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RADIOTHERAPY FOR HEAD AND NECK PARAGANGLIOMAS:

A 10 year retrospective review 2005-2014 at Groote Schuur Hospital and UCT Private academic hospital.

Date of submission:

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DECLARATION

I, Wegoye Emmanuel, hereby declare that the work on which this dissertation/thesis is based is my original work (except where acknowledgements indicate otherwise) and that neither the whole work nor any part of it has been, is being, or is to be submitted for another degree in this or any other university.

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ABSTRACT

Objective. Over the last two decades there has been increasing evidence that radiosurgery and radiotherapy management of skull-base paragangliomas is as effective as microsurgical resection and carries less morbidity. This 10 year retrospective review of 24 patients in a single institution, treated over 10 years assesses tumour control rates and morbidity associated with radiosurgery and radiotherapy treatment.

Method. Patients with a radiological diagnosis of skull-base paragangliomas were treated with different techniques of stereotactic and image-guided radiotherapy delivering hypo fractionated irradiation. Techniques used included conventional radiotherapy or intensity modulated radiotherapy (IMRT), dynamic arc (DA) and volumetric modulated arc therapy (VMAT).

Analysis of local tumour control was performed using RECIST criteria and the Kaplan-Meier method. 69% of patients received 14-16gy in 1-3 fractions while 31% received 48-50gy in 25 fractions. Radiation-associated toxicity was graded according to the commonly used Radiation therapy Oncology group (RTOG) toxicity criteria.

Results. 24 patients with skull-base paragangliomas were treated with a median follow up of 43 months. One patient lost to follow up and was excluded. Tumour control was achieved in 96% of patients.

76% of patients treated reported no radiation associated toxicity. 24% of patients had some radiation associated toxicity: the conventional group 12%, stereotactic radiosurgery 8% and stereotactic radiotherapy 4%. 43% of patients in the conventional group had progression of hearing loss in the affected ear. One patient in the radiosurgery group developed osteonecrosis of the temporal bone at 5 year follow up.

Conclusion. Radiosurgery and radiotherapy are efficacious in achieving tumour control with minimal morbidity. Tumour control rates in the study are similar to control rates in literature. Radiation associated toxicities are mainly minor. Study is limited by the retrospective nature and limited duration of follow up.

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ABBREVIATIONS.

EBRT External Beam radiotherapy

PHN Paragangliomas of Head and Neck

CBT Carotid body Tumours.

CTB Computerised Tomograms of Brain

GTR Gross Total Resection.

MRI Magnetic Resonance Imaging

SRT Stereotactic radiotherapy

SRS Stereotactic radiosurgery

VMAT Volumetric modulated Arc therapy

IMRT Intensity modulated radiotherapy

RTOG Radiation therapy Oncology Group.

CHAPTER 1

LITERATURE REVIEW

REVIEW METHOD

An online search with key words: Base of skull paraganglioma, jugulotympanicum paraganglioma, History of head and neck paraganglioma, Genetics of head and neck paragangliomas, imaging of head and neck paragangliomas, embolization of head and neck paragangliomas, observation for head and neck paragangliomas, surgery for head and neck paragangliomas and radiotherapy for head and neck paragangliomas was performed. Review and original articles in the English language found to be clinically relevant were included.

LITERATURE REVIEW

Paragangliomas of the head and neck are tumours arising from chromaffin cells which are derived from cells of the neural crest [1, 2, 3, 4, 5]. Clusters of chromaffin cells within the base of skull are organised into small flattened ovoid structures called glomus bodies [2, 3, 4, 8, 21,]. These glomus bodies are commonly found at four sites within the head and neck: the bifurcation of the common carotid artery, the adventitia of the jugular bulb and the bony wall of the tympanic canal which transmits the tympanic branch of the glossopharyngeal and vagus nerve in close proximity to the parasympathetic ganglia [4, 3].

Paragangliomas of the head and neck (PHN) are named according to the location of the glomus body of origin and include glomus caroticum, glomus jugulare, glomus tympanicum and glomus vagale [4]. The jugulo-tympanic group constitute tumours arising at the base of skull. Glomus jugulare tumours arise from the jugular bulb and invade the petrous bone while glomus tympanicum tumours arise in the bone of the promontorium close to the mucosa of the middle ear mucosa and are confined to the middle ear cavity [3, 4]. These tumours have historically also been referred to as glomus tumours, chemodectoma or non-chromaffin paragangliomas [4].

These tumours are rare with an incidence of 0.02-0.1 per million [6, 7]. Glomus caroticum, also known as carotid body tumours (CBT), account for the majority of PHN. Overall glomus tumours account for 0.6% of tumours found in this region and 80% of tumours in the jugular foramen [7]. The incidence is two to five times higher in women compared to men [6].

The majority of paragangliomas of the skull-base occur sporadically, with approximately 15% being hereditary. Some hereditary tumours occur as a result of mutations at the Succinate dehydrogenase enzyme complex D and SDHB genes located on chromosome 11.q23. [4,7]. The hereditary tumours usually present during the 2nd and 3rd decade while the sporadic group commonly present during the 4th and 5th decade of life [1, 7].

Natural history

Base of skull paragangliomas, usually grow slowly with a median growth rate of 0.8-1.0mm per year and a median tumour doubling time of 4.2 years, except for malignant subtypes [8]. Whereas the clinical course of benign glomus tumours is insidious, they can be locally aggressive with destruction of surrounding bony structures and encasement of critical neurovascular structures [9].

Only 1-3% of glomus tumours are malignant. Metastatic disease is diagnosed on the basis of the presence of chromaffin tumours in locations where chromaffin cells are not usually found [7]. They commonly metastasise to lymph nodes, bone, liver, lungs and kidneys [10]. The 5 year survival for benign and malignant PHN stands at 97% and 23%-43 respectively [1, 7].

Clinical Presentation

Glomus tympanicum and Glomus jugulare tumours most commonly present with pulsatile tinnitus (80%), conductive hearing loss (60%), otalgia, otorrhagia (7%), vertigo (9%) and dizziness (4 %) [11]. These symptoms are secondary to mass effect on surrounding structures including vasculature or lower cranial nerves [12]. Due to the slow growth of these tumours they may only present when they are of considerable size. Carotid and Vagal paragangliomas commonly present as neck masses with associated dysphagia and hoarseness [7, 11].

Imaging

PHN have characteristic imaging features on Magnetic Resonance imaging (MRI), Computerised tomograms (CT) and digital subtraction angiograph (DSA). The MRI appearance is that of a lesion with low signal intensity on T1 and high signal intensity on T2 weighted images. Multiple areas of high and low signal intensity representing high and low flow give these tumours the characteristic salt and pepper appearance [13]. The localisation of each type of PHN contributes to the typical specific radiological diagnosis, for example with Carotid body tumours splaying the carotid bifurcation, and glomus vagale tumours displacing

the internal carotid artery anteriorly. High resolution CT shows expansion and a moth-eaten pattern of erosion of the jugular foramen for jugulotympanicum paragangliomas [13, 14].

The combination of typical imaging characteristics with localisation, typical vessel displacement, enlarged feeding vessels, and intra- tumoural flow signal makes the diagnosis of paragangliomas highly likely. When radiological diagnosis based on MRI and CT is in doubt, a DSA can confirm the diagnosis showing a specific vascular supply to paragangliomas [13, 15]. Based on these characteristic imaging features, some argue that a biopsy is not necessary for the non-surgical management of these tumours [7].

Classification

Historically, radiological classification of base-of-skull paragangliomas has guided microsurgical therapy. Fisch classified glomus tumours of the temporal bone into 4 main types labelled A-D with subtypes in C and D [16, 17]. Type A includes glomus typanicum that are confined to the tympanic cavity. Type B includes tumours that originate in the hypo tympanic bone plate with extension into the hypo tympanum and mastoid bone. Type C represents glomus jugulare tumours with sub-classification based on involvement of the vertical and horizontal segments of the carotid canal. Type D represent glomus jugulare tumours with intracranial extension and a distinction between extradural and intradural tumours [16].

Glasscok-Jackson classified glomus jugulare tumours into 4 classes, type I being small tumours involving the jugular bulb, middle ear and mastoid. Type II extends into the internal auditory canal, type III extends into the petrous apex and type IV extends beyond the petrous apex into the clivus or infratemporal fossa and may have intracranial extension [18].

Management

The treatment options for PNH are guided by our understanding of the natural history of these tumours, tumour control rates associated with each of the different treatment modalities, and the morbidity and mortality associated with each type of treatment. These treatment options include watchful waiting, preoperative embolization followed by tumour resection or microsurgical resection only, fractionated external beam radiation therapy, and stereotactic radiosurgery [1, 7, 8, 19, 20, 21, 22]. Microsurgical resection was the favoured primary treatment option for these tumours until 2 decades ago 23. Radiotherapy and radiosurgery have, over

the last 2 decades, come into favour as the primary treatment option as our understanding of the natural history, tumour control rates and treatment risks has improved [1, 7, 8, 19, 20, 21].

Observation

Watchful waiting with serial imaging has been proposed for asymptomatic incidental tumours [7, 8]. This is because of the slow indolent growth pattern of these tumours. The patient is spared the morbidity and mortality associated with surgery and radiotherapy until symptomatic. However as the tumour increases in size and involves critical neurovascular structures, the morbidity associated with surgery and radiotherapy is significantly increased. As a result, watchful waiting must be weighed against the immediate risks associated with any intervention and the risk of delayed intervention [6, 7].

Surgery

Based on Fisch's classification, preoperative embolization is indicated for type C and D tumours. Preoperative angiography and embolization performed 1-2 days prior to tumour resection minimises intraoperative haemorrhage and can assess collateral blood flow should the primary vessel need to be sacrificed during tumour resection. Types A and B are considered small and as a result do not warrant the risks associated with embolization [16, 17]. Embolization as a treatment option confers upon the patient minor and major risks which include otalgia, fever and postoperative poor wound healing. Major complications include stroke and VII and IX-XII cranial nerve palsies [26].

Microsurgery has historically been the preferred primary treatment for jugulo-tympanic glomus tumours until 2 decades ago. The goal of microsurgical intervention has over the years shifted from gross total resection to surgical tumour reduction aimed at preserving function [6, 23]. Initial attempts at gross total resection (GTR) of these tumours resulted into unacceptable surgical morbidity. This was as a result of the close proximity of these tumours to critical neurovasculature structures, location at the base of the skull, hyper-vascularity, poor preoperative imaging and poor intraoperative visualisation of these tumours [23].

These slow-growing hypervascular tumours have a tendency to be locally infiltrative and encase critical neurovascular structures [24, 25]. The growth pattern of glomus jugulotympanicum tumours usually results in the encasement of the jugular bulb, sigmoid sinus and internal carotid artery [6, 24, 25]. With intracranial extension, these tumours compress

the brain stem and involve the lower cranial nerves and cavernous sinus. These tumour factors have made surgery in this region a formidable challenge [6, 16, 23, 24, 25].

The emergence of high definition CT and MRI has improved pre-operative surgical planning. Furthermore, preoperative angioembolisation and advances in base of skull microsurgical techniques have enhanced the possibilities of obtaining a gross total resection [13, 14, 26].

In the present era, documented tumour control for GTR range from 81-91% [21]. Complications associated with surgery to glomus jugulare include stroke (8-20%) and cranial nerve injury (33-44%) and overall mortality of 5-13% [29].

Despite these advances tumour surgical access remains difficult and post -operative mortality due to injury to neurovascular structures remain high [6, 23]. Microsurgery is primarily indicated in cases with raised intracranial pressure, brain stem compression, secreting tumors, and tumour progression after radiation, facial paralysis, malignant transformation, and when there is a low risk of lower CN injury [6, 7, 17, 23].

Radiotherapy

The high morbidity associated with microsurgical resection coupled with advances in the various modalities of delivering radiotherapy have led to the shift from surgery to radiotherapy as the primary treatment option for these tumours over the last two decades [12,30,31]. Advances in medical imaging and computing have made it possible to treat these tumours more precisely. These advances include conventional external beam radiotherapy with 3D conformal radiotherapy with or without intensity modulation and stereotactic radiosurgery [12, 32, 34]. The goal of treatment with radiotherapy is to achieve tumour control and to preserve neurological function in the management of PHN.

Theories of how ionisation radiation achieves tumour control;

Direct cell death from Ionising radiation.

The critical target of ionising radiation is deoxyribonucleic acid, although damage to cellular, nuclear membrane and other organelles is also considered important [30]. DNA damage manifested as break of both single- and double- strand covalent bonds of the sugar-phosphate backbone of DNA molecule results into activation of signalling pathways within the nucleus [30, 31]. The activation of these pathways leads to co-ordinate network of signal transduction pathways involved in cell cycle arrest, apoptosis, stress response and activation of DNA

repair process. If DNA damage sustained by a cell is too great for survival, apoptosis is initiated [31].

Indirect tumour cell death due to Immune response.

High dose hypo-fractionated radiotherapy irradiation of tumours induces dose dependant indirect cell death most likely by causing destruction of vascular thereby deterioration intra-tumour microenvironment [31]. High dose hypo-fractionated irradiation (SRS) promotes anti-tumour immunity whereas multi-fractionated radiotherapy with low dose per fraction supresses the immune competency of the host. SRS results into the massive release of immune-modulators molecules that elevates the host anti-tumour response. The anti-immune response, which is elevated 1-2 weeks after irradiation may inhibit the proliferation of surviving tumour cells leading to suppression of recurrence and metastasis [30, 31].

Modalities of External beam radiotherapy;

Conventional External beam radiotherapy

Conventional external beam radiotherapy(EBRT) delivering photons at doses of 45-50 Gy in 20-25 sessions has historically been used as an adjunct to Microsurgery for jugulotympanicum paragangliomas with tumour control rates of > 70% [15]. Over the years EBRT was extended as primary treatment in patients with multiple comorbidities, advanced age and post-microsurgical tumour recurrence. With advances in EBRT, tumour control rates of 100% and 98.7% at 5 and 10 years respectively have been reported [19].

The treatment field in Conventional EBRT is based on the height and width of the tumour. This is associated with exposure of peritumoural tissue to radiation and increased risk of complications such temporal bone radio-necrosis, cranial nerve palsy or even secondary tumours [33, 34, 35]. Advances in imaging technology have made it possible to treat the tumour more precisely.

3D Conformal Radiotherapy.

Basing irradiation field on CT and MRI data conformal radiotherapy allows intensity of the irradiation delivered to be adapted to shape and size of the tumour limiting exposure of normal tissue to irradiation [33, 35].

Intensity- Modulated Radiotherapy (IMRT).

IMRT is a mode of high precise radiotherapy that uses computer-controlled multi-leaf collimators to deliver radiation dose that conform more precisely to the 3D shape of the target. These multiple beams from various directions, of dynamically varied intensity conformed to the 3D shape of the tumour [33]. As a result of precise delineation, irradiation is modulated in terms of time and dose: high dose to the tumour 2 to 2.2 Gy/session, lower doses to tumour margins (1.6Gy/session), and theoretically very low doses to normal tissue [33]. IMRT requires multiple session, 5 days a week for 5-8 weeks and longer duration of planning [33].

Stereotactic Radiosurgery (SRS).

In the last 2 decades radiosurgery has gained favour as the primary treatment option for the treatment of jugulo-tympanic paragangliomas [12]. Radiosurgery allows for the delivery of high radiation doses to the tumour either as a single dose, stereotactic radiosurgery or high dose hypo-fractionated irradiation stereotactic radiotherapy SRT with rapid dose fall off in surrounding structures [7,33].

Most recent data of literature show that Gamma knife and Linac and/or Cyberknife achieve good tumour and symptom control rates, ranging from 71%-100% and 88%-100% respectively, with much lower morbidity than surgery [7, 12, 34, 35, 38, 39, 40]. The risk of complications increases with the size of target volume. Toxicity increases rapidly once the volume of brain exposed to >12 Gy is > than 5-10cm3 [7, 36, 37, 42, 45].

SRS also is delivered over a much shorter duration. And the cost of in-patient care and loss of income to patients is limited. As a treatment option in low and middle income countries, SRS may not be readily available because of the high cost related to the acquisition and establishment of a functional unit.

Radiation associated toxicity.

The complications related to treatment with ionising radiation can be classified as either acute, early delayed or late delayed depending on the time duration from commencement of treatment. Radiation-associated toxicity is graded according to the Radiation therapy Oncology group (RTOG) toxicity criteria [40]. This criteria grades toxicity from 0(none) -5

(death) depending on severity of adverse effect. A major adverse event is defined as death, hospitalisation or new cranial nerve palsy. A minor adverse event was defined as new symptoms or worsening of existing symptoms [40].

Acute CNS complication occur during actual treatment period and majorly manifests as acute encephalopathy characterterised by headache, drowsiness, fever, vomiting and worsening neurological function [41,42]. This is attributed to disruption of the blood brain barrier, affects 50% of patients receiving high does or fractions of radiation. Transient morbidity such as nausea and vomiting, alopecia, tinnitus, mucositis and skin changes are unusual with modern techniques and resolve after treatment [41, 42, 43].

Early delayed complications occur up to 6 months post radiotherapy treatment. Somnolence syndrome is characterised by drowsiness, excessive sleep, nausea, vomiting commonly occurs 2 months post radiation with and incidence of 13-56%. Transitory cognitive disturbances manifesting as disturbances in short term memory and attention deficits occur in 36% of patients receiving 54-55.8Gy in 1.8 fractions [42, 44, 45].

Late delayed complications occur over 6 months to several years after treatment and include focal cerebral and bone radio-necrosis, hypopituitarism and neurocognitive impairment and occurrence of secondary neoplasms. Xerostomia with dysphagia, ear problems otitis media or external otitis and stenosis of external carotid artery [41, 42, 43, 44, 45].

Focal cerebral radio-necrosis occurs in white matter, neuropathological is characterised by necrosis with severe vascular lesion including stenosis, thrombosis, and haemorrhage. Focal delivery of large radiation dose 5-20Gy has increased incidence. The upper limit for safe dose 55-60Gy at 1.8-2.0 Gy fractions in a restricted field [42, 45].

These complications must be weighed against the natural history of these benign lesions as well as against the significant immediate and permanent risk of cranial nerve deficit if the tumour is surgically resected.

There still exists uncertainty of the risk: benefit ratio of the role of radiotherapy in the management of skull of base paragangliomas. Data on the outcome of long term follow-up for patients treated with SRS is limited both due to the rarity of these tumours and the fact that radiosurgery has only come into favour over the last 2 decades.

With controversy still existing on the optimal treatment for skull of base paragangliomas there is need to further investigate efficacy and complications related to radiotherapy and

radiosurgery. To date no clinical audit on the efficacy of radiotherapy for the management of glomus tumours had been done in our patient population at Groote Schuur hospital and UCT private academic hospital.

This study aims to establish the tumour control rates and toxicities related to radiotherapy treatment as well as patient survival. In addition, we wanted to compare the treatment outcomes in our low to medium income country institution and compare this to international trends.

The objectives of the retrospective analysis of patients with glomus tumours treated with radiotherapy as the primary treatment was to:

- To establish tumour control rates.
- To establish the acute and late morbidity related to radiotherapy.

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CHAPTER 2

Radiotherapy for skull- base paragangliomas: A 10 year retrospective review 2005-2014 at Groote Schuur Hospital and University of Cape Town Private academic hospital.

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Key words: Jugulotympanicum paraganglioma, skull-base paraganglioma, Head and neck paragangliomas, Management of Glomus tumours.

Brief Title: Radiotherapy for skull- base paragangliomas

INTRODUCTION

Paragangliomas are tumours arising from chromaffin cells which are derived from the neural crest. [1, 2, 3, 4] Clusters of chromaffin cells within the base of skull are organised into small flattened ovoid structures called glomus bodies. [3, 4, 5, 8, 21] Skull-base paragangliomas arise in the vicinity of the middle ear; the glomus jugulare from the adventitia of jugular bulb just beneath the floor of the middle and glomus tympanicum from within the middle ear cavity. [4, 5]

Skull base paragangliomas commonly present with pulsatile tinnitus (80%), conductive hearing loss (60%), otalgia, otorrhagia (7%), vertigo (9%) and dizziness (4 %) [11].These symptoms are secondary to mass effect on the surrounding structures including vasculature and lower cranial nerves [12]. Due to the slow growth of these tumours they may present when they are of considerable size [7, 11].

Paragangliomas, usually grow slowly with a median growth rate of 1.0mm per year and a median tumour doubling time of 4.2 years except for the malignant subtypes [8, 9]. Whereas the clinical course of paragangliomas is insidious, they can be locally aggressive with destruction of surrounding bony structures and encasement of critical neurovascular structures [9, 10]. Only 1-3% of glomus tumours are malignant and these metastasise commonly to lymph nodes, bone, liver, lungs and kidneys. [1, 7, 11] The 5 year survival for benign and malignant PHN stands at 97% and 23%-43% respectively [1, 7].

The treatment options for these slow growing benign lesions include; watchful waiting, preoperative embolization followed by tumour resection or microsurgical resection only, fractionated external beam radiation therapy (EBRT), and stereotactic radiosurgery (SRS). [1, 7, 8, 19, 20, 21, 22] The risk: benefit ratio of each treatment option must be weighed against the natural history of these benign lesions. [14, 30]

Over the last two decades the morbidity associated with microsurgical resection coupled with advances in the various modalities of delivering radiotherapy have led to a shift from surgery to radiotherapy as a primary treatment option.[20, 21, 22, 24, 25] The goal of treatment with radiotherapy is to achieve tumour control and preserve neurological function.

(EBRT) was historically been used as an adjunct to Microsurgery for jugulotympanicum paragangliomas with tumour control rates of 70%. [18, 26, 27] Over the years, the use of (EBRT) was extended to include patients with multiple comorbidities, advanced age and

post-microsurgical tumour recurrence. With advances in EBRT, tumour control rates of 100% and 98.7% at 5 and 10 years respectively have been reported. [12, 15, 19 33, 34, 35]

Radiosurgery has gained favour as the primary treatment option for the treatment of jugulo-tympanic paragangliomas. Tumour control rates of 71% to 100% have been reported with SRS. [7, 12, 27, 28, 29, 34, 35, 36, 37, 38, 39, 40] The benefit of tumour control with radiotherapy must be weighed against toxicity associated with radiotherapy [41, 42, 43, 44, 45].

Data on the outcome of long term follow-up for patients treated with SRS is still limited both due to the rarity of these tumours and the fact that radiosurgery has only come into favour over the last 2 decades. With controversy still existing on the optimal treatment for skull of base paragangliomas there is need to add to the current knowledge on the management of these tumours. In addition, we wanted to know and compare the treatment outcomes in our middle-income country institution to international trends.

METHODS AND MATERIALS

Ethical approval for this research was obtained from the Human research Ethics committee HREC REF 920/2014. A retrospective study from January 2005 to December 2014 of patients from Groote Schuur Hospital and UCT Private Hospital with radiological features of base of skull paragangliomas treated with radiotherapy was undertaken. The diagnosis was done based on the typical radiological characteristics of base of skull paragangliomas on Computerised tomograms (CT), magnetic resonance imaging (MRI) and angiogram of the head and neck.

The radiotherapy database was used to select patients and data chart was used to capture information. Clinical files were reviewed and grouped according to patient's biographic data, clinical presentation, treatment offered, time spent in hospital, and subsequent follow-up visits using Excel spread sheet. For patients lost to follow up, telephonic follow up was done. Where available, pre- and post -treatment images were reviewed to assess tumour control. Patients who had had prior surgery and lost to follow up were excluded from the study.

Patient selection for SRS or conventional beam & IMRT.

Patients with a maximum tumour diameter less than 3cm in any dimension were treated with SRS while those with tumour diameter greater than 3cm were treated with either 3D conformal radiotherapy, IMRT or VMAT.

Follow up protocol

The follow-up protocol for our patient population included clinical re-examination and serial scanning with MRIs every 6 months for the first year, annually for the next 2 years, and every other year thereafter. Telephonic follow up was done if patients lived too far away and were unable to visit the hospital.

Tumour Control rates

Tumour control was defined as stability or regression of clinical signs and absence of radiological progression. Treatment failure was defined a persistence or progression of symptoms and/or radiological evidence of tumour progression in spite of treatment.

Treatment adverse events

A major adverse event was defined as death, hospitalisation or new cranial nerve palsy. A minor adverse event was defined as new symptoms or worsening of existing symptoms.

Statistical analysis

Descriptive statistics were used to characterise the study groups in terms of demographics, clinical control, including mean, median and range. Analysis of local tumour control was performed using the Kaplan-Meier method and the RECIST criteria.

RESULTS

26 patients with a radiological diagnosis of base of skull paragangliomas were reviewed during this period. 46% were treated at Groote Schuur Hospital and 56% University of Cape Town Private Academic hospital. Two patients were excluded from the study; one was found to have a massive tumour with brain stem compression and palsies of the lower cranial nerves with associated cachexia rendering the patient unfit for radiotherapy. The other was a foreign national who was lost to follow up.

The 24 patients included in the study consisted of 18 female and 6 male patients with a ratio of 3:1. The mean age of presentation was 53 years with a range of 15-77. 21 patients had sporadic tumours while 3 had familial tumours. 2 patients with familial paragangliomas had multifocal lesions. Mean follow up was 53.7 months for 23 patients.

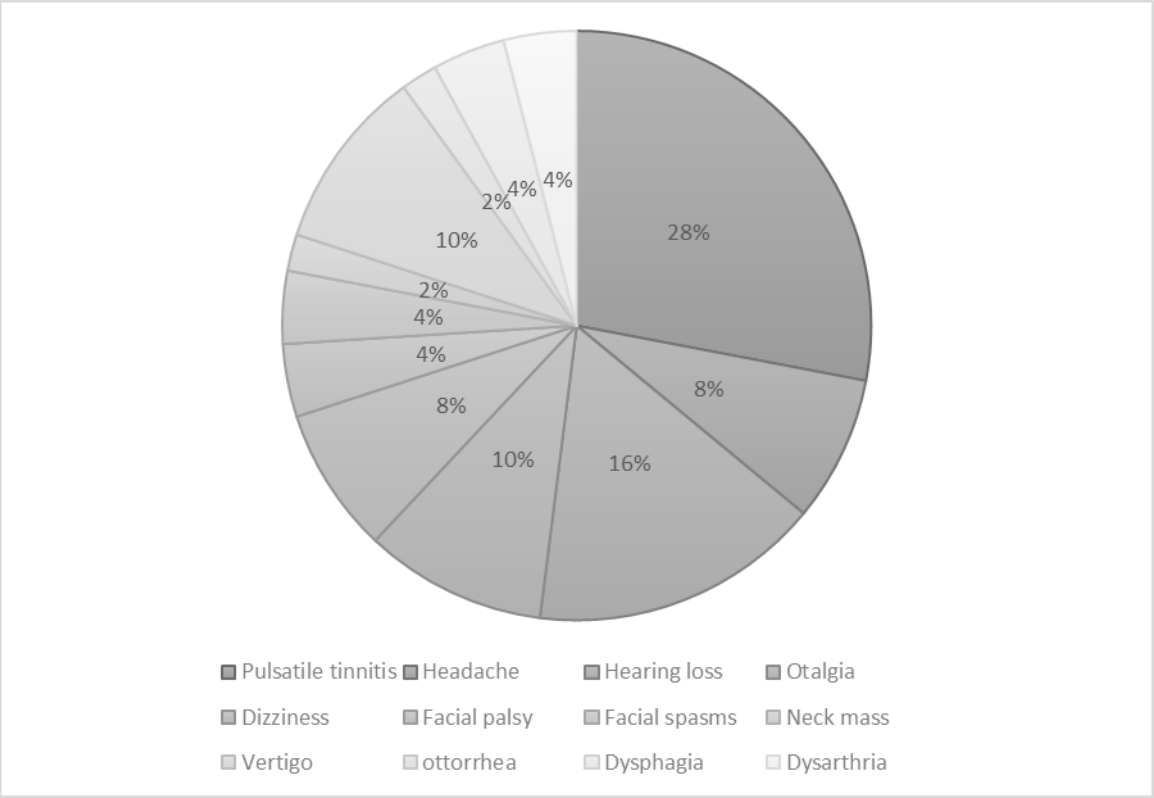
Clinical presentation.

Individual patients presented with multiple symptoms (Table 1 and Fig 1). 44% of patients presented with pulsatile tinnitus (28%) and hearing loss (16%). Excluding hearing loss, cranial nerve dysfunction accounted for 12.2% of patient symptoms (Fig.1).

Table.1 summarises clinical symptoms of patients with Skull base paragangliomas.

Presenting Complaint	**Number of patients**
Pulsatile tinnitus	19
Headache	4
Hearing loss	13
Otalgia	5
Dizziness	4
Facial palsy	2
Facial spasms	2
Neck mass	1
Vertigo	4
Ottorrhea	1
Difficulty swallowing	2
Slurred speech	2

Fig. 1 Percentage of clinical symptoms among patients with skull-base paragangliomas. Pulsatile tinnitus and impaired hearing accounting for the majority 44%.



Tumour Characteristics.

A total of 26 skull-base paragangliomas were irradiated, 62% glomus jugulare and 38% glomus tympanicum. 21 lesions were sporadic and 5 familial. Mean pre-treatment volume 3.86cm3 with a range of 0.41-15cm3 (Table 2).

Treatment.

69% (SRS 27%, SRT 42%) of patients were treated with 14-16Gy in 1-3 fractions while 31% received 48-50Gy in 25 fractions (Table 2). The mean tumour volume of patients treated with unfractionated radiosurgery was 1.05cm3. The mean tumour volume of patients treated with fractionated radiosurgery was 3.26cm3. The mean tumour volume of patients treated with fully fractionated radiotherapy was 6.77cm3.

Table 2. Summarising Tumour volume and treatment.

Tumour	Pre treatment volume	Post treatment volume	Treatment
GJ	3.83	2.0	7Gyx3#
GJ	4.8	4.8	7GyX3#
GJ	5.7	5.6	7GyX3#
GT	3.10	3.1	7GyX3#
GT	3.81	3.81	8Gyx3#
GT	3.12	3.12	8Gyx3#
GJ	4.22	4.21	7.4Gyx3#
GT	3.16	2.07	6.57gyx3#
GT	3.67	1.89	7.4Gyx3#
GJ	1.03	1.03	8Gyx3#
GJ	2.60	2.4	7GyX3#
GJ	15.33	11.91	50.4Gy/1.8#
GJ	5.00	1.6	48gy/2#
GJ	2.22	2.22	2Gyx25#
GT	1.0	1	50.40Gy/ 1.8Gy #
GJ	10.78	12.09	1.8Gyx27#
GJ	5.00	4.7	50.4GY/1.8#
GJ	6.52	6.52	50.4GY/1.8#
GJ	8.33	8.33	48Gy
GT	0.52	0.51	15Gyx1#
GJ	0.41	0.41	15Gy1#
GT	1.53	1.51	14Gy
GJ	1.1	0.9	14 Gy
GJ	1.32	1.32	14Gy
GT	1.58	0.93	15Gy
GT	0.901	0.90	14Gy

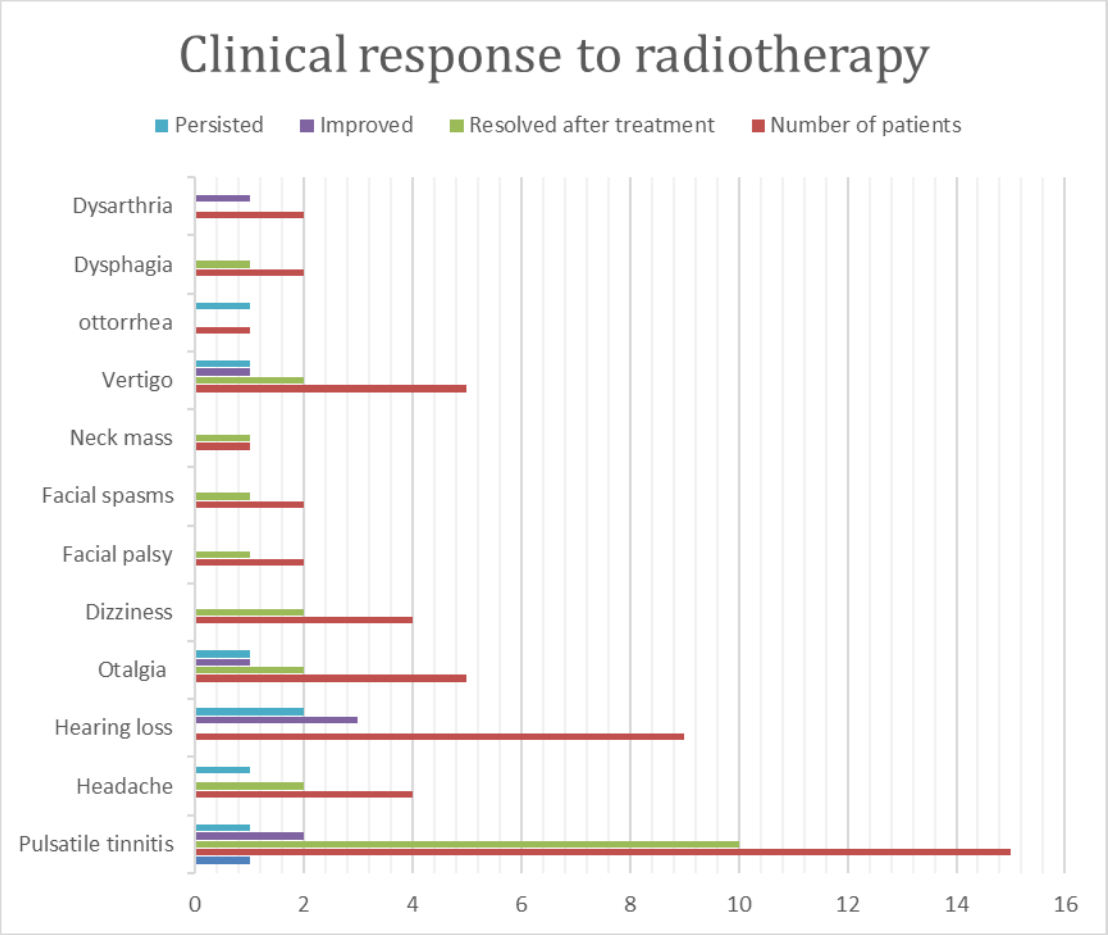
GJ Glomus jugulare GT Glomus tympanicum

Clinical control.

92% of patients reported non progression of symptoms, 42% reported complete resolution of symptoms, 30% had improvement and 20% were unchanged while 8% reported progression of symptoms. 89.4% of patients with pulsatile tinnitus reported either complete resolution or improvement (Fig2).

70% of patients presenting with hearing loss reported non progression of this symptom whilst 54% had improvement, 16% were unchanged and 30% had progression of hearing loss. One patient had clinical progression of symptoms with radiological evidence of tumour progression at 24 months of follow up (Fig2).

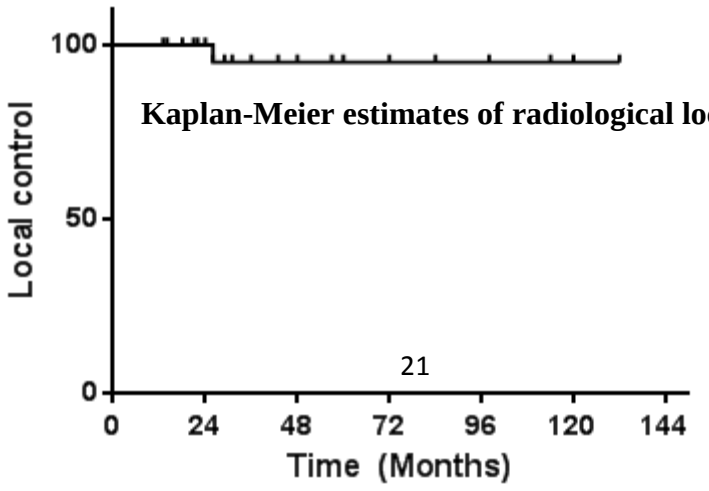
Fig2. Graph illustrating Clinical Response to radiotherapy



Radiological tumour control.

96% of irradiated tumours had no increase in tumour volume after treatment with 73% of tumours remaining unchanged and 23% had documented regression in tumour size. 100% radiological control was achieved in patients receiving both unfractionated and fractionated radiosurgery. 27% of the fractionated radiosurgery group had regression of tumour volume. Radiological control was achieved in 87.5% of patient 3D conformal radiotherapy. A single patient in this group had tumour progression at 24months follow up Fig 3.

Fig.3 **Kaplan-Meier estimates of radiological local tumour control**



Radiation associated toxicity

76% of patients treated reported no minor or major toxicities associated with treatment. 3 out of 7 patients (43%) receiving conformal radiotherapy reported minor toxicity. 2 out of 7 patients (28%) in the radiosurgery group had complications related to treatment. One patient had documented osteonecrosis of the temporal bone 5 years after therapy, complicated with ottorrhea. 1 of 11 irradiated with stereotactic radiotherapy had a minor complication.

Table 3 summarising toxicities associated with different treatment modalities.

Grading	**3D Conformal RT 3/7**	**SRS 2/7**	**SRT 1/11**
Minor	Chronic uveitis x2, Insomnia Nausea, Otalgia, Ottorrhea, Tympanic membrane perforation, vomiting. Hearing lossx3	Ottorrhea, Dizziness, Otalgiax2, Hearing Loss	Dermatitis
Major	Non	Osteonecrosis 1	Non

Numerator: patients with complication Denominator: patient in treatment group

DISCUSSION.

Over the last 2 decades there has been growing evidence favouring radiotherapy over surgery as the primary treatment option for paragangliomas. The goal of management is to achieve tumour control with preservation of neurological function. The rate of morbidity due to cranial nerve deficits after surgery remains high when compared to radiotherapy or radiosurgery, CN IX 38% vs. 9.7%, CN X 26% vs. 9.7%, CN XI 40%vs12% and CN XII 12% vs.8.7% [7, 21, 34, 35, 36, 39].

Prior to 2004 jugulo-tympanic paragangliomas at GSH/UCT were primarily managed surgically, an experience characterised by incomplete tumour resection and morbidity associated with new cranial nerve palsies particularly for tumours involving the petrous bone. A combination of our surgical experience and the increasing body of evidence favouring radiotherapy resulted into a switch from surgery to radiotherapy as the primary management for these tumours in our unit.

This 10 year retrospective review demonstrates the efficacy of different techniques of radiotherapy, achieving local control of skull-base paragangliomas. Clinical and tumour control rates are equivalent or better than rates in literature [21]. 30% regression of tumour volume is similar to rates reported in the literature [7, 32, 37, 39]. A clinical control rate of 96% with absence of new cranial nerve deficits except for hearing loss highly favours radiotherapy as the primary treatment for skull-base paragangliomas.

No conclusion can be drawn as to the effect of tumour size on local control, although the only patient with an increase in tumour size had a large tumour with a volume of 10.78cm^3. An argument for safe cytoreduction surgically followed by radiotherapy maybe appropriate.

The study further demonstrates that radiation associated toxicity is mainly minor. The only patient with a major complication had a radiological diagnosis of temporal bone necrosis after treatment with SRS at 5 year follow up. The least complications were noted in patients receiving fractionated radiosurgery. Though the conventional group had most complications these were mainly transient. Late complication of radiosurgery maybe under reported as longer follow up for the treatment population is needed.

This study is limited by its retrospective nature and the duration of follow up for these benign tumours. As a result long term radiation- associated toxicity such as secondary malignancy may be under-reported

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APPENDICES

TELEPHONIC CONSENT FORM GLOMUS JUGULARE STUDY

Personal Introduction

•Hello, my name is Dr Wegoye Emmanuel from the University Of Cape Town Division Of Neurosurgery.

- I work with Prof Allan G Taylor and Prof. Jeannette Parkes
- I am contacting you because we are conducting a follow up study on patients diagnosed with Glomus Jugulare tumour who received radiotherapy as a form of treatment.
- Would you like to hear more about this study?
- If a participant declines participation, I will thank them for their time and end the call.

Do you have any questions before we get started? You can stop me at any time and ask questions

Description of the Purpose of the Study

- To establish clinical improvement or deterioration in patients who received radiotherapy
- To establish tumour control rates in patients who received radiotherapy.
- To establish the complications related to radiotherapy as a form of treatment.

Description of Participation

- If you agree to be in this study, you would answer a telephonic questionnaire regarding your clinical outcome following treatment with radiotherapy.
- After I start asking you the study questions, you can refuse to answer any questions that you don't want to, or tell me that you want to stop answering the questions and that would be fine.
- If I feel that the questions are making you uncomfortable, I may stop the study questionnaire.

Description of Payments and Costs

- There is no cost to you to participate in this research study.

Description of Confidentiality

- The records of this study will be kept private. In any sort of report we may publish, we will not include any information that will make it possible to identify you. Research records will be kept in a locked file and available only to Prof Allan G Taylor, Prof David Le feuvre, Dr Jeannette Parkes and Dr Wegoye Emmanuel.

- All electronic information will be coded and secured using a password protected file.

Contact Information

- If you have any questions about the study, please contact DR. Wegoye Emmanuel, 0739268681

- If you have no questions, we can begin the study; do you give your consent to participate in this study?

☐ Affirmative

☐ Negative

GLOMUS JUGULARE DATA CAPTURE FORM

Demographics

Patient Code Age Sex

Clinical Assessment

Follow up period

Presenting symptoms Pre-radiotherapy Progression Regression

Pulsatile tinnitus

Vertigo

Hearing Loss

Flushes

Dysphasia

Palpitations

Vocal cord Paralysis

Horner's syndrome

Facial Paralysis

Paresis of neck muscles.

Altered taste

Neck Mass

Weak trapezius and SCM

Examination findings

Radiological Characteristics

CTB or MRI

Follow up Period

Tumour parameters Pre-radiotherapy Radiological Progression/Regression

Location

Size

Extent

Unconstrasted

Constrasted

Radiotherapy Associated Complications

Dose

Immediate Acute Long term

Mortality

Cause

GLOMUS JUGULARE PATIENT QUESTIONNAIRE

Date

Clinical Progression

1 .Do you remember your main presenting complaints at the time of diagnosis that you had a Glomus Jugulare tumour?

Yes No

2. If yes, what was your presenting Complaints?

3. What has been the course of your presenting complaints from the time of diagnosis to date?

Treatment.

4. Did you receive radiotherapy as the only mode of treatment for your tumour?

5. What was the effect of radiotherapy on your presenting complaints?

- Resolved
- Unchanged
- Progressed

6. Did experience any complications after Radiotherapy?

Thanks for participation in this study.