Robotic radiosurgery for temporal bone paragangliomas: single-center experience and review of the literature

Original Article

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Abstract

Objective: To report the experience of a single center in the treatment of temporal bone paragangliomas with Robotic Radiosurgery.
Study Design: Single-center retrospective analysis
Material and Methods: Between 2017 and 2021, 8 patients with temporal bone paragangliomas were treated with Cyberknife in the Department of Radiation Oncology of Instituto CUF Porto.
Results: Half of the patients were diagnosed with recurrent tumors after surgery +/- embolization. The median follow-up was 33 months. Regarding clinical outcomes, 4 patients showed improvement in pre-radiosurgery symptoms, 2 remained symptom-free and 2 demonstrated neurological stability. All tumors revealed regression (n=5) or stable dimension (n=3) during follow-up MRI, with local control of 100%. There was no grade ≥3 or late toxicities.
Conclusion: Robotic Radiosurgery seems to be a helpful therapeutic approach in the management of temporal bone paragangliomas, either after surgery and/or embolization recurrences or as a single and radical treatment.

Keywords: Paraganglioma; Cyberknife; Radiosurgery

Introduction

Paragangliomas (PGs), also known as chemodectomas or glomus tumors, are hypervascular neuroendocrine tumors that originate from the sympathetic or parasympathetic paraganglia.[1-3] In the head and neck, carotid body tumors are the most common type, followed by jugular, tympanic, and less commonly vagal tumors.[3,4]

These lesions are rare, accounting for <0.5% of all tumors of the head and neck.[4] The annual incidence is estimated to be 0.7 per 100 000 people.[5] PGs typically appear between the ages of 50 and 60 years and affect 3- to 6-fold more women than men.[5] Most are benign and

slow-growing, with a median annual growth rate of approximately 1 to 2 mm.[6] Depending on their location, size, and hormonal activity, they can cause various symptoms, ranging from pulsatile tinnitus, headache, hypoacusia, vertigo, and lower cranial nerve paralysis in jugular tumors, to tachycardia and blood pressure changes in catecholamine-secreting PGs.[7] For many decades, surgical resection was considered the treatment of choice for these tumors, except in elderly patients or those with bilateral PGs.[8,9]

However, total macroscopic resection is often hampered by the proximity of these lesions to neurovascular structures.[4,10] Currently, the therapeutic options include surgical resection, endovascular embolization, conventional external radiotherapy (RT), stereotactic radiosurgery (SRS), or a combination of these modalities.[11,12]

SRS has recently emerged as a less invasive treatment option. Several studies have shown that it is associated with lower mortality and morbidity than surgical resection, as well as a high local control rate.[8,10]

Several types of equipment are available for performing SRS, including the Gamma Knife (Elekta AB, Stockholm, Sweden), Cyberknife (Accuray Inc., Sunnyvale, California, USA), and linear accelerators (LINAC).[13] However, studies on the results of SRS with Cyberknife are scarce.[12] The primary objective of this study was to retrospectively evaluate the clinical response, local tumor control, and SRS-associated toxicity in patients with temporal bone PGs who were treated with Cyberknife in the Department of Radiation Oncology Júlio Teixeira SA, CUF Institute, Portugal. Additionally, we conducted a review of the literature on the treatment of PGs with SRS.

Materials and Methods

Between August 2017 and July 2021, eigh t patients with PGs of the temporal bone were treated with Cyberknife SRS in our institution. We collected information on the medical history, previous treatments, and follow-up from the clinical files of the patients. At follow-up visits, patients were evaluated for symptoms, adverse effects, and response to treatment by performing objective examination and magnetic resonance imaging (MRI). The clinical response was based on the objective examination and symptoms reported by the patient during follow-up.

Local tumor control was assessed by evaluating the follow-up MRI images according to *Response Evaluation Criteria in Solid Tumors* (RECIST) criteria. The tumor response was defined as follows: complete response, disappearance of the lesion; partial response, ≥30% reduction in the tumor diameter; local progression, ≥20% increase in the tumor diameter; and stable disease, not fulfilling the criteria for complete response, partial response, or local progression. [14] Local control was defined as the absence of disease progression. Toxicity was classified according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 scale.

All patients underwent fine-sliced planning computed tomography (CT) scan (1 mm) and planning contrast-weighted MRI with T1- and T2-weighted images, both with a thermoplastic face mask.

Subsequently, CT was merged with the planning MRI and the treatment volume was delineated according to the imaging findings, with the addition of a margin of 2 to 5 mm. All patients received SRS through the Cyberknife®M6™ system using 6 MV photons. Follow-up time was calculated as the time between the last treatment fraction and last follow-up visit. Additionally, an online search was performed in the PubMed database by using various combinations of the following keywords: "paraganglioma," "chemodectoma," "glomus jugulare," "cyberknife radiosurgery," "radiation therapy," and "radiosurgery." The articles included in the literature review were published within the last 10 years, had full text available in English, and described the outcomes of patients with PGs treated with SRS.

Results

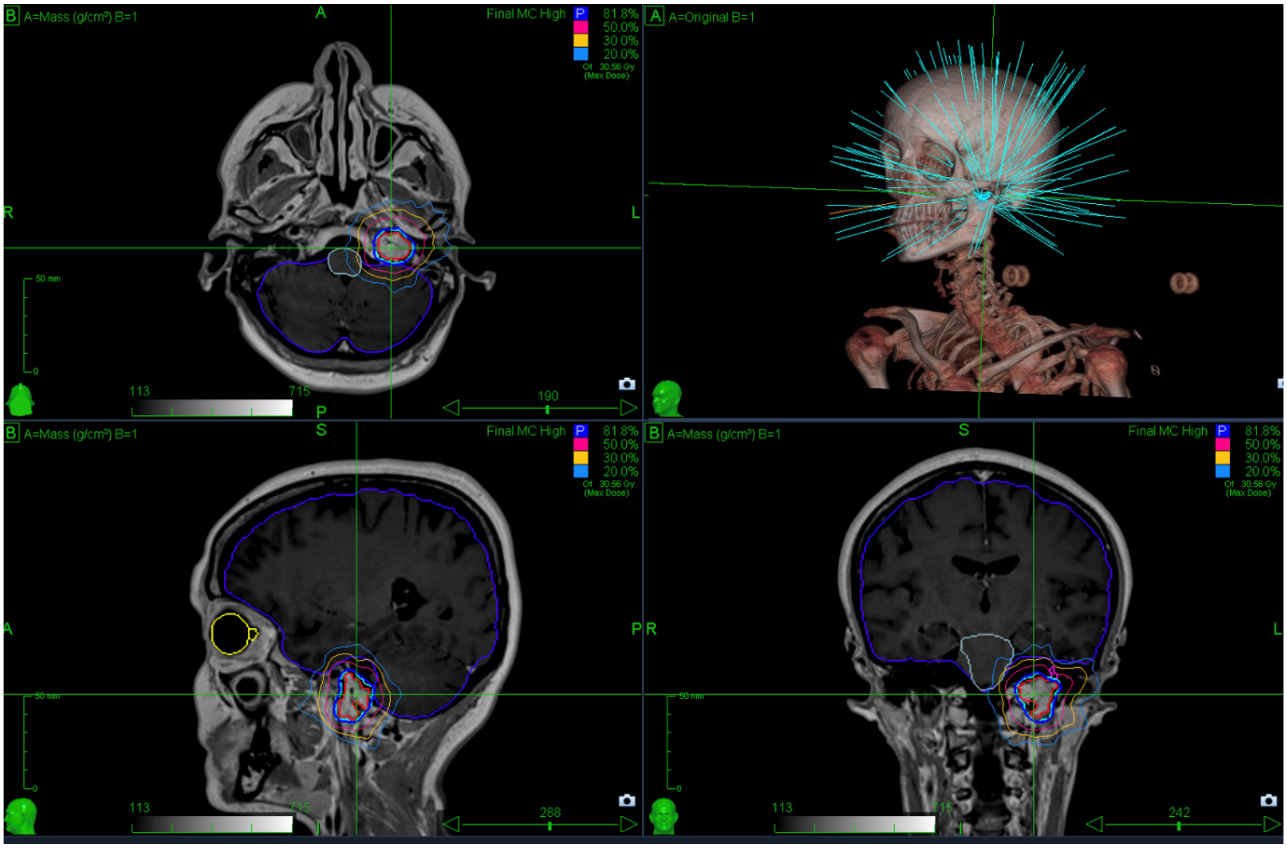
Patient characteristics and treatment parameters are described in Table 1. Figure 1 illustrates the treatment plan of the patient identified with the number 4 in Table 1. Six (75%) women and two (25%) men, aged between 27 and 79 years (median age 47 years) were analyzed in this study. Seven (87.5%) patients had jugular PGs and one (12.5%) had a tympanic PG. All patients had only one lesion. The most common symptoms were conduction hypoacusia (three patients), followed by

Table 1
Patient characteristics and treatment parameters

Patient number	Age (years)	Sex	Laterality	Previous treatment(s)	Tumor volume (cc)	Total Dose (Gy)	Dose/fraction (Gy)	Isodose line (%)
1	47	Male	Right	Surg. + Emb.*	11,23	25	5	89
2	27	Female	Left	Surg. + Emb.*	39,21	21	7	71
3	79	Female	Left	None	3,32	25	5	85,3
4	45	Female	Left	None	6,34	25	5	81,8
5	30	Female	Left	Surgery	17,27	24	8	80
6	79	Female	Right	Surgery	0,84	12	12	79
7	35	Female	Right	None	7,14	25	5	85
8	57	Male	Right	None	6,65	25	5	84

*Surgery + Embolization

Figure 1
Cyberknife treatment plan of Patient number 4



headache (two patients) and dysphonia (two patients). Other reported symptoms were pulsatile tinnitus (one patient), left scapular contracture (one patient), paralysis of the left vocal cord (one patient), and dysphagia (one patient). Half of the patients had tumor recurrences after surgery +/- embolization.

The prescribed dose ranged from 12 Gy to 25 Gy (median dose 25 Gy), in 1 to 5 treatment fractions (median 5 fractions). Prescription isodoses ranged from 71% to 89% (median 82.9%). The median treatment volume was 6.9 cc (range 0.84–39.21 cc). The median total treatment time was 5 days (range 1–5 days).

The median follow-up time was 33 months (range 14–62 months). Regarding the clinical response, four (50%) patients showed an improvement in the pre-SRS symptoms, two (25%) remained asymptomatic, and two (25%) demonstrated neurological stability. None of the patients had a worsening of the pre-existing symptomatology. All tumors showed regression (n=5) or dimensional stability (n=3) at follow-up MRI, with a local control rate of 100%. All patients well tolerated the treatment. Acute RT-related adverse effects included grade ≤2 nausea (three patients), grade 2 vomiting (one patient), and grade ≤2 headache (three patients). These symptoms were easily resolved through conservative medical treatment. Half of the patients did not experience any acute side effects. No patient developed *de novo* neurologic deficits. No Grade 3 or 4 toxicity was observed, and no late adverse effects were reported. The pre- and post-treatment clinical characteristics are summarized in Table 2.

Discussion

This retrospective study, with a median follow-up time of 33 months, presents the outcome of eight patients with tympanojugular PGs who were treated with the Cyberknife. Half of these cases consisted of tumor recurrences after surgery +/- embolization. At a median total dose of 25 Gy, the tumor control rate was 100% and symptom improvement was achieved in 50% of the patients. Complications associated with treatment were low-grade and easily resolved through conservative measures.

Our results are in agreement with the first multicenter retrospective study of 101 patients with tympanojugular PGs who underwent robotic radiosurgery, leading to local control in 99% patients and symptomatic improvement in 56% patients, with a median follow-up time of 35 months. Moreover, most of the complications in this study were low-grade, ranging from nausea, vertigo, headache to transient cranial neurological deficits, with

Table 2
Pre- and post-treatment clinical characteristics

Patient number	Pre-treatment symptoms	Post-treatment symptoms	Tumor response	Follow-up time (months)
1	Asymptomatic	Asymptomatic	Regression	62
2	Dysphonia, scapular contracture, dysphagia	Improvement in dysphagia	Stable	61
3	Conduction hypoacusis, headache	No changes	Regression	14
4	Dysphonia, vocal cord paralysis	No changes	Stable	14
5	Asymptomatic	Asymptomatic	Stable	47
6	Pulsatile tinnitus, conduction hypoacusis	Improvement in tinnitus and hypoacusis	Regression	16
7	Headache	Improvement in headache	Regression	40
8	Conduction hypoacusis	Improvement in hypoacusis	Regression	25

a complication rate of 7%.[7] A more recent retrospective analysis, which included 29 patients with head and neck PGs treated with Cyberknife, reported a local control rate of 97% and symptomatic improvement in 45% patients. In this study, 55% of the patients had undergone previous procedures. In terms of toxicity, one patient experienced asymptomatic cerebellar radionecrosis, while another patient developed permanent facial nerve palsy (House-Brackmann grade II).[12]

Although some meta-analyses have assessed the role of SRS in head and neck PGs, these included a limited number of studies on robotic radiosurgery.[4,10]

A systematic review and meta-analysis by Ong *et al.* that included 23 studies (18 on Gamma Knife, four on LINAC, one on LINAC and Cyberknife) demonstrated a tumor control rate of 95% and symptomatic improvement in 47% of the patients with tympanojugular PGs treated with SRS.[10]

Another meta-analysis comprising 37 articles and 1117 patients, in which the majority received treatment with the Gamma Knife (61%) and only 14.6% received Cyberknife or LINAC, showed a local control rate of 94.2% and clinical improvement in the neurological status of 48.7% cases, with a median follow-up time of 44 months. In addition, there were no statistically significant differences in terms of local control depending on the SRS technique used. However, Gamma Knife was associated with transient or permanent neurological deficits in 4.9% patients, LINAC in 1.1%, while only 0.5% of patients developed complications after treatment with Cyberknife.[4-]

Although several studies have clearly demonstrated the efficacy of SRS/RT in the treatment of head and neck PGs, doubts remain regarding the best therapeutic strategy for these tumors: surgery (with or without previous embolization) or RT (SRS or conventional RT).[15]

Despite the technical difficulties and high morbidity rates, surgery, when possible, can achieve complete resection of the tumor. In contrast, although SRS has shown good local control and a low morbidity rates, the long-term tumor recurrence rate (after 10–20 years) remains unknown.(16) Based on these data, several authors have suggested SRS as the primary treatment of PGs.[17]

Local and symptom control

Some studies have compared the clinical and radiological efficacy of surgery with SRS/RT. In a systematic review, primary SRS/RT was 78% more likely to achieve local tumor control compared to surgery alone (odds ratio [OR]: 0.22: 95% confidence interval [CI]: 0.09–0.57; p=0.02). The local control rate was reportedly 81.3% for surgery and 94.1% for SRS/RT.[4]

Another recent meta-analysis evaluated the treatment of complex tympanojugular PGs (Fisch classification C and D). The rate of tumor control in 852 patients from 19 studies was 96.3% (95% CI: 93.4%–99.2%) with SRS and 83% (95% CI: 76.8%–89.3%) with total surgical resection.[5]

Furthermore, a review of 69 studies by Suárez *et al.* (including 1084 surgically-treated and 254 SRS-treated patients) showed that local control after surgery was higher than that observed after RT or SRS (89.6% vs 83.7%), although the risk of morbidity after surgery was higher (26% vs 11%).[6,8]

Similarly, Gottfried *et al.* conducted a review of the literature comparing surgery with SRS for the treatment of tympanojugular PGs, and found a tumor control rate of 92.1% with surgery and 97.8% with SRS.[10]

Complications

In contrast to surgery, SRS has a lower risk of complications, especially in terms of neurological damage.[7]

The high morbidity associated with resection is due to the proximity of the nerve structures and hypervascular nature of PGs.[3] Thus, the major complication associated with surgery is cranial nerve injury.[1] A systematic review by Fatima *et al.* showed that surgery (total or subtotal) was associated with twice as much morbidity (transient or permanent neurological deficits) compared to primary

SRS/RT (relative risk [RR]: 2.08; 95% CI: 1.05–4.15; p=0.04).[4] Most studies on SRS reported a complication rate of less than 10%.[7] A systematic review showed that after SRS, transient neurological deficits, including headache, nausea, vomiting, hemifacial spasms, and paresis of the XII cranial pair occurred in 5.8% patients, while 2.1% developed permanent deficits. Treatment with Cyberknife was associated with a lower likelihood of transient (0.9%) or permanent (0.1%) deficits.[4] Galland-Girodet *et al.* evaluated the quality of life of 30 patients with head and neck PGs according to the selected therapeutic modality (surgery/embolization +/- RT). They found that patients undergoing RT alone had better scores for speech, hearing, and trismus.[7]

However, the complication rate associated with a total macroscopic resection ranges from 54–60%, and seems to vary according to the size and location of the tumor, and type of resection.[3,4] Gottfried *et al.* described the occurrence of complications such as cerebrospinal fluid fistulas (8.3%), aspiration (5.5%), and wound infection/ischemia (5.5%) in patients with surgically-treated tympanojugular PGs.[10] In another study, Al-Mefty *et al.* found that cerebrospinal fluid fistulas occurred in 14% patients and otological infections in 18% patients who underwent surgery for tympanojugular PGs.[10] Similarly, Suárez *et al.* reported major complications, such as cerebrospinal fluid fistula, aspiration, infection, meningitis, stroke, and death in 28% of patients treated with surgery for PGs.[7]

Therapeutic selection

The therapeutic approach should be selected after taking into account the location, size and growth of the tumor, as well as the patient's age, symptoms, medical comorbidities, patient preferences, expected morbidity of treatment, and previous treatments.[3,6,17]

Typically, surgery is considered in young people, jugular PGs located in areas associated with a low surgical risk, small to medium-sized carotid body tumors (<5 cm and Shamblin class I or II), secretory tumors, rapidly growing tumors, or those at risk of malignant progression.[3] Patients with large PGs or neurological deficits of the lower cranial nerves may be candidates for total or subtotal resection.[3,5] However, although subtotal resection can prevent treatment-induced neurological deficits, it has been associated with a low rate of local control, increased treatment morbidity, and high rate of salvage therapies.[3,6]

Historically, RT was reserved for patients with contraindications for surgery, after subtotal resection, or in cases of tumor recurrence after initial resection. [2,4] However, given the slow growth and favorable prognosis of early-stage tympanojugular PGs, previous studies have suggested extending the use of SRS to younger patients and surgical candidates. This has opened up the potential for SRS to be considered as the treatment of choice in tympanojugular PGs <3 cm in diameter.[10]

Hong *et al.* developed a treatment algorithm for head and neck PGs, in which they recommend an approach based on the presence of symptoms and hormone production. If the patient is asymptomatic, clinical and imaging follow-up can be performed. In cases of functional PGs in symptomatic patients, surgical excision followed by hypofractionated SRS is recommended. In symptomatic non-functional PGs, hypofractionated SRS is considered to be the best primary treatment for symptomatic control.[12]

Dharnipragada *et al.,* also proposed a treatment algorithm for tympanojugular PGs, based on the Fisch anatomical classification and other variables. For Fisch A or B PGs, they recommend total surgical resection. For Fisch C or D PGs without mass effect, with high surgical risk, or in patients without pre-existing lower cranial neuropathies, SRS is recommended.[5] For Fisch A or B PGs with mass effect and high surgical risk, subtotal resection followed by SRS may be considered.[5]

Limitations

The limitations of this study include its retrospective nature and limited sample size,

Table 3
Modified Fisch classification for temporal bone paragangliomas

Classification	Description
Type A (tympanic glomus)	Limited to the mesotympanum
Type B (hypotympanic glomus)	Limited to the tympanomastoid area without erosion of the jugular bulb
Type C	Invasion of the infralabyrinthine compartment
C1–C4	Increasing invasion of the carotid canal
Type D	Intracranial extension
De1–De2	Dural displacement from De1 (<2 cm) to De2 (>2 cm)
Di1–Di3	Intradural extension of <2 cm (Di1), >2 cm (Di2), or unresectable intracranial invasion (Di3)
Type Ve, Vi	Invasion of the extradural vertebral artery (Ve) or intradural vertebral artery (Vi)

which was related to the rarity of this pathology and availability of Cyberknife in cancer centers in our country. Further multicenter, prospective studies are needed to compare not only SRS with surgery, but also the various SRS techniques and fractionations.

Conclusion

SRS with Cyberknife appears to be a useful therapeutic approach for the management of temporal bone PGs, both for recurrences after surgery +/- embolization and as a single radical treatment. Despite the complex planning of RT in these tumors, mainly due to their localization, SRS has shown high rates of local control and low toxicity. However, a longer follow-up time is needed, as well as a higher number of patients to confirm these favorable results.

Conflicts of Interest

The authors declare that there is no conflict of interests regarding the publication of this paper.

Data Confidentiality

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

Protection of humans and animals

The authors declare that the procedures were followed according to the regulations established by the Clinical Research and Ethics Committee and to the 2013 Helsinki Declaration of the World Medical Association.

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Availability of scientific data

There are no datasets available, publicly related to this work.

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