Manuscript Accepted Early View Article

Journal Name: Journal of Case Reports and Images in Oncology

doi: To be assigned

Early view version published: August 18, 2017

How to cite the article: BELHAJJAM L, ELMASNAOUI A, KOUADIR A, BOUHAFA T, ELMAZGHI A, HASSOUNI K. Paraganglioma: Complex entity with different locations. Literature review. Journal of Case Reports and Images in Oncology. Forthcoming 2017.

TYPE OF ARTICLE: Case Series

TITLE: Paraganglioma: Complex entity with different locations. Literature review

AUTHORS:

LOUBNA BELHAJJAM[1],
AYOUB ELMASNAOUI[2],
ASMAA KOUADIR[3],
TOURIA BOUHAFA[4],
ABDERAHMANE ELMAZGHI[5],
KHALID HASSOUNI[6]

AFFILIATIONS:

[1]Resident Doctor, department of radiotherapy Hassan II University Hospital, Faculty of Medecine and Pharmacy of Fez, Sidi Mohamed Ben Abdellah University, Fez, Morocco, Loubna.belhajjam86@gmail.com

[2]Resident Doctor, department of radiotherapy Hassan II University Hospital, Faculty of Medecine and Pharmacy of Fez, Sidi Mohamed Ben Abdellah University, Fez, Morocco,ayoubmasnaou@gmail.com

[3]Resident Doctor, department of radiotherapy Hassan II University Hospital, Faculty of Medecine and Pharmacy of Fez, Sidi Mohamed Ben Abdellah University, Fez, Morocco,kouadirasmaa@gmail.com

[4]Associate Professor, department of Radiotherapy Hassan II University Hospital, Faculty of Medecine and Pharmacy of Fez, Sidi Mohamed Ben Abdellah University, Fez, Morocco,bouhafatori@gmail.com

[5]Associate Professor, department of Radiotherapy Hassan II University Hospital, Faculty of Medecine and Pharmacy of Fez, Sidi Mohamed Ben Abdellah University, Fez, Morocco, abderrahmaneelmazghi@gmail.com

[6]Professor and head of the department, department of Rdiotherapy Hassan University Hospital, Faculty of Medecine and Pharmacy of Fez, Sidi Mohamed Ben Abdellah University, Fez, Morocco, nkhalidhassouni@gmail.com

CORRESPONDING AUTHOR DETAILS

LOUBNA BELHAJJAM

Residence ALMIFTAH; ZOHOR 2; N°28, FEZ, MOROCCO, 30000

Email: Loubna.belhajjam86@gmail.com

Short Running Title: Paraganglioma

Guarantor of Submission: The corresponding author is the guarantor of submission.

ABSTRACT

Introduction

Paragangliomas or chemodectomas are rare neuroendocrine tumors arising from germinal cells of the neural crest, located in the sympathetic extra adrenal ganglia. They are benign tumors but locally aggressive, with a small female predominance and the possibility to sit in difficult locations.

Case Series

In this study we report restropectively different locations of paragangliomas through seven patients treated all with radiotherapy alone in our department of radiotherapy during 5 years. And we review the relevant literature and bullet points conclusions and we discussed clinocopathological features and therapeutic management of this complex entity.

Conclusion

Paragangliomas are considered as a difficult pathology. The knowledge of the diverse appearance of paragangliomas can result in early initial diagnosis thereby effecting patient management and prognosis. Imaging is an essential tool for the diagnosis of the paragangliomas and their extension before proceeding with surgical treatment wich is actually the curative treatment and radiotherapy is an effective alternative to surgery for inextirpable paragangliomas. Clinical and biological monitoring should be prolonged for long term recurrence.

Keywords: paragangliomas; chemodectoma; Head and neck paragangliomas; surgery; radiotherapy.

INTRODUCTION

Paragangliomas (PGL) or chemodectomas are rare neuroendocrine tumors very vascularized, hereditary in 1/3 of the cases occurring then early in an isolated or syndromic frame. These tumors generally have a benign natural history and can occur at any age and there are no known risk factors except for certain genetic syndromes.

Paraganglia cells originate from the neural crest but differenciate into sympathetic and parasympathetic subtypes that can give rise to paraganglioma [1]. Sympathetic paraganglioma secrete norepinephrine, parasympathetic PGL are non-secretory and typically occur in head and neck region like carotid body PGL [2, 3] 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. 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.

CASE SERIES

Case 1

A 33 year-old female consulted for a painful abdominal mass at the left flank, evolving for the last 8 months. The past medical history and the patient's family history is negative. Physical examination reveals a huge left mass in the abdomen.

A blood and urine test was performed and demonstrated elevated levels of Normetanephrine at 23444 ug/24h, Metanephrine at 7812 ug/24h, Methoxytyramine at 95845 ug/24h.

CT scan of the abdomen was performed and showed a large retroperitoneal mass surrounding vessels and organs with a necrotic center (fig 1).

The patient benefited from explatory surgery which concluded a non-resectable mass, and the histology confirmed the diagnosis of retroperitoneal paraganglioma.
A conformational radiotherapy 3D was performed at a dose of 50 Gy (fig2).
At 6 months of follow up, there is a clinical improvement and radiological stability and the patient was referred for a genetic assessment.

Case 2

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 (fig 3). A biopsy was performed showing a paraganglioma.
View of the difficult location of the tumor an exclusive an exclusive IMRT radiotherapy has been at a dose of 50,4 Gy. After a follow up of 14 months, the case was stable and the patient did not complain of obvious discomfort.

Case 3

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. Given the location and the tumor volume, an exclusive IMRT have been realized at a dose of 60 Gy (fig 2).
After a follow up of 15 months, the case was stable with clinical improvement.

Case 4

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 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 (fig 2), allowing a local control maintained with a 14 month follow-up.

Case 5

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.

The patient received a 3D conformational radiotherapy at a dose of 50 Gy. 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.

Case 6

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. An exclusive 3D conformational radiotherapy was delivered at a dose of 50 Gy. After 6 months, the patient presented a tumor progression.

Case 7

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 80x70 mm, hypervascularized rapidly enhancing after injection of contrast product. 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. After a follow up of 14 months we noticed a stability and clinical improvement.

Features common

The seven patients are all women, without a past medical history, the median age was 45,5 years (33-69 years); the first symptom for consultation was a lateral cervical mass in the four patients with the carotid paraganglioma. All the seven patients with the different locations benefited by computing tomography scan, And the CT scan was completed by magnetic resonance imaging in 5 patients and for the Diagnosis was made in front of all the clinical and radiological signs in 4 patients and histological exam in 3 others;

The seven cases were unresectable, hence the realization of the exclusive radiotherapy for the 7 patients , dose 50-60 Gy in classic splitting and spreading, and it was intensity modulated radiotherapy for 3 patients and 3D conformal radiation therapy for 4 patients.

The median follow-up was one year and the evolution was marked by clinical improvement in all patients, stability in 5 patients and tumor progression in one other patient of those with carotid PGL.

DISCUSSION

PGL are rare chromaffin cell tumor, affecting 2 to 5 people per million per year. described for the first time in 1886; PGL mainly occur at body part with rich paraganglia [4] such as head and neck, madiastinum, adrenal gland, posterior peritoneum, bladder, duodenum and thyroid as reported. 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. Although PGL can occur either sporadically or to germline mutations with at least 9 suspect genes identified [2,5,6] but recent research suggest that the current list of associated genetic mutations is not complete and we have to be more and more aware of the role that genetics play in the pathogenesis of PGL [7]

PGL has long been considered as the disease of 10% (10% metastatic, 10% familial, 10% reccuring, 10% extradrenal, 10% occurring in children) however improved diagnosis techniques showed that the rule of 10% accurately characterized PGL.

Pathological diagnosis of PGL depends on the characteristic histological features [8, 9, 10] and immunohisto chemical detection of neuroendocrine markers. It's known that malignant potential of PGL is difficult to be assessed, assessment systems have been proposed in the pathology reporting of PGL in order to predict the malignant behavior of the tumor; but actually no reliable histologic features can currently distinguish between benign and malignant tumors [11]. In addition to local reccurence at the site of surgical resection, hematogenous and lymphatic metastases are common. Many pathologic markers of malignancy used in other tumors were evaluated for PGL but to date none could be sufficiently confirmed as a diagnosis or prognostic tool, the single way diagnosis malignancy is the presence of metastases [12].

The diagnosis of PGL remains a challenge because patient do not present with characteristic signs and symptoms and, if untreated, PGL can have a devasting 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 [13], 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 [14] 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 [15].

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 [16].

HEAD AND NECK PGLs (HNPs)

HNPs are rare tumors; the yearly 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. PGL in the

nose, the paranasal sinuses, parotid gland, cervical sympathetic chain, larynx, thyroid gland, parathyroid gland, esophagus or the orbit are exceedingly rare [17]. HNPs may occur at any age with a clear female predominance. the management f HNPs remains controversial; the current treatment options include complete surgical resection wich represent the only curative treatment option [18], conventional radiotherapy, stereotactic radiosurgery (for jugulotympanic PGL only), permanent embolisation and a combination of those modalities, and due the fact that HNPs are usually slow growing tumors it may be appropriate under certain circumstances to withhold any kind of invasive therapy and to observe tumor growth with serial magnetic resonance imaging studies “wait and scan” policy. A number of factors have to be considered when therapy is planned on an individual basis for every patient depending on tumor size number and location, the patient age and general status and pretherapeutic cranial nerve status.

The aim of conventional radiation therapy in HNPs is to achieve long term tumor control in up to 96% of cases. The dose commonly recommended is 45 to 56 Gy. Permanent cranial nerve deficit seem to be less common after radiation therapy of cervical HNPs when compared to surgical resection. In our opinion radiotherapy of cervical HNPs should be considered when a tumor is clearly not resectable without reasonable risk, when the patient is in poor health or does not want any surgical procedure or in the setting of multiple HNPs.

Retroperitoneal paraganglioma

Retroperitoneal forms would be less frequent than other sites [19, 20, 21] and Before any suspicious in front of retroperitoneal mass, it is necessary to think before any invasive action to seek an excessive secretion of catecholamines [21].

They have a significant local and metastatic infiltrative power. Treatment requires multidisciplinary care and surgery remains the only curative treatment provided if it is complete [22]. It allows survival rates of 75% and 45% at 5 and 10 years respectively. The choice of the surgical procedure between the conventional and laparoscopic route remains very controversial in view of the undesirable effects of laparoscopy [22]. Complementary therapies such as chemotherapy and radiotherapy may find their place in metastatic forms with a positive response in approximately

50% of cases, but without significantly affecting the prognosis, only surgical excision allows a significant improvement with an uninterrupted survival rate Recurrence of 75% at 5 years and from 45% to 10%. Their postoperative evolution may be marked by homolateral or controlateral recurrence. The average survival is of the order of 3 years in the metastatic forms and of 4 years in case of incomplete excision [22].

CONCLUSION

Although these tumors have traditionally been associated with 10% rule, improves imaging detection and outcome data show that the true story is more complex and prognosis varies depending on the tumor type and location, so a high index of suspicion should be applied as PGL occur in diverse site; also awareness of the need of updated pathological and immunological data are essential for proper management of patients with PGL.

CONFLICT OF INTEREST

The authors do not declare any conflicts of interest.

AUTHOR'S CONTRIBUTIONS

Loubna Belhajjam

Group 1- Conception and design, Acquisition of data, Analysis and interpretation of data

Group 2- Drafting the article,

Group 3- Final approval of the version to be published

Ayoub El massnaoui

Group 1- Conception and design, Acquisition of data, Analysis and interpretation of data

Group 2- Drafting the article,

Group 3- Final approval of the version to be published

Asmaa Kouadir

Group 1- Conception and design, Acquisition of data, Analysis and interpretation of data

Group 2- Drafting the article,

Group 3- Final approval of the version to be published

Touria Bouhafa: Pr. Bouhafa

Group 1- Analysis and interpretation of data

Group 2- Critical revision of the article

Group 3- Final approval of the version to be published

Abderrahmane EL MAZGHI: Pr. EL MAZGHI

Group 1- Analysis and interpretation of data

Group 2- Critical revision of the article

Group 3- Final approval of the version to be published

Khalid HASSOUNI: Pr. HASSOUNI

Group 1- Analysis and interpretation of data

Group 2- Critical revision of the article

Group 3- Final approval of the version to be published

All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

REFERENCES

1. Baysal BE. Hereditary paraganglioma targets diverse paraganglia. J Med Genet 2002; 39; 617–622.
2. Van der Mey AG, Maaswinkel-Mooy PD, Cornelisse CJ. Genomic imprinting in hereditary glomus tumours: evidence for new genetic theory. Lancet 1989; 2: 1,291–1,294.
3. Opocher G, Schiavi F. Genetics of pheochromocytomas and paragangliomas. Best Pract Res Clin Endocrinol Metab 2010;24: 943_956.

4. Blake MA, Kalra MK, Maher MM. Pheochromocytoma; an imaging chameleon. Radiographics 2004; 24: S87_S99.
5. Drovdlic CM, Myers EN, Peters JA. Proportion of heritable paraganglioma cases and associated clinical characteristics. Laryngoscope 2001; 111: 1,822–1,827.
6. Neumayer C, Moritz A, Asari R. Novel SDHD germ-line mutations in pheochromocytoma patients. Eur J Clin Invest 2007; 37: 544–551.
7. Kathryn S. King1 and Karel Pacak1; Familial Pheochromocytomas and Paragangliomas ; Mol Cell Endocrinol. 2014 April 5; 386: 92–100.
8. Farthouat P, Platal JP, Meusnier F, Pourrire M, Thouard H. Paragangliome rétropéritonéal sécrétant: à propos d'un cas. J Chir.1997; 134 (5-6): 248-251.
9. Giudicelli T, Bruneton JN, Duplay H, Abbes M, Balu Maestro C, Raffaelli C et al. Imagerie des paragangliomes rétrpéritonéaux non fonctionnels: à propos d'un cas. J Radiol.1991; 72: 617-619.
10. Salame, K., Ouaknini, G.E.R., Yossipov, J., Rochkind, S. Paraganglioma of the pituitary fossa: diagnosis and management. Journal of neuro-oncology 2001; 54, 49–52.
11. Pagliano G, Michel PH, La Fay Th, Duverger V. Paragangliomes de l'organe de Zuckerkandl. Chirurgie. 1994-1995; 120: 128-133.
12. Deb, P., Sharma, M.C., Gaikwad, S., Gupta, A., Mehta, V.S., Sarkar, C. Cerebellopontine angle paraganglioma-report of a case and review of literature. Journal of neuro-oncology 2005; 74, 65–69.
13. Hayes WS, Davidson AJ, Grimley PM, Hartman DS. Extraadrenal retroperitoneal paraganglioma: clinical, pathologic and CT finding AJR Am. J Roentgenol. 1990; 155: 1247- 1250.
14. Bessell-Browne R, O_Malley ME. CT of pheochromocytoma and paraganglioma; risk of adverse events with i.v. administration of nonionic contrast material. AJR Am J Roentgenol 2007; 188: 970-974.
15. Juan C. Baeza, Jyothi P. Jagannathanb, Katherine Krajewskib, Kevin O, Pheochromocytoma and paraganglioma: imaging characteristics ; Cancer Imaging 2012;12, 153-162

16. Miliaras, G.C., Kyristis, A.P., Polyzoidis, K.S. Cauda equina paraganglioma: a review. Journal of neuro-oncology 2003; 65, 177–190.
17. World Health Organization. Pathology and Genetics: Tumours of Endocrine Organs. Lyon, France: IARC; 2004.
18. Shamblin WR, ReMine WH, Sheps SG, Harrison EG. Carotid body tumor (chemodectoma). Clinicopathologic analysis of ninety cases. Am J Surg 1971; 122: 732–739.
19. Desmonts JM, Marty J. Anaesthetic management of patients with phaeochromocytoma. Br J Anaesth 1984; 56:781–9.
20. Puche P, Jacquet E, Colombo PE, Jaber S, Alric P, Carabalona JP, et al. Prise en charge chirurgicale d'un paragangliome préaortique : à propos d'un cas. Ann Chir 2006; 131:559–63.
21. Kinney MA, Narr BJ, Warner MA. Perioperative management of pheochromocytoma. J Cardiothorac Vasc Anesth 2002; 16:359–69.

FIGURE LEGENDS

Figure 1: Axial (A) and frontal (B) CT scan image of a huge retroperitoneal paraganglioma.

Figure 2: Radiotherapy IMRT of cervical paraganglioma (A) and of the apex petrous paraganglioma (C); radiotherapy 3D of a huge retroperitoneal paraganglioma (B).

Figure 3: Sagittal CT scan image of a paraganglioma of the ear.

FIGURES

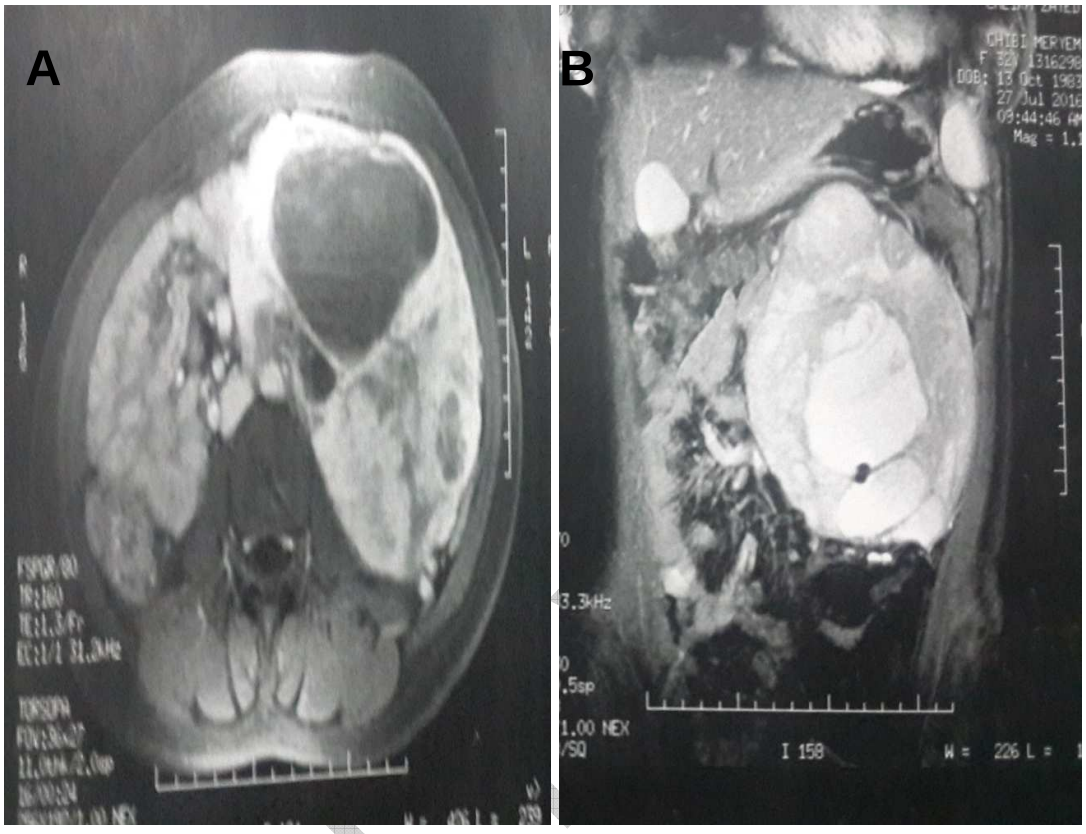

Figure 1: Axial (A) and frontal (B) CT scan image of a huge retroperitoneal paraganglioma.

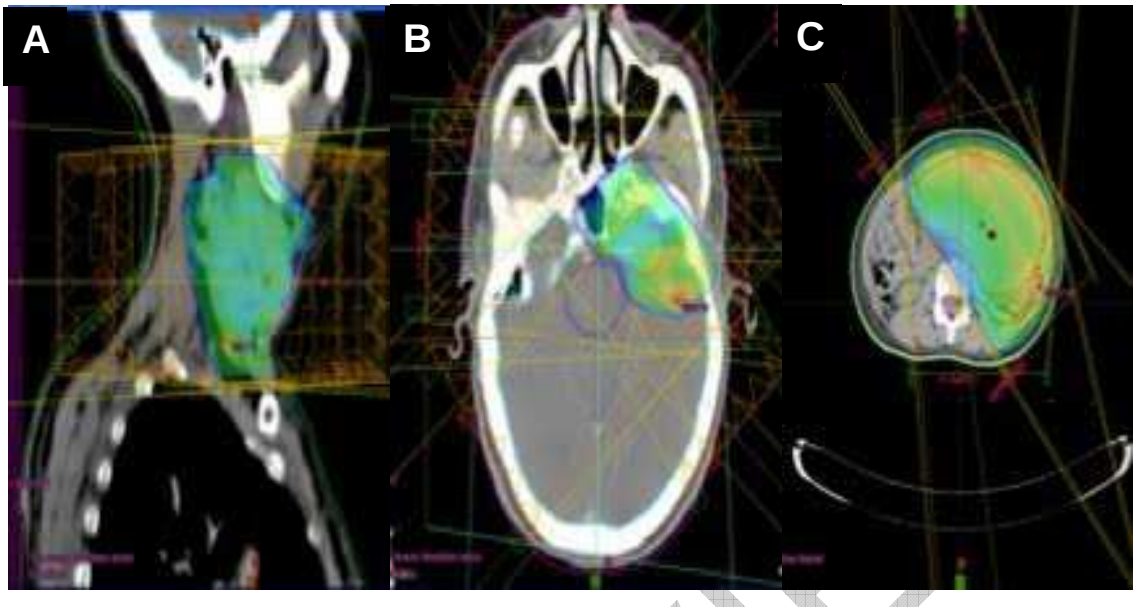

Figure 2: Radiotherapy IMRT of cervical paraganglioma (A) and of the apex petrous paraganglioma (B); radiotherapy 3D of a huge retroperitoneal paraganglioma (C).

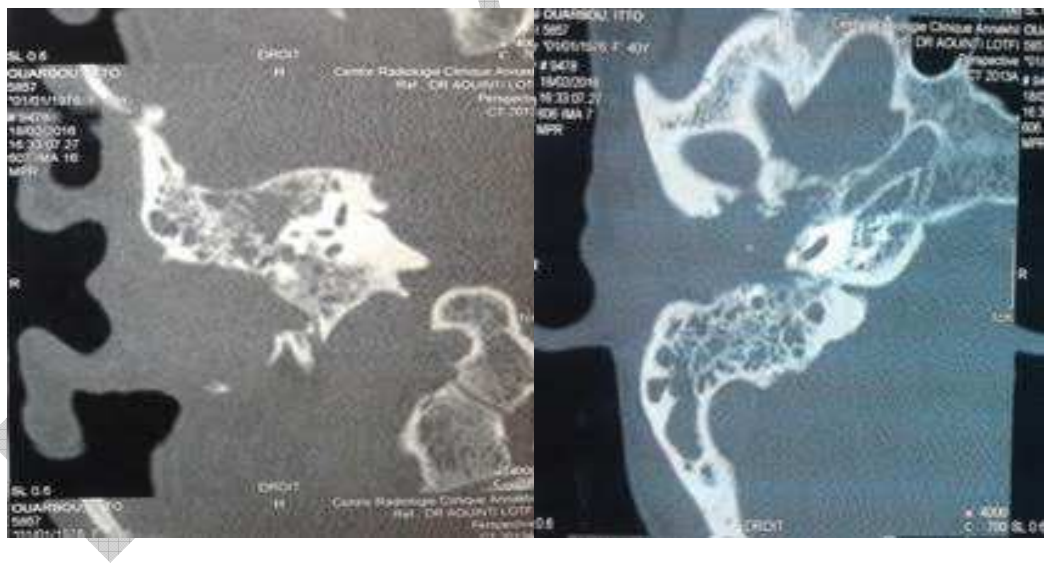

Figure 3: Sagittal CT scan image of a paragangliome of the ear.