively. The following sequelae have been reported after surgery: facial paralysis in 8 (33%) patients, deafness and dizziness in 4 (16%), and hoarseness in 2 (8%).

Globally, 9 patients (75%) (3 cases of primary treatment and 6 cases of secondary treatment) responded to PRRT according the established criteria (decrease of the mean SUVt (Tumor Standardized Uptake value) and imagiological and/or symptomatic stability after three treatment cycles. The symptoms observed were tinnitus and headaches. The decrease of the mean SUVt was higher in patients with no previous surgery or radiotherapy.
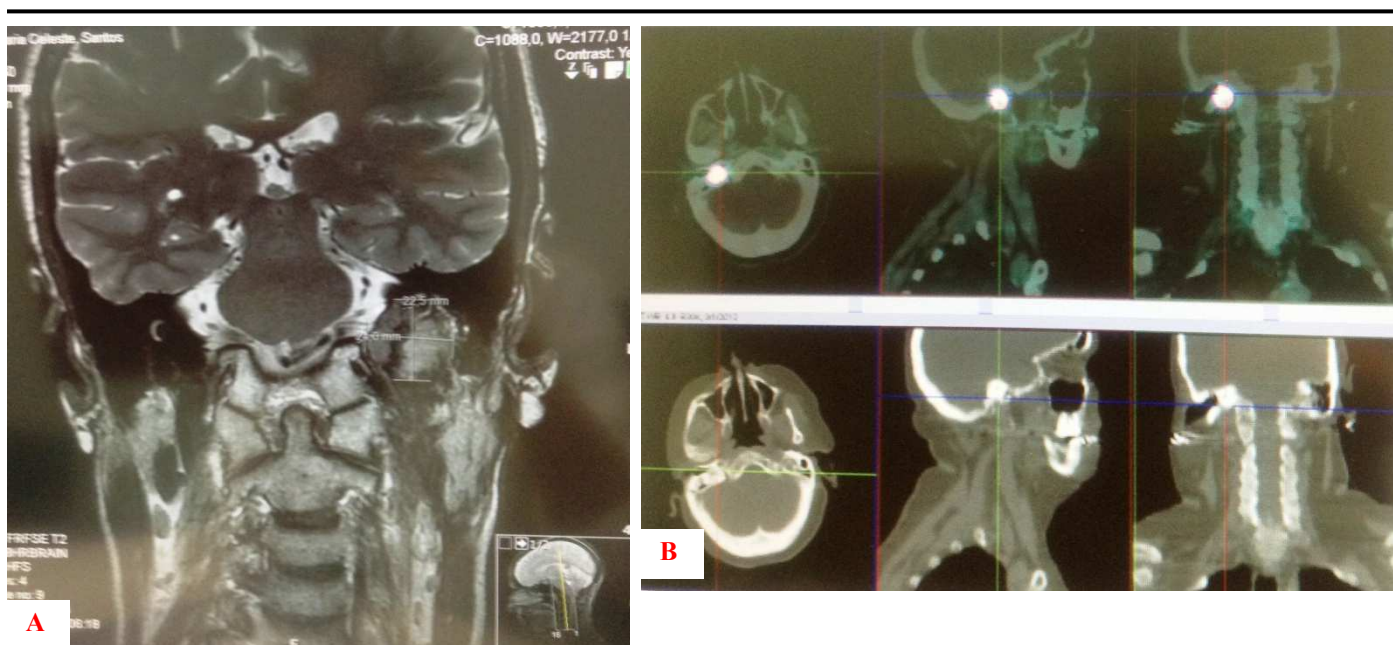

Figure 3: Cases of JTPG.

A: cervical MRI reveal lobulated lesion of the left jugular foramen , which fills the hypotympanum and mesotympanum and displays intense enhancement after contrast.

B: 68 Ga-PET SRP: focus of intense hyperfixation of 68 Ga-DOTA-NOC in the jugular-tympanic region on the right suggesting PG.

Discussion

In our series of 32 patients, JTPG represent 75% of all tumors; CBT 18% and VPG 6%. The predominance of JTPG is in agreement with similar series[1,2,5]. The incidence of PG is usually higher in females. Twenty five of our patients (78%) were females, in concordance with some other series as Jackson et al[1] were 106 (79%) of 134 cases were also females.

In the initial management of the patient with HNP, a complete examination of the ORL sphere is essential. This must include assessment of facial and lower cranial nerve function, which can occasionally be altered on diagnosis. Personal history usually reveals a painless cervical mass in the case of a CBT or a VPG, or a history of hearing loss and pulsatile tinnitus when a JTPG is involved. The family history is an important as that of the patient. For this reason, patients should be systematically questioned about antecedents, including the causes of death for relatives, as a possible tumour history in the family that would have gone unnoticed can be found behind these deaths. Until recently, the hereditary nature of these tumours ranged around 10%. However, over the last years, many studies have demonstrated that approximately a third of PG cases are caused by germinal mutations [6]. There are 4 basics syndromes of hereditary PG (PGL1-PGL4), and we know the genetic base that causes all of them. The genes responsible codify subunits or cofactors of SDH, which is located in mitochondrial complex II and carries out a fundamental role in the Krebs cycle. These mutations of the SDH genes cause 70% of the familial forms of PG [7]. Most hereditary PG originate from mutations in SDHD and SDHB, respectively responsible for the PGL1 and PGL4 syndromes. In this study one patient had a germ line mutation in SDHB, but without family history of PG and other had a germ line mutation in SDHD, and a familiar history of PG and multicentric tumors. The presence of SDHB mutations are associated with worse disease free survival after resection in patients with CBT; and this was showed in one case of CBT[8].

Most cases presented with single tumors, except in the case of a young man who had multiple HNPs, in atypical locations. The economic cost linked to the request for genetic tests must be taken into consideration. Some authors indicate that they should be limited to patients with a family history. However, in the last few years, various studies have shown that approximately a third of patients with PG, apparently sporadic, present alterations in the SDHD, SDHB and SDHC genes [7]. At present, we recommend asking for genetic tests systematically for all patients with paraganglion tumours, especially if the patient is aged less than 50 years, or if they are family, malignant or multifocal cases.

Is generally accepted that malignancy in paragangliomas is characterized by the presence of metastasis to non-neuroendocrine tissues. In one of our patients, metastasis in non-neuroendocrine tissues (in liver) appear confirming malignancy. Locally aggressive behavior of paraganglioma does not by itself imply malignancy. Clinical findings remain the most reliable criteria for malignancy, that are most frequents in case of functional paragangliomas. VP are the HNPs with the greatest potential for malignant transformation. Less than 10% of HNPs are malignant [9].

After taking the clinical history and carrying out the physical examination of the head and neck region, the use of complementary imaging tests is indispensable. Contrast CT and MRI imaging with gadolinium are the initial tests of choice, given that they allow use to have an idea of anatomical location, tumour exten-

sion and limits, vascularization and relationship with neighboring structures. In CBT , the external carotid is typically displaced in an anterior-medial direction, while the internal carotid is located posteriorly and laterally; in contrast, in VPG cases both carotids (internal and external) are usually displaced in an anterior direction and internal jugular vein is located in the posterior area[10] . High-resolution CT is useful to evaluate jugular and tympanic paragangliomas as it presents a very sensitive imaging procedure for the diagnosis of bony destructions and their extension, and this is important to classify those tumors. The preoperative classification of JTPG is essential, since the operative approach will be chosen depending on the tumor stage. MRI with gadolinium provides useful information, revealing the characteristic "salt and pepper" appearance and ruling out the presence of other PG in the cervical-cranial area. Angiography, as it is an invasive procedure with possible adverse effect, is a test we prefer to avoid for diagnosis; we only request it for planning PG embolization in the days before surgery. And in surgical patients, only one was embolized. This procedure is used routinely in some institutions with the aim of reducing the risk of bleeding. Paradoxically this patient that has not a very big tumor and surgical bleeding was expressive. There are opinions referring that this procedure can be associate with cerebral complications, and, otherwise, the plane of cleavage can be obscured owing to an acute inflammatory response to embolization particles[4].

In our centre, we have somatostatin receptor gammagraphy available, which lets us confirm the nature of the PG and search for possible multifocal tumours. The somatostatin receptor image has sensitivity greater than 90% by using 111 In-octreoide[11].

The different therapeutic options include surgery, radiotherapy, PRRT therapeutic; or the combined use of all of these. Due to very slow progression of the disease, in some cases a "wait and scan policy" may be employed. In the spite of multiple possibilities of treatment, the only option that is curative and that guarantees complete resection of the PG is still surgery. However, and because of PG´s vascularity and involvement of critical vascular and neural structures, the total removal of these lesions is accompanied by significant morbidity. The choice of treatment method depends on many factors, such as the age and general health of the patient, location and extensions of the tumor, tumor size and growth rate, carotid artery involvement, cranial nerve deficits and potential risks connected with particular treatment modality.

Surgical approach has been during many years the standard treatment to paragangliomas. Cure rates between 89 to 100% have been reported in literature[12]. In this serie, cure rates with surgical approach was 42%. This low percentage could be explained by the fact that in this series predominate advanced tumors, mainly in the group submitted to surgery (predominance of stage D JTPG – 46%).

In CBT tumors, surgery was the treatment of choice. Resection in CBT tumors is carried out using a cervical approach, controlling the large veins proximally and distally. In experienced hands, there is generally low incidence of lesion of cranial nerves. In this study, none of the 6 patients in our study with a CBPG have had postoperative cranial nerve deficits as complication of surgery. As would be expected, the rate of neural complications is higher in patients with Shamblin type II and III tumors. The reported incidence of cranial nerve palsy as a complication of carotid body tumor surgery ranges from 10 to 40%[13].

Most authorities consider surgery to be the treatment of choice in cases of VPG[10]. These tumours can generally be approached only through via cervical. Unfortunately, VPG surgery generally brings about in-

traoperative sacrifice of the vagal nerve, which involves important comorbidity, especially in patients of advanced age. For that reason, in the latter type of patients, is preferable to observe the tumour and, if it drows, radiate it.

The approach chosen for resection of a temporal paraganglioma depends on the location and extend of the tumor. In patients with tympanic PG (classes A and B), surgery clearly represents the best option, because it is associated with a low risk of damaging the cranial nerves. In cases categorized as Fish A and B, a transmeatal approach or a surgical approach via mastoidectomy, including posterior tympanotomy and exposure of the facial nerve, may be adequate[14]. The different treatment modalities have been a matter of discussion in international literature when it comes to JTPG´s types C and D. Thanks to development and implementation of microsurgical techniques, it is possible to resect these tumors completely, and local tumor control can be achieve in 80-90% of cases [14]. JTPG types C and D are usually resect via an infratemporal approach. It is important to note that because these tumors are adherent and occasionally invade cranial nerves IX-XII, a higher complication risk concerning cranial nerve deficits is anticipated for the postoperative outcome. As shown by *Moe et al* [15], the ability to preserve the lower cranial nerves is directly proportional to the size of the tumor, with worse outcomes when intradural tumor is encountered (83% of preservation in class C tumors and 55% in class D). In respect to the postoperatively sequelae of JTPG, the dominant group in our series was facial palsy, seen in 8 patients (33%) – according to the House-Brackmann classification: 4 patients present a grade IV; 2 grade V and 2 grade VI; deafness and dizziness in 4 (16%); hoarseness observed in 2 (8%). Current literature shows that the long-term success rate following surgical therapy of jugular tumors is 72-95%; however, it should be noted that comparison of results emerging from different studies is difficult because parameters such as Fisch classification and follow-up intervals are not consistent between studies [14]. In thirty-eight percent of cases residual disease was observed in JTPG treated surgically.

In contrast to surgery, the objective of radiotherapy is controlling tumour growth, but it is not a curative option. Radiotherapy is a palliative treatment, not a cure, and there is a potential risk of radiation-induced malignancy. This may be a treatment option in this type of tumors namely in patients with large lesions where surgical morbidity and probability of recurrent disease is higher[16]. Because it is a non invasive procedure, associated with few complications and, high rates of local control, this option may be selected as a first-line treatment[16]. Hinerman et al reported tumor control rates of 96 to 100% after 45 Gy of radiation therapy for cervical PG[17]. However, radiotherapeutic control is difficult to define, because it is based on cessation of tumor growth rather than in tumor disappearance[18]. In this series RT was initially used in cases of unresectable tumors, patients with poor general condition, or those who refused surgery. The RT was mainly a second treatment option, in cases of tumoral persistence or recurrence.

In April 2011 our Center adopt PRRT (peptide receptor radionuclide therapy) treatment concept to these tumors as an alternative or, as complementary treatment in some patients. For patients selection, first is necessary to analyze with Galium DOTA NOC and if positive, patients agree and no contraindications were present, treatment was effectuated with three cycles with Lutetium-labelled peptide $_{117}$Lu-DOTA-TATE. Until now 14 patients have been treated with this method. Ten of these (71%) had JTPG and four (29%)

CBT. After treatment, the majority of patients (71%) showed decrease of symptoms (tinnitus and/or aural plenitude) and we can observe stabilization and/or decrease of the tumor SUV (standardized uptake value). These aspects were most frequent in JTPG tumors, which appear to respond better than CBT. This could be explained by the fact that patients with CBT showed an inferior pre-treatment SUVt than JTPG which may correspond to an inferior concentration of somatostatin receptors in the cellular membrane of these lesions. One explanation is that the fixation of $_{117}$Lu-DOTA-TATE in these tumours is diminished and consequently the treatment is less efficient. In fact CBT are considered to have a more aggressive behavior pattern than JTPG. They also have distinct embryological origin, and clear histological differences. JTPG are related with the first and second brachial arch, and CBT are related with the third brachial arch[19]. Histologically JTPG are often fragmented and tend to be comprised of smaller nests of cells and high vascularity[20]. Pre-treatment tumor SUV seems to be the factor with greater influence in treatment response. Patients in which PRRT was the first treatment option showed a slightly higher SUVt and a greater decrease of SUVt after therapy than patients in which PRRT was used as a complementary treatment. One possible explanation is that surgical manipulation or RT could damage somastotatin receptors in the cellular membrane of the tumor cells, and therefore decrease somastotatin analogues uptake, compromising the diagnosis and treatment[21].

In the case of multifocal tumours (one case in this study), we believe that knowing all the modalities of treatment is especially relevant, and there are many parameters that should be analysed: patient age and general state of health, biological behavior of the tumour, tumour number, location and size, presence or absence of genetic mutations, bilaterally, presence of cranial nerves upon diagnosis and their surgical risk and, of course, the individual´s personal circumstances. In young patients, below the age of 65 years, many other parameters should be analysed. First of all, the presence of genetic mutations: patients with mutation of SDHD (our case), as they have a tendency to develop new lesions over time, should be promptly operated before the appearance of new metachronous tumours. Secondly, cranial nerve function, tumour number and size and, of course, the existence of bilateral lesions should be analyzed.

Patients with these tumors must undergo prolonged periods of follow-up because recurrences can develop after many years. In our series recurrence rate was 21%. Once again, the predominance of advanced stage tumors in this series will explain this elevated rate of recurrence. The follow-up should include clinical examination and radiological imaging.

Conclusion

The management of HNPs remains a challenge and continues to be controversial in the medical literature. Treatment must be individualized, with clinicians taking into account patient`s age, tumor localization and size, multicentricity, and preexisting cranial nerve deficits. There is no consensus regarding the choice of the better therapeutic option: surgery, radiotherapy, peptide receptor radionuclide therapy or even expectancy. Although surgery is the only curative option, is still controversial because it may be complicated by significant morbidities[3].

Conflicts of interest: No conflict of interest was declared by the authors.

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