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Case report
Olgu sunumu

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Contribution of radiation therapy of head and neck paragangliomas: About 6 cases presentation

Baş ve boyun paragangliomalarında radyasyon tedavisinin katkısı: 6 vaka sunumu

Sanae Ghammad [1], Fadwa Allouche [1], Terrab Fatima Zahra [1], Ghita Chebihi Hassani [1], Alami Zineb [1], Bouhafa Touria [1], Hassouni Khalid [1]

[1] Radiotherapy Department at University Hospital Center of Fez, Morocco

ORCID ID of the authors
SG: 0000-0002-7940-8396
FA: 0000-0002-6793-4911
TFZ: 0000-0001-6508-5066
GCH: 0000-0003-2714-1957
AZ: 0000-0003-3349-1793
BT: 0000-0002-9857-1594
HK: 0000-0002-1442-255X

Abstract

The neck's paraganglions are bilateral nodular structures, with the same embryological origin which is the cephalic neural crest. They have a branchiomeric distribution. They have an important secreting function during the embryonic life, and then regress when the adrenal medulla starts functioning. Then only carotid and aortic paraganglions have chemoreceptor, baroreceptor and endocrine proved functions. The paragangliomas are tumors developed at the expense of paraganglions by proliferations of the chief cells (of type I) most of the time. Generally these tumors exhibit a slow growth rate, most often presenting asymptomatically as a space occupying mass lesion witnessed clinically or radiographically. The secreting tumors are very rare (5%). The benignity is the rule but the localization near noble structures makes it a highly risky tumor. This disease is often monofocal but it may also be part of a multifocal disease (6%). Advances in imaging have facilitated the diagnosis and the assessment of this disease. Diagnosis is generally made through a combination of clinical findings and radiographic studies. Surgery is the treatment of choice through total subadventitial resection, and rebuilding of the carotid axis when necessary. Surgery may lead to significant morbidity, resulting from major cranial nerve injury and especially at a late stage in the evolution of the disease. The preoperative embolization can facilitate ablation and reduce morbidity. Precisely, external radiotherapy can de indicated for recurrences, tumoral operating residues, and counter indications.

Keywords: Paraganglioma, Radiotherapy, Head and neck, Pheochromocytoma

Öz

Boynun paraganglionları, sefalik sinir kreti olan aynı embriyolojik kökene sahip iki taraflı nodüler yapılardır. Branşmerik dağılımları var. Embriyonik yaşam boyunca önemli bir salgılama fonksiyonuna sahiptirler ve adrenal medulla çalışmaya başladığında gerilerler. O zaman sadece karotis ve aort paraganglionları kemoreseptör, baroreseptör ve endokrin kanıtlanmış fonksiyonlara sahiptir. Paragangliomalar, çoğu zaman baş hücrelerin çoğalmasıyla (tip I) paraganglionlar pahasına geliştirilen tümörlerdir. Genellikle bu tümörler, klinik veya radyografik olarak tanık olan bir yer kaplayan kitle lezyonu olarak asemptomatik olarak ortaya çıkan yavaş bir büyüme hızı gösterir. Salgılanan tümörler çok nadirdir (%5). Benign olması kuraldır ama asil yapılara yakın lokalizasyon onu oldukça riskli bir tümör yapar. Bu hastalık genellikle monofokaldir, fakat aynı zamanda multifokal bir hastalığın parçası olabilir (%6). Görüntüleme alanındaki ilerlemeler, bu hastalığın teşhis ve değerlendirmesini kolaylaştırmıştır. Tanı genellikle klinik bulgular ve radyografik incelemelerin bir kombinasyonu ile yapılır. Cerrahi, total subadventitial rezeksiyon ve gerektiğinde karotis ekseninin yeniden inşası ile tercih edilen tedavi yöntemidir. Cerrahi, önemli kranial sinir yaralanmasından kaynaklanan ve özellikle hastalığın evriminde geç bir aşamada ciddi morbiditeye yol açabilir. Preoperatif embolizasyon ablasyonu kolaylaştırabilir ve morbiditeyi azaltabilir. Kesin olarak, dış radyoterapi nüks, tümörlü çalışma artıkları ve karşı endikasyonlar için gösterilebilir.

Anahtar kelimeler: Paraganglioma, Radyoterapi, Baş ve boyun, Feokromositoma

Introduction

Paragangliomas (PGL) of the head and neck are rare, slow-growing, generally benign tumors of neuroendocrine cells associated with the peripheral nervous system that commonly involve the carotid body, jugular bulb, vagal ganglia, and temporal bone. Treatment options include surgery, radiotherapy (RT), stereotactic radiosurgery (SRS), and observation. This article briefly reviews our 45-year institutional experience treating this neoplasm with RT.

Paraganglia cells originate from the neural crest but differentiate into sympathetic and parasympathetic subtypes that can give rise to paraganglioma [1]. Sympathetic PGL secrete norepinephrine, parasympathetic PGL are non-secretory and typically occur in head and neck region like carotid body PGL and jugulotympanic PGL. In fact PGL can occur from the base of skull to the pelvic, anywhere there are paraganglia. Unlike other types of cancer, there is no test that determines benign from malignant tumors.

Corresponding author / Sorumlu yazar:
Ghammad Sanae
Address / Adres: Department of Radiotherapy, Chu Hassan II Hospital, Fez, Morocco
e-Mail: sanoua1010@gmail.com

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The diagnosis is focused on clinical signs and imaging. The reference treatment is surgery, but radiotherapy is an excellent therapeutic alternative for inextirpable tumors and can be indicated in case of recurrence for these tumors which are readily recurrent. Approximately 50% of patients with recurrent disease experience distant metastasis and the five years survival in the setting of metastatic disease is 40% to 45%. Long term follow up is therefore recommended for all individuals with PGL [2-5].

Genetic aspect

The genetic predisposition to HNPGLs and adrenal/extra-adrenal PGLs caused by heterozygous mutations by SDHD, SDHC, and SDHB is transmitted in an autosomal dominant fashion with age-dependent and incomplete penetrance [6-8]. Mutations in the SDHD gene show a parent-of-origin effect (transmitted mostly from the father) [4,5]. Despite this pattern of inheritance, SDHD shows bi-allelic expression in normal tissues and neural crest derived cancers with no promoter hyper-methylation in neuroendocrine tissues and related tumors [9]. In 2009, Hao et al. [8] evaluated a previously reported large Dutch family with an autosomal-dominant pattern of PGLs; they identified a mutation (G- to A- transition at nucleotide 232 of exon 2) in the SDHAF2 gene. The pattern of inheritance seen in this family was suggestive of an SDHD-like inheritance. However, more studies are needed to elucidate the mechanism. More recently, mutations in SDHA were reported in a limited number of kindred with PGL and/or PCC (figure 1).

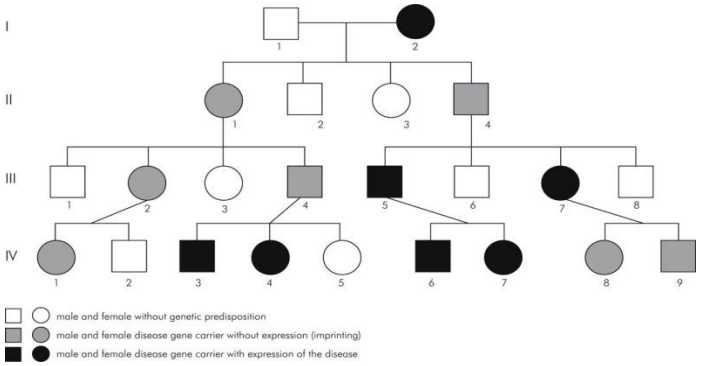

Figure 1: Imaginary example of a family with hereditary paragangliomas and genomic imprinting. The pedigree has four generations (I-IV). Expression of the disease skips one or two generations. In these generations, the genetic predisposition is present. In the first generation (I) the mother (I 2) is a carrier of the paraganglioma disease gene and has expression of the disease. Her daughter (II 1) inherited the mutated paraganglioma gene, but will not develop paragangliomas. She will transfer the mutated paraganglioma gene to two of her children (daughter III 2 and son III 4). These children will not develop the disease, but pass the predisposition to the next generation. The granddaughter of (II 1) IV 1 has the predisposition but no expression, whereas the grandson IV 3 and granddaughter IV 4 have both the predisposition and expression of the disease. The son (II 4) of I 2 has also inherited the disease gene from his mother, but will not have symptoms. His son (III 5) is a paraganglioma carrier and will have complaints just the same as his sister III 7. His children (IV 6 and 7) have predisposition for paragangliomas and will have the disease. The son and daughter (IV 8 and 9) of III 7 do inherit the mutated paraganglioma gene from their mother, but will not have symptoms (10)

Case presentation

Case 1

A 41 year-old female complained of a right hearing loss since 2 months, her past medical history was unremarkable and no similar cases were found in her family. Her physical examination did not reveal any others abnormalities. The CT scan and the MRI of the head and neck were performed and showed a tumor process of the middle and outer ear (figure 2). A biopsy was performed showing a paraganglioma (figure 3-5).

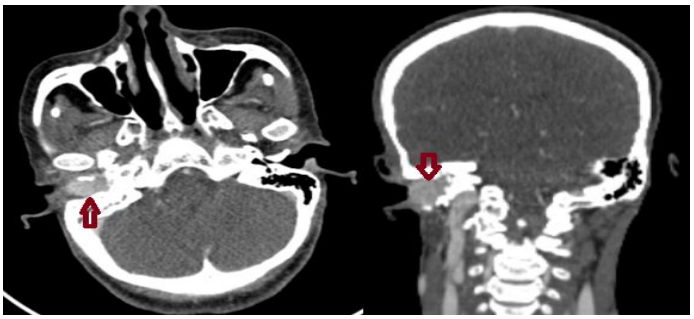

Figure 2: Axial scan images showing a paraganglioma of the right ear

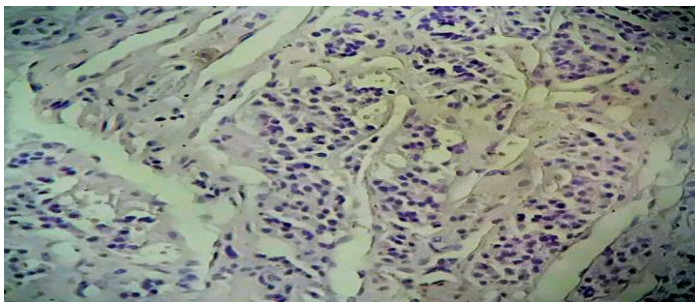

Figure 3: Histological aspect typical of a paraganglioma of the patient N°1 showing a tumor proliferation arranged in nests (HESX200)

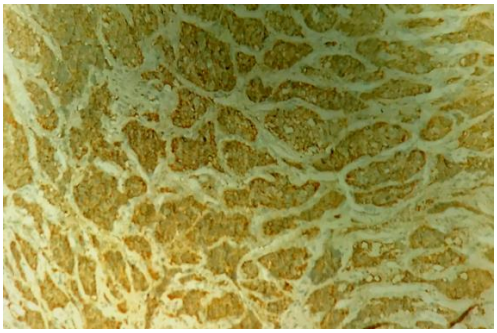

Figure 4: Immunohistochemical aspect expressing synaptophysin by tumor cells

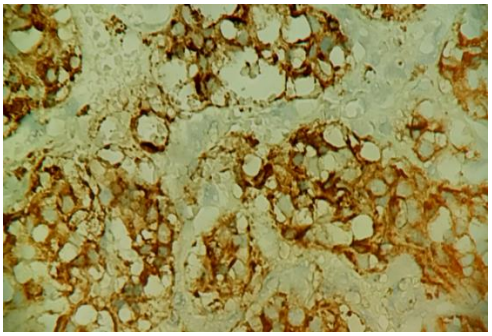

Figure 5: Immunohistochemical aspect expressing chromogranin by tumor cells

View of the difficult location of the tumor an exclusive IMRT radiotherapy has been at a dose of 50.4 Gy (28 fraction of 1.8Gy) (figure 6). After a follow up of 14 months, the case was stable and the patient did not complain of obvious discomfort.

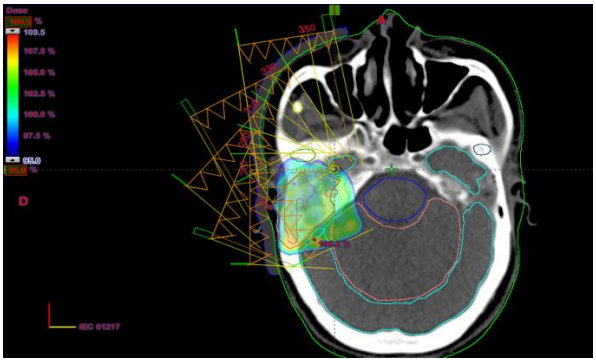

Figure 6: Radiotherapy IMRT of the right ear paraganglioma

Case 2

A 58 year-old female complained of a right otorrhagia. The past medical history and the family's history were negative and the clinical examination eliminated other primary lesion. The CT scan and the MRI of the head and neck showed a paraganglioma of the apex petrous with cavernous extension (figure 7). Given the location and the tumor volume, an exclusive IMRT have been realized at a dose of 60 Gy (figure 8). After a follow up of 15 months, the case was stable with clinical improvement.

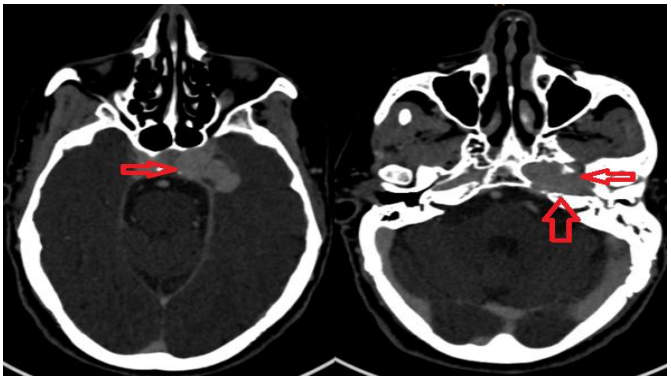

Figure 7: Axial scan images showing a paraganglioma of the left apex petrous with cavernous extension

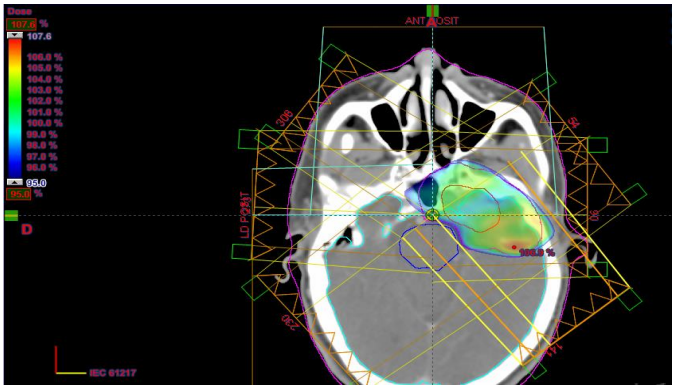

Figure 8: Radiotherapy IMRT of the apex petrous paraganglioma

Case 3

A 59 year-old female complained of a non-painful right lateral cervical mass progressively increasing in volume for the last month. The past medical history and the patient's family history were negative. Physical examination did not reveal any serious abnormalities except the right lateral cervical mass.

The cervical CT scan and the MRI showed an adherent mass to 160 the right carotid, very extensive locally in favor of a carotid paraganglioma. Account of the extent of the lesion, the patient received an external radiotherapy IMRT at a dose of 50 Gy in 25 fractions (figure 9), allowing a local control maintained with a 14 month follow-up.

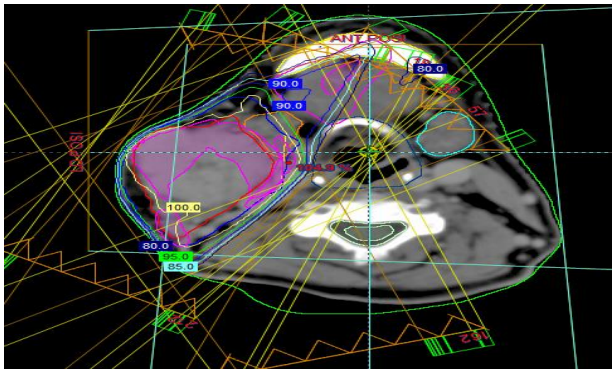

Figure 9: Radiotherapy IMRT of the big carotid paraganglioma

Case 4

A 69 year-old female was treated for a carotid paraganglioma, four years ago, and complained, for the second time, of a lateral cervical mass. The feature in the CT scan and the MRI of the head and neck confirmed recurrent homolateral carotid paraganglioma (figure 10). The patient received a 3D conformational radiotherapy at a dose of 50 Gy (figure 11). After the end of the treatment the patient was followed for 16 months and we noticed a clinical improvement and the tumor did not recrudesce.

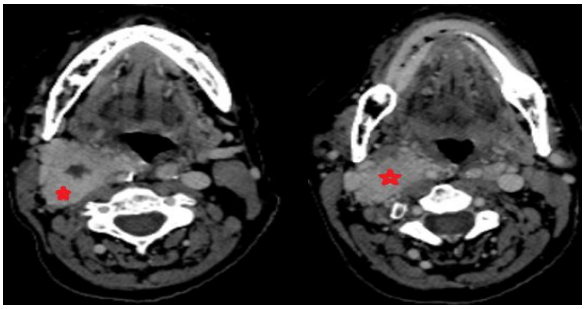

Figure 10: Axial scan images showing a left cervical paraganglioma

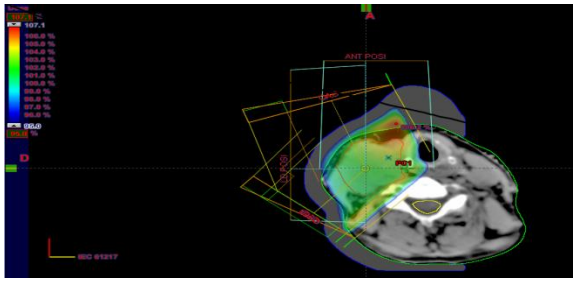

Figure 11: 3D conformational radiotherapy of the carotid paraganglioma

Case 5

A 47 year-old female complained of a lateral cervical mass for the last months. The past medical history was negative.

The CT scan and the MRI of the head and neck showed a huge mass in favor of a carotid paraganglioma (figure 12). An exclusive 3D conformational radiotherapy was delivered at a dose of 50 Gy (figure 13). After 6 months, the patient presented a tumor progression.

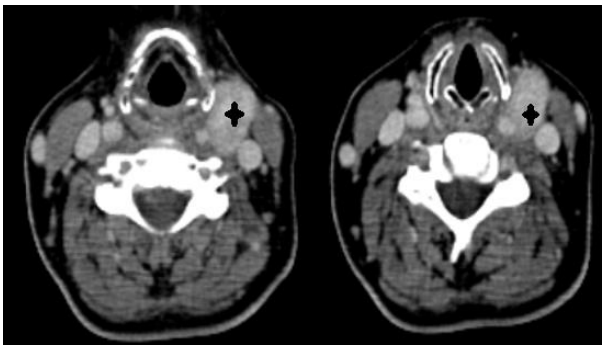

Figure 12: Axial scan images showing cervical paraganglioma

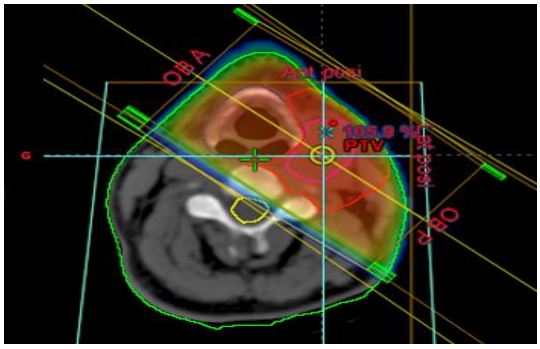

Figure 13: 3D conformational radiotherapy of the carotid paraganglioma

Case 6

A 45 year-old female complained of a left non painful lateral cervical swelling for the last year, the past medical history was negative. The cervical CT scan showed a well-limited left laterocervical mass of 8x7 cm, hypervascularized rapidly enhancing after injection of contrast product (figure 14).

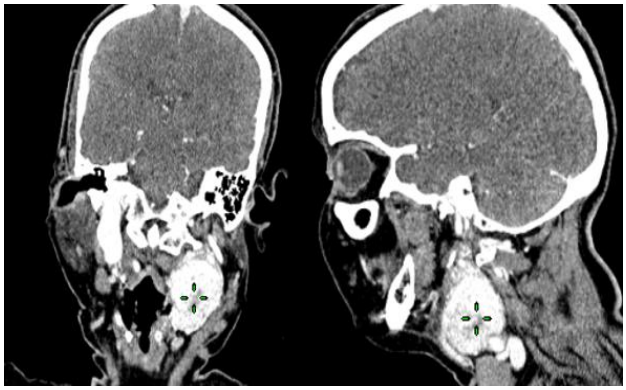

Figure 14: Two CT scans of the patient. Coronal to left and axial to a new carotid paraganglioma left (green sign) raised after injection

A biopsy was performed and confirmed a carotid paraganglioma. Faced with the impossibility of surgery, the patient received a 3D conformational radiotherapy at a dose of 54Gy (figure 15). After a follow up of 14 months we noticed a stability and clinical improvement.

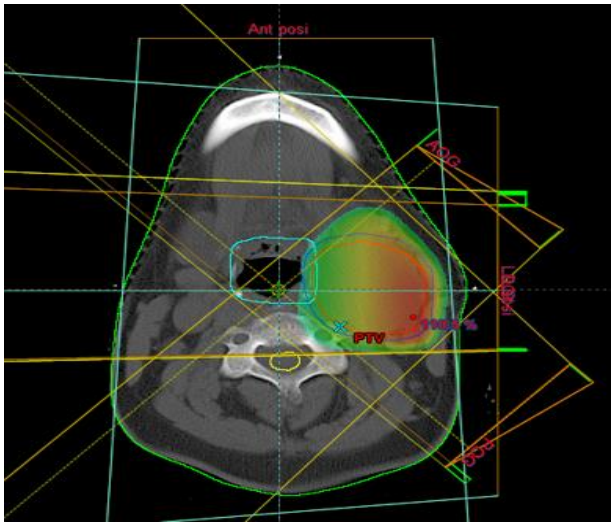

Figure 15: 3D conformational radiotherapy of the carotid paraganglioma

Features common

The six patients followed for head and neck paragangliomas; they are all female, the median age was 45.5 years (between 33-69 years).

The first symptom of consultation was a latero-cervical mass in 4 patients; the others are diagnosed with hearing loss and otorrhagia. All patients received scan imaging with MRI in 4 patients. The diagnosis was made in front of the clinical and radiological assessment in 4 patients and before the histological examination in the 2 others. All the tumors were considered unresectable, hence the indication of exclusive radiotherapy, at the dose between 50 and 60 Gy, 3 patients received intensity-modulated radiotherapy and the three others received conformational 3D radiotherapy. Median follow-up was one year, tumor stability was observed in 5 patients, and tumor progression was observed in a patient with carotid paraganglioma.

Discussion

PGL are rare, affecting 2 to 5 people per million per year. PGL are slowly growing tumors, presented as painless masses and have a culture doubling time of approximatively 42 years. Up to 30% of PGL appear to present in a hereditary manner and to date current research has stressed the increased importance of genetic predisposition in the development of PGL.

The diagnosis of PGL remains a challenge because patient do not present with characteristic signs and symptoms and, if untreated, PGL can have a devastating outcome even the tumors are potentially low grade malignant; however invasive biological behavior have been reported. Patients can be asymptomatic or symptomatic depends on their location, so clinical suspicion for PGL often begins with the patient history and is confirmed with biochemical testing [11], for this measurement of plasma and urinary metanephrine levels has long been used effectively in the diagnosis of PGL; also is bases on imaging finding [12] although there is no consensus on the order in with radiologic test should be performed for patients with suspected neural crest tumors; in fact locating and staging these tumors requires a combination of anatomic imaging with computing tomography or magnetic resonance imaging and functional imaging [13].

Thus, patients with PGL ultimately require follow-up because metastatic disease or recurrence can appear even after decades free of disease, the follow-up of these patients remains clinical, radiological and biological. And the best prognostic is that of carotid topographies [14].

The HNPs incidence is estimated to be at around 0,001%.Carotid body tumor represents the most common type, other PGL that are frequently detected in the head and neck include jugular PGL and tympanic PGL [15].

HNP surgery is a challenge to the surgeon because of the tumor's location in the vicinity of important blood vessels and cranial nerves. As well as pre-operative impairment of nerve function, surgery may result in deficits of cranial nerves VII, VIII, IX, X, XI, and XII [16].

From a retrospective study of Gilbo et al. [17] From 131 patients with 156 benign paragangliomas of the temporal bone, carotid body, jugular bulb, or glomus vagale were treated with RT at the University of Florida; a median dose of 45 Gy in 25 fractions. The mean and median follow-up times were 11.5 years and 8.7 years, respectively. Conventional RT, 86 patients (55%); non-coplanar stereotactic RT (SRT), 14 patients (9%); and intensity-modulated RT (IMRT), 56 patients (36%); in our study there are three patients treated with conventional RT and the three others with IMRT [17]. The treatment options for patients with head and neck paragangliomas include surgery, fractionated RT, and observation. The choice of treatment depends on tumor size and location. Five of 156 (3.2%) tumors recurred locally at 1.3 years, 4.4 years, 4.9 years, 8.1 years, and 8.4 years after RT [17].

A recent systematic review from Suarez et al focused on the management of jugular and vagal paragangliomas and found that the likelihood of local control was better after RT (P=0.002) and that the probability of a major complication was lower (p =0.003) compared with surgery. Although there are fewer data pertaining to SRS, which is suitable for skull base tumors; the

advantage of SRS compared with RT is convenience; the disadvantage is that the risk of hearing loss is 50% [18-20].

A fourth management option is observation, which is a reasonable approach for asymptomatic patients with a limited life expectancy.68 However, physicians taking this approach should recognize that cranial nerve deficits that may result from tumor progression are typically permanent, and should be weighed against the relatively low morbidity of RT [17].

Conclusion

The diagnosis of the neck paraganglioma is often late. The surgical treatment of the advanced forms is technically difficult and is a source of peripheral neurological after-effects. The tumors operated at an advanced stage are the most incriminated by far. The radiotherapy remains a complementary (additional) treatment to the surgery and can even represent an alternative with convincing result.

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