Clinical symptoms and volumetric radiological responses of acoustic neuroma patients, treated with hypo-fractionated image guided radiotherapy (IGRT) at Groote Schuur hospital between 2013 and 2016

by

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DECLARATION

I, *Dr Alison Riddick,* 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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1. Acknowledgements and contributions

I wish to thank the people involved in this research:

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- J. Parkes and H. Burger for their contributions with the proposal and article
- N. Bhim and M. Parker for their assistance with designing Red Cap data capture forms and data analysis respectively.

2. List of tables and figures

Table 1.*Patient and tumour characteristics*

	N (%)
Gender	
Female	4 (30.8%)
Male	9 (69.2%)
Age (y) at initial visit	
Mean	60.4y
	Range 45-79y
Tumour location	
Left	7 (53.8%)
Right	6 (46.2%)
Koos classification	
Stage I (intracanalicular)	1 (7.7%)
Stage II (CPA)	9 (69.2%)
Stage III (CPA reaching pons)	3 (23.1%)
Stage IV (deforming pons shifting 4th ventricle)	0
Alive	
Yes	8 (61.5%)
No	5 (38.5%)
Previous surgery	
Yes	2 (15.4%)
No	11 (84.6%)
Tumour size (MLD)	

<10mm	0
11-20mm	12 (92.3%)
21-30mm	1 (7.7%)
31-40mm	0
>41mm	0
ECOG	
0	0
1	12 (92.3%)
2	1 (7.7%)
3/4	0
Neurofibromatosis type II	2 (15.4%)

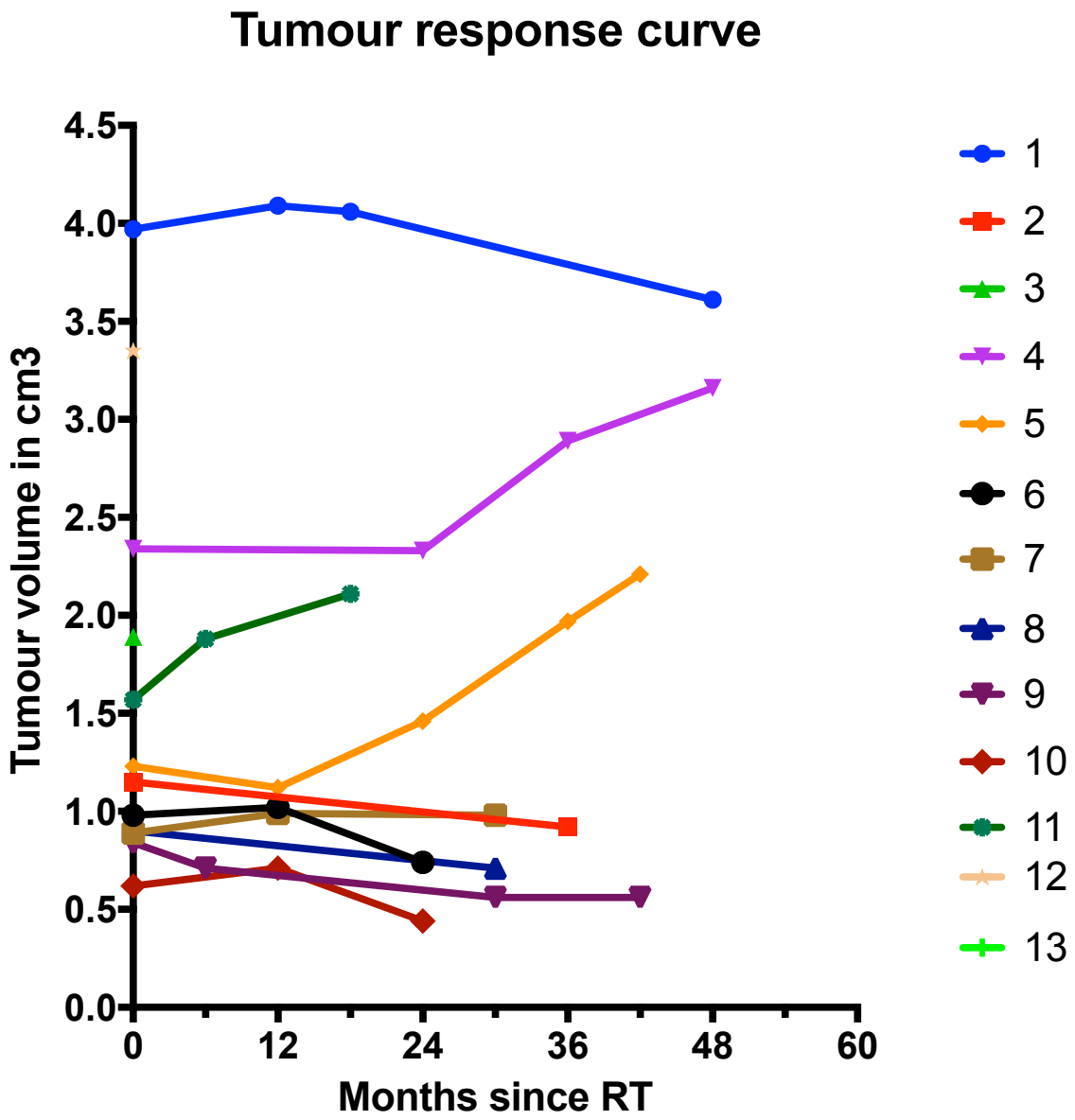

Figure 1.*Individual tumour response trend after SRT*

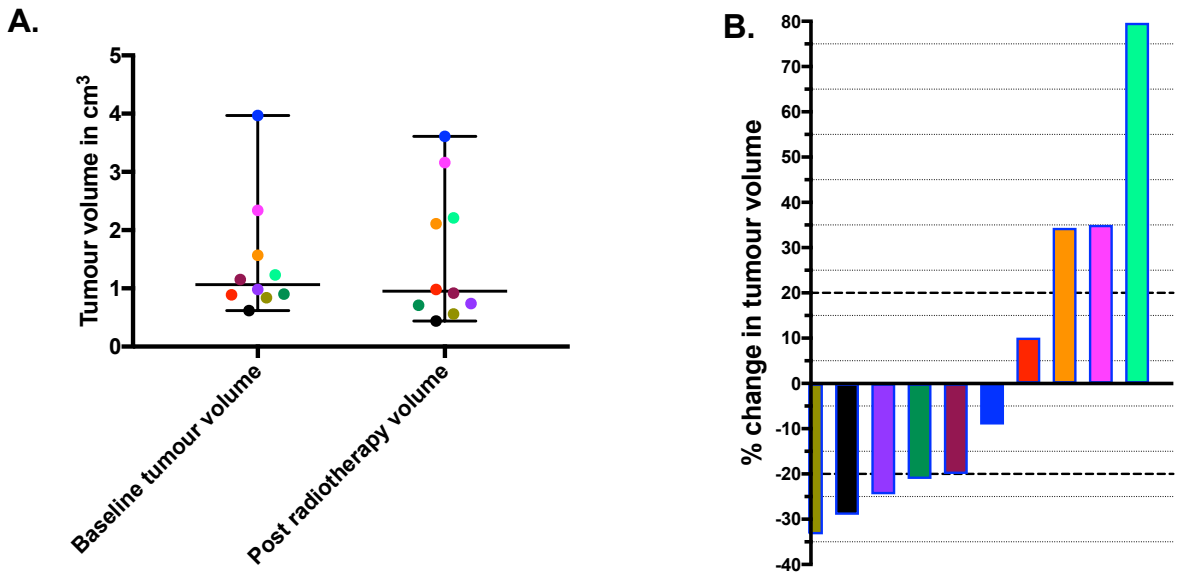

Figure 2*. Changes in tumour volume from Baseline*

A. Wilcoxon plot depicting pre- and post-RT volumes for 10 patients , at time of last imaging (range 18- 50 months) . Maximum, minumum and median TV are depicted by the superior, inferior and middle lines.

B. Waterfall plot showing post treatment volumes. Stable disease is between the dashed lines (-20% and +20% change in tumour volume).Tumour progression can be seen in 3 patients, stable disease in 3 patients, and regression in 4 patients.

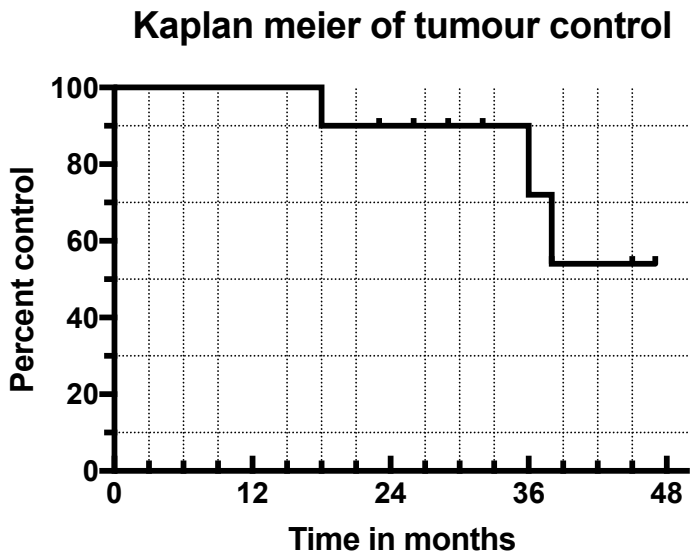

Figure 3. *Kaplan-Meier curve showing radiological tumour control after hypofractionated SRT*

Correlation of radiologist reported 2D TV versus calculated TV

Radiologist reported axial measurements were plotted against calculated TV for MRIs (fig 4).

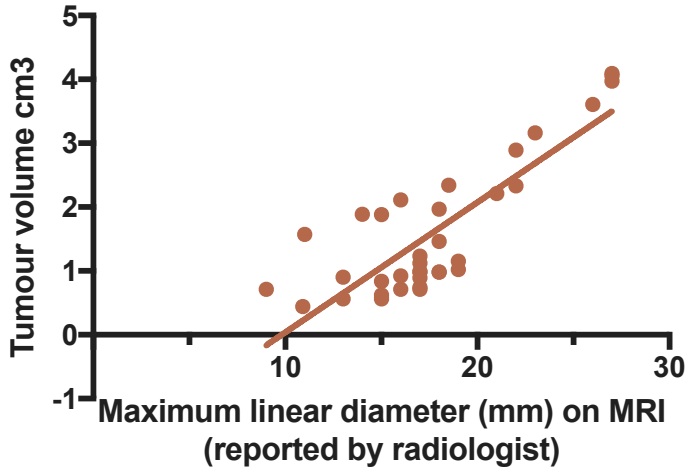

Figure 4. *Radiology correlation*

3. Abbreviations

AN	Acoustic neuromas
RT	Radiotherapy
SRS	Stereotactic radiosurgery
SRT	Stereotactic radiotherapy
DCA	Dynamic conformal arc
CPA	Cerebellopontine angle
GSH	Groote Schuur Hospital
MRI	Magnetic resonance imaging
Gd	Gadolinium
NF2	Neurofibromatosis type 2
TPS	Treatment planning system
TP	True positive
TN	True negative
FP	False positive
FN	False negative
CT	Computed tomography
Linac	Linear accelerator
MLD	Maximum linear diameter
LMIC	Low and middle income country
IGRT	Image guided radiotherapy
RTOG	Radiation Therapy Oncology Group
ECOG	Eastern Cooperative Oncology Group
CN	Cranial nerve
GTV	gross tumour volume
PTV	Planning tumour volume
TV	Tumour volume
BTV	Baseline tumour volume
RTV	Radiologist tumour volume

4. Abstract

Background:

Stereotactic radiosurgery (SRS) is the gold standard for treatment of small and medium sized tumours, although fractionated regimens are well described. Access is limited in resource-constrained settings. There are no South African data describing outcomes of AN patients treated with fractionated stereotactic radiotherapy (SRT) using photons. We describe clinical and radiological outcomes of AN patients treated with SRT at an academic centre in Cape Town, South Africa.

Objectives:

To describe patient demographics, tumour characteristics and patients' symptoms and changes in symptoms at follow-up. To investigate tumour local control (LC) rates at last follow up MRI, and compare LC rates described for SRS in the literature. To correlate radiologists' serial 2D maximum linear diameter (MLD) measurements with calculated 3D tumour volume (TV).

Methods:

Fifteen AN patients treated with modified SRT (18.0gy/3fractions, were identified from the planning database; 13 were included. Patient data and tumour characteristics (size, laterality and previous surgery) were retrospectively extracted from clinic folders. Initial planning data was accessed and checked. Tumour volumes were contoured by the author on all subsequent MRI's per patient and validated by a second investigator; tumour volume (TV) was automatically calculated. Radiologist's 2D MLDs were compared with 3D TV. Sensitivity and specificity of radiologist reported change of MLD as a measure of actual change in TV was calculated. LC was calculated, from time of treatment to time of last MRI or time of progression (defined as ≥20% increase in TV).

Results:

Mean age was 60.4years (range 45-79years), with 4 (30.8%) being female. Seven patients (53.8%) had left sided tumours and median tumour size was 1.15cm^3 (mean 1.59 $cm^{3;}$ range 0.62-3.35 cm^3). Nine patients (69.2%) had Koos stage 2 ANs, 3 (23.1%) had stage 3 tumours and 1 (7.7%) had a stage I tumour. Two patients had NF2.Median follow-up time

was 29 months (range 0-50 months). Median baseline TV, as was 1.15 cm^3 (mean 1.59cm^3 with range 0.62-3.35 cm^3).

Three patients had no follow-up MRIs: 2 demised and 1 declined further follow-up. In total 5 patients died, 4 of unrelated causes and 1 of unknown cause (median time to death after RT 24 months, range 6 – 36 months). LC was 74% at 36months. Hearing preservation rate was 67%. No new facial or trigeminal nerve symptoms were noted. Radiologists correctly reported tumour growth in 100% of tumours that grew, and specificity was 77.3% in those that were stable.

Conclusion:

This is the first local study in hypofractionated SRT using photons. We show lower LC rates than seen in literature; our numbers are small and short follow up time short, with high attrition rates. Acute treatment toxicities were absent. Longer term follow-up is needed to assess late RT effects. A prospective study using this method of treatment would better define LC.

5. Introduction and Literature Review

Anatomy and pathology

Acoustic neuromas (AN) are benign intracranial lesions (WHO I) arising from the myelin producing Schwann cells which encapsulate the vestibulocochlear nerve(CNVIII). Ninety percent of tumours have their origin in the inferior division of CN VIII(1). Tumours usually arise from the nerve in the internal auditory canal (IAC), where the narrow bony anatomy limits expansion, but may occur anywhere along its length. Extrameatal tumours expand into the cerebellopontine angle (CPA) and may compress the brainstem. Part of the nerve's course in the posterior fossa and base of skull runs close to the facial and trigeminal nerves (CN VII and CN V respectively), and tumours found here may cause CN neuropathies.

Epidemiology

Relatively common tumours, ANs make up 5-10% of adult intracranial tumours and as much as 80-85% of cerebellopontine angle (CPA) tumours (2-4) They arise mainly unilaterally (90%) where they are sporadic. Where bilateral, they are usually associated with neurofibromatosis type 2 (NF2). The median age at diagnosis is 55 years, with a roughly equal female and male distribution (3). The incidence of ANs varies greatly across time periods and geographical areas, from 1.9-20 ANs/million of the population/year. A Polish group described a crude surgical incidence of 1.9 AN/million inhabitants per year (based on a questionnaire answered by ENT and neurosurgeons) (5). In contrast in 2004, a large Danish group quoted an incidence in their population of 17.4/million/year(6). These data are based on a registry of AN which is updated prospectively with all newly diagnosed tumours and are thus more accurate. Other registry based data have been published by groups in Cambridge, England (annual incidence of 20 ANs/million inhabitants for the 10-year period 1981-1991)(7), and Manitoba, Canada (7/million/year for the period 1987-1991)(8). Part of the increasing incidence noted is explained by earlier diagnosis and availability of sophisticated imaging modalities such as magnetic resonance imaging (MRI) and computed tomography (CT)(3, 9). Median size has decreased with earlier diagnosis, while age at diagnosis has remained static. One theory to explain this phenomenon is that elderly patients are also being offered imaging earlier(3)

Natural history

Decisions for treatment of these benign tumours depend largely on their growth patterns, as it is when they undergo progressive growth, especially in the CPA, that they can cause significant morbidity and rarely mortality. Much has been published in the literature on the natural history of ANs, but numbers in these observational studies are small(10-13). They are also fraught with patient selection bias (e.g. older patients with co-morbidities, those unwilling to have an intervention or unfit for surgery).

A small study by Hoistad et al found only 44% of tumours displayed growth during a mean follow-up period of 28.2 months. They grew on average 2.17mm per annum(14)

More recently a systematic review was published reviewing studies on patterns of AN growth in patients undergoing observation(4). A total of 42 papers were analysed in this review. It confirmed that there are no predictors for growth including age, gender, tumour size at baseline, laterality or symptoms at presentation. The authors noted that most studies did not specifically describe patterns of growth, but the few that did detail these patterns, identified multiple patterns of variable frequencies: these included continuous growth in 15 to 25%, stability followed by growth (13-20%), growth to stability or regression (3-40%), stability (20-50%) and regression in 5-8%(15, 16).

In the largest study on the natural history of ANs, a Danish group published data on their one-centre cohort of all AN patients diagnosed in Denmark over 30 years until 2005 (17). Of these 1,818 patients, 729 were observed with serial MRIs and 552 had at least 2 scans. The authors defined growth in IAC tumours as extension out of the internal auditory meatus, while an increase in largest diameter of 2mm or more was considered growth in CPA tumours. Of the 230 IAC tumours, 17% expanded to become extrameatal. This was statistically significantly fewer than those extrameatal tumours that exhibited growth (28.9% of 322; $p<0.001$). Of those that grew, neither the IAC nor the CPA tumours exhibited any growth after 5 years of observation post diagnosis; as such they suggest annual scans for the initial 5 years, and thereafter scans are repeated biennially (year 7 and 9), and at year 14 (18).

Tumours reaching 20mm have a higher risk of becoming symptomatic, and this is often the critical point at which an intervention will be planned with the patient.

Tumour size and grading

First outlined in 1976, the Koos grading system(19) defines tumour extent, and has been used widely in the literature as a classification system over the past 4 decades.

Koos grading system:

Grade 1 tumours are confined to the internal auditory canal.

Grade 2 tumours extend into the CPA but doesn't involve the brainstem.

Grade 3 tumours encroach the brainstem.

Grade 4 tumours have mass effect on the brainstem, may cause hydrocephalus and compress cranial nerves.

A recent study published by Erickson et al has shown the Koos system to still be a valuable and reliable tool for characterizing ANs(20). Tumours may also be categorized by size into the following groups(6):

Small:	1-10mm
Medium:	11-20mm
Moderately large:	21-30mm
Large:	31-40mm
Giant:	≥ 41mm

Presentation and symptoms

Despite their non-malignant pathology, ANs can be associated with significant morbidity. Presenting symptoms are most commonly hearing loss, tinnitus and vertigo related to CN VIII involvement. Less frequently, compression of the trigeminal and/or facial nerve (CNs V and VII respectively) results in facial numbness, weakness or facial paralysis. Large and giant tumours may uncommonly lead to compression of the brainstem or cerebellum and in rare cases cause obstruction of the ventricular system resulting in hydrocephalus.

Vestibulocochlear dysfunction (CN VIII): unilateral sensorineural hearing loss and tinnitus are the 2 commonest presenting symptoms in acoustic neuromas, present in up to 95% and 63% of patients, respectively, (21). Unsteadiness is also frequent, seen in one study in 61% of patients at presentation, with true vertigo being less common.

Degree of hearing loss at audiogram is assessed using the Gardner-Robertson classification system(22). Pure tone audiogram and speech discrimination are scored as follows, and hearing classified from I-5:

Gardner-Robertson Classification	Speech discrimination	Pure tone audiogram
Class 1 (good)	70-100%	<30dB
Class 2 (serviceable)	50-69%	31-50dB
Class 3 (non-serviceable)	5-49%	51-90dB
Class 4 (poor)	1-4%	>91dB
Class 5 (none)	0%	none

Classes I and 2 are considered serviceable hearing, and classes 3-5 non-serviceable.

The facial and trigeminal nerves (CN VII and CN V respectively) closely follow the course of CNVIII through the base of skull and patients may present with neuropathies of these cranial nerves.

Facial nerve dysfunction (CN VII): compression of the facial nerve by ANs (seen in 6% of patients (21)) may cause varying degrees of facial weakness, and uncommonly taste disturbance and xeropthalmia may be seen. Facial paresis is graded using the House-Brackmann scoring system I-VI(23)

Grade I Normal

Grade II Mild dysfunction (slight weakness, normal symmetry at rest)

Grade III Moderate dysfunction (obvious but not disfiguring weakness with synkinesis, normal symmetry at rest) Complete eye closure with maximal effort, good forehead movement

Grade IV Moderately severe dysfunction (obvious and disfiguring asymmetry, significant synkinesis) Incomplete eye closure, moderate forehead movement

Grade V Severe dysfunction (barely perceptible movement)

Grade VI Total paralysis

Trigeminal nerve impairment (CN V): occurs in 9% of AN patients(21), and presents as facial numbness, facial pain or trigeminal neuralgia along any or all the branches of CNV (ophthalmic, maxillary or mandibular branches)

Other neurological symptoms including ataxia, dizziness, headaches, vomiting may also be presenting symptoms in cases of large tumours having a pressure effect on the brainstem or cerebellum, or due to hydrocephalus.

Radiological diagnosis

Unilateral sensorineural hearing loss is the usual presenting complaint prompting patients to seek medical attention. CT scans were initially used as the diagnostic modality until the mid 1980's when MRI became commercially available. The addition of gadolinium (Gd) to MRI further improved imaging, and this is now the standard of care. Typically, ANs enhance with Gd contrast on MRI and CT, and are noted to expand the IAC on bony windows on CT.

Up to 12% of ANs are discovered incidentally (24), and these asymptomatic and minimally symptomatic ANs pose a therapeutic dilemma, due to their variable natural history(4, 12, 17, 25). Many lesions remain stable over long periods of time displaying slow growth of 1 to 2mm/year. However, others grow more rapidly, enlarging upward of 2-4mm annually while still others may show growth and then spontaneous regression (4, 17).

Evolution of treatment

ANs may be treated with several modalities: historically this was surgery (26). More recently treatment options are "wait and scan", microsurgery and stereotactic radiosurgery/ radiotherapy has been added to the armamentarium(2).

Patients with cystic tumours and NF2 require special mention. Radiotherapy is not recommended for cystic lesions, as this modality may induce rapid enlargement, causing significant morbidity and may be life threatening (17). In NF2, as patients frequently have bilateral ANs and are at risk of other central nervous system tumours, management should be individualized (27). Hearing preservation is of the utmost importance.

Observation

A "wait and scan" approach is controversial, but is an acceptable option where tumours are indolent on serial imaging and patients are not experiencing unacceptable symptoms (2, 6, 17). This is also a valid option in elderly patients who are not fit for surgery and in those who decline intervention. Hearing loss is, however, a risk in this strategy as it has been described in up to half of patients (28). In younger patients with small tumours and good hearing, the recommendation at the 7th International conference on acoustic neuromas is for early intervention (29).

Surgery

Sub-total resection of an acoustic neuroma was first described by Balance in 1907(26). Tumours were usually large and symptomatic at presentation, with significant morbidity from both the tumour and its surgical resection. Mortality rates described were up to 84%(30) and cranial neuropathies were severe post-surgery.

Microsurgery

With the development of microsurgery, newer surgical techniques and increased expertise, outcomes have vastly improved over the past few decades. Mortality post-surgery is now very low, with rates of 0.2-1% reported (31-33). Approaches include retrosigmoid, to preserve serviceable hearing; translabyrinthine for the removal of large lesions and where hearing has already been lost, and via the middle cranial fossa in lesions of <1.5cm. Subtotal resection is intentionally done in some cases with a view to hearing or facial nerve preservation, but complete resection is usually feasible. Where resection is incomplete, recurrence can occur in up to 15%(34). Surgical debulking in large tumours for symptom relief is followed by SRS to ensure LC rates are improved.

Other commonly reported significant surgery-associated morbidity is trigeminal nerve fallout, facial nerve damage and less commonly CSF leaks, infections and vascular complications. Intraoperative monitoring of cranial nerves improves facial nerve and vestibulocochlear nerve damage.

Stereotactic radiosurgery and radiotherapy

Stereotactic radiosurgery (SRS) using cobalt sources was first introduced in the 1950s (Leksell Gamma Knife), with a fixed head frame for immobilisation. Doses of a single 16Gy fraction were initially delivered, but significant rates of facial paralysis and numbness were seen (27). Subsequent dose reduction to 13Gy (to the marginal dose) has resulted in improved CN toxicities and similar tumour control rates to the higher dose(35). Patients can be treated as outpatients, and there is no post-operative recovery period required compared with surgery.

Subsequently, linear accelerators (LINACS) have been adapted to enable delivery of SRS without head frames. Online image guidance facilitates accurate positioning of patients and allows a high dose to be delivered to the tumour volume with submillimeter accuracy (36, 37). Conventional fully fractionated RT (FSRT), hypofractionated stereotactic radiotherapy (SRT) and single fraction stereotactic radiosurgery (SRS) have all been used with excellent outcomes(35, 37, 38).

Current treatment guidelines

Reports have shown lower morbidity and no mortality with radiotherapy compared to surgical treatment of ANs(39, 40). In 2013 Wolbers et al published a review of 6 controlled studies comparing microsurgical and radiosurgical outcomes for the treatment of small and medium ANs (<30mm). All showed better outcomes in those patients treated with radiosurgery(33).

Persistent sensori-neural hearing loss is common, regardless of the treatment modality used, and rarely improves post-microsurgery or post-SRS. Rates of functional hearing preservation quoted in the literature are variable, with 2 recent reviews describing microsurgical preserved hearing rates of 0-40%(33) versus 25-75 % for SRS (33, 41). Fractionation of radiotherapy exploits the radiobiological repair of normal tissues, and may improve hearing preservation (42).

SRS has become the gold standard for managing small and medium sized AN tumours. In addition to short treatment time, SRS has the benefit of outpatient treatment, no post-operative recovery period and no surgical morbidity. Recent literature reviews describe various fractionation regimens, some comparing tumour control with SRS versus SRT (33, 36). Hearing preservation rates for SRS historically were 51% (43, 44) but with dose de-escalation and current marginal doses of 12-14Gy, large series report hearing preservation rates of between 41-79% for Gamma knife (2). Multiple studies such as Meijer et al and Collen et al have directly compared single fraction SRS with SRT and found no significant benefit for hearing preservation using fractionated RT(45).

In terms of other cranial nerve function, high rates of preservation of facial nerve (95-100%) (2)and trigeminal nerve (99-100%)(42, 46) function is reported for SRS and SRT. No significant differences have been described in studies comparing hypofractionated regimens with SRS (2, 47).However, there is a still a paucity of data describing hypofractionated methods, and to the author's knowledge, none using photons have been published in South Africa.

Radiological tumour measurement and definition of tumour control

ANs are asymmetrical "ice-cream cone" shaped tumours with different growth patterns depending on whether they are purely intra-canalicular or involve the CPA. This makes accurate measurement challenging. Both the method of measurement of ANs and the definition of tumour control post treatment are poorly defined in the literature (12, 48). The American Academy of Otolaryngology –Head and Neck Surgery defines a method

measuring the square of the mediolateral x anteroposterior dimension of the tumour(49). This method is however not utilized in the literature or in practice.

Traditionally, radiological evaluation of tumour growth has been according to the RECIST criteria using change of maximal linear diameter(MLD). This estimates 3D tumour volume, using 2D tumour diameter, and assumes symmetrical growth. Given the irregular dimensions of the ANs, MLD on MRI is less accurate than tumour volume, and can result in gross underestimation of tumour growth and regression rates (12). Using an equation cited by a Hong Kong group for tumour volume (50)

$$V \text{ (volume)} = k \text{ (constant)} \times D^3 \text{ (maximal diameter)}$$

a 10mm lesion which shrinks by 30% will only show a 1mm reduction in diameter.

Stangerup et al, who have the largest prospective observational study in the natural history of ANs, defined growth for intracanalicular lesions as extension of the tumour to involve the extrameatal region. Extrameatal lesions' growth was defined as >2mm growth in diameter(17).

These various methods of measurement of tumour response post treatment make it difficult to compare outcomes. Also, studies do not adequately define what is meant by tumour control, and where defined, there is variation as to the cutoff for growth (the literature quotes 1-3mm change in MLD) (51). It has been previously shown that radiologists cannot accurately or reproducibly measure change in tumour size of less than 2mm(51).

More recent studies (52, 53) have highlighted the inaccuracies of 2D measurement and validated volumetric measurements to assess tumour response to therapy; there is increasingly a trend in the literature to describe tumor control in terms of tumour volume, and has previously been defined as less than a 20% increase in tumor volume (TV), measured in cubic centimeters, after a minimum of 24 months of imaging(46, 50, 52, 53).

At the 7th International Conference on Acoustic Neuromas, held in Shanghai in 2016, radiotherapy radiological outcomes were graded 1 to 3: grade 1 tumours were controlled, with diameter reduction of >2mm and >10% reduction in tumour volume; Grade 2 tumours were stable (tumour diameter reduction<2mm and volume<10%; grade 3 tumours exhibited growth(29).

Table 3 Radiotherapy outcome for acoustic neuromas.

Grade	Description
1	Tumor control, tumor diameter is reduced by more than 2 mm, and the volume is reduced by more than 10%
2	Tumor stability, tumor diameter reduction is less than 2 mm, and the volume reduction is less than 10%
3	Tumor growth, the tumor does not shrink or tumor size re-increases after shrinking

In addition to the lack of consensus in the literature on the precise definition of AN growth after radiotherapy, it is also unclear which of these patients whose tumours enlarge indeed require additional intervention (microsurgery or repeat SRT). In his 2006 analysis of ANs that grew after SRS, Pollock quotes enlargement in as many as 14% of 208 patients treated with SRS between 1990 and 2001. Median tumour volume increase was 70%. He describes 3 “types” of enlargement Type 1 tumours initially enlarge and then shrink back to a similar pre-treatment size; type 2 tumours enlarge and remain larger than their original volume, but do not progress and type 3 tumours are characterised by progressive growth on serial imaging(54). He postulates that it is only type 3 tumours who may benefit from further intervention.

There is no definitive schedule for imaging. It is well documented that ANs show transient increase in size in the 9- 18 months’ post SRS and SRT(2, 29, 50), before stabilizing or decreasing in size. Post RT imaging schedules should account for transient oedema by delaying initial post-RT MRI to prevent unnecessary early intervention (2). However, the International Stereotactic Radiosurgery Society (ISRS) guidelines do not prescribe follow-up imaging intervals(2).

One institution in the Netherlands suggests initial follow-up MRI after 2 years, and the next at 5years (45) At our institution we scan annually for 5 years, and biennially thereafter.

Our setting

Where SRS is the gold standard globally in the treatment of small to medium sized ANs, in the low and middle income country (LMIC) setting such as ours, resource constraints mean that expertise and equipment dictate management of AN patients.

This GSH technique was recently described and validated in a separate study (55) as a dosimetrically acceptable alternative to SRS. As a follow-on study, planned to assess the radiological tumour control and clinical symptoms in this group of patients treated with the described regimen of hypofractionated SRT. Tumour control rates and pre-defined

symptoms, i.e. hearing preservation, facial nerve and trigeminal nerve dysfunction, and other neurological symptoms, will be described and compared with that described in the literature as being achievable by SRS(36). We also wish to assess how accurate radiologist reported 2D MLD were after treatment as a measure of calculated tumour volumes.

A simple abbreviated course of radiotherapy, which is safe and effective, has advantages for both patient and service provider in that the patient is spared a protracted course of treatment, and the radiotherapy resources are optimally utilized. It is hoped that this hypofractionated IGRT alternative technique will be able to be utilized by similar resource constrained settings.

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6. Article

Clinical symptoms and volumetric radiological responses of acoustic neuroma patients, treated with hypo-fractionated image guided radiotherapy (IGRT) at Groote Schuur hospital between 2013 and 2016.

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Introduction

Acoustic neuromas (AN) are common benign intracranial lesions arising from myelin producing Schwann cells of the vestibulocochlear nerve (Cranial Nerve VIII). They make up 80-85% of cerebellopontine angle (CPA) tumours (1, 2). With improved access to MRI in the past decade, their apparent incidence has increased to 20 per million/year(3, 4) and median size has decreased (3). Most ANs arise sporadically and are unilateral, but they may be associated with neurofibromatosis type 2 (NF2), where they are frequently bilateral and may associated with other tumours. ANs have an intracanalicular (internal auditory canal) portion, limited in terms of expansion by bony anatomy, and may extend into the cerebello-pontine angle (CPA) giving them a classic “ice-cream cone” shape.

Clinically ANs most commonly present initially with hearing loss, tinnitus and vertigo. Rarely, trigeminal and facial nerve involvement (cranial nerves V and VII respectively) leads to facial numbness, weakness or facial paralysis. Large CPA lesions may cause brainstem compression. They are grouped by size into small (1-10mm), medium (11-20mm) moderately large (21-30mm), large (31-40mm) and giant (>41mm)(5). Tumors are also classified by the Koos grading system, which describes the extent of the tumour by degree of extrameatal extension and brainstem compression: Grade I lesions are purely intracanalicular; grade II tumours extend into the CPA, not reaching the pons; grade III tumours reach the pons and grade IV tumours deform the pons and shift the 4th ventricle (6)

ANs display a variable natural history (5, 7) and management options vary accordingly: - options include a “watch and scan” approach, surgery and radiotherapy.

Observation may be appropriate in small tumours exhibiting slow growth (1-2mm/year). Morbidity of treatment must be weighed against patients' symptoms.
However, when lesions are larger or growth is more rapid, microsurgery or stereotactic radiosurgery (SRS) becomes necessary to prevent compressive symptoms.
Surgical outcomes have vastly improved over the past 2 decades with increased expertise and newer techniques. Mortality post-surgery is low, with rates of 0.2-1% reported(8-10). Standard approaches are retrosigmoid to preserve serviceable hearing, translabyrinthine (suggested for removal of large lesions and where hearing is lost(11) and the middle cranial fossa approach in <1.5cm lesions(12). Surgery should be done in high volume centres of excellence to reduce morbidity and mortality. Subtotal or gross total resection may be attempted for small or large lesions, with consideration given to tumour location and anticipated operative risks, as well as neurosurgical experience.

Over the past 2 decades, since the advent of Gamma Knife surgery, SRS has become the gold standard in the treatment of AN's <2cm because of improved functional outcomes when compared to surgery (13, 14). In addition to short treatment time, SRS has the benefit of outpatient treatment, no post-operative recovery period and no surgical morbidity.

Recent literature reviews describe various fractionation regimens, some comparing tumour control with SRS versus SRT (4, 10) However, there is still a paucity of data describing hypofractionated SRT, and to the authors' knowledge, none describing use of photons has been described in South Africa.

In poorly resourced settings such as South Africa, access to highly skilled neurosurgeons, otorhinolaryngologists and sophisticated RT is limited, posing a problem for the management of these patients. Groote Schuur Hospital (GSH) treated 25 AN patients from 2008 to 2012 with SRS, using a Radionics system. When this became defunct, SRS was no longer an option for state sector patients. A 6MV Varian Unique ™ was installed in 2013, with megavoltage image-guided radiotherapy (IGRT) software allowing for accurate repositioning of patients to within 1.5mm. Using the new Unique™, a modified hypofractionated dynamic conformal arc (DCA) technique was developed and implemented for treatment of small and medium sized ANs. Patients received 3 daily fractions of 6.4Gy per fraction, to a total dose 19.2Gy delivered within one week. This technique is described by Burger et al in a prior publication(15).

There is no data describing outcomes of AN patients in South Africa treated with SRT using photons. We describe demographics and clinical and radiological outcomes of AN patients treated with a modified SRT technique at a single academic centre in Cape Town, South Africa.

Research methods

Patients and symptoms

Of fifteen AN patients who were retrospectively identified from the planning database as having received DCA SRT between February 2013 and January 2016, 13 were included in the study. Three patients did not have follow-up imaging after treatment, and are discussed separately.

One patient was excluded as radiologically he had a trigeminal nerve schwannoma. A second was excluded due to dose reduction and inadequate tumour coverage, to ensure the brainstem dose constraint was met. All patients were over 18 years old and were permitted to have had previous surgery to their tumours.

Clinical information was extracted from radiotherapy folders at baseline and follow-up visits. Patients' demographics (age, gender, ECOG performance status at baseline), tumour characteristics (previous surgery, Koos grade, size and laterality) symptoms including CN V, VII and VIII neuropathies, and length of follow-up were all recorded.

Follow-up and imaging

Clinical follow-ups were planned for six weeks after RT, then 6 monthly for 1 year, annually until 4 years and biennially thereafter. MRIs were scheduled annually after completion of SRT for the first 4 years, and biennially thereafter. However, in practice, the frequency of clinical follow up and imaging varied. Three patients had no follow-up MRIs after treatment and mean duration of follow-up was 35,1months (range 0-50months).

Tumour measurement and control

For each MRI, maximal linear diameter (MLD) was recorded, as measured by the radiologist according to RECIST criteria for solid tumours. A 2mm change from the previous scan was deemed to be significant growth or shrinkage.

The baseline MRI was fused to the planning CT and was used at time of radiotherapy planning to delineate the gross tumour volume (GTV). This volume was used for this study as the baseline tumour volume (BTV) per patient for the study. Follow up MRI images were imported into the Eclipse™ treatment planning system (TPS) and fused to the original planning CT. The tumour on serial scans was contoured by the author using the gadolinium enhanced T1W images, and TV calculated by the treatment planning system (TPS). Volumes were validated by a second investigator.

To account for transient tumour expansion, tumour control was defined using follow up MRI scans done at least 12 months from the time of treatment, unless an increase from BTV of ≥20% was seen. Patients were censored at time of last MRI.

Correlation of radiologist tumour measurements with calculated tumour volumes

For this correlation, radiologist reported 2D measurements (maximum linear diameter, TV or AP in mm) and calculated tumour volume (TV) was depicted graphically for each MRI.

To determine if the radiologist's assessment of increase in tumour size at last follow-up scan (*i.e.* 2mm larger) can be confidently used to diagnose tumour growth, the sensitivity, specificity and accuracy were calculated:

$$Sensitivity = TP/(TP + FN)$$

$$Specificity = TN/(TN + FP)$$

$$Accuracy = (TN + TP)/(TP + FP + FN + TN)$$

Where:

TP is true positive (i.e. radiologist reports growth where there **IS increase in** tumour volume)

TN is true negative (where radiologist reports stable/smaller tumour where there **IS NO increase in** tumour volume)

FP is false positive, and *FN* is false negative.

Assessment of hearing and facial nerve dysfunction

Hearing was graded using the Gardner-Robertson classification as serviceable (Grade I-II) or non-serviceable (Grade III-V), using available clinical and audiogram information. Facial nerve dysfunction was scored using the House-Brackmann system (Grade I being normal, grade II is mild dysfunction, grades III and IV are moderate and moderately severe dysfunction, grade V is severe dysfunction and grade VI is total paralysis).

Tumour size classification

The Koos classification was used to categorize tumours using available radiological information.

Radiotherapy treatment planning

For radiotherapy planning, all patients had a localisation Gd-contrasted MRI. Images were imported and fused with the contrasted planning CT on the Varian Eclipse™ treatment planning system. The GTV was drawn using the enhancing tumour on the MRI, and a 2mm margin expanded to the PTV to account for setup error as stereotactic equipment was not available. For this study, the GTV was used as the initial tumour volume, with no margin. The dose was prescribed to the 80% isodose line, and renormalized to 100%, as per RTOG quality assurance guidelines for radiosurgery(16).

Treatment and quality assurance

For scanning and treatment, patients were immobilised using a 5-point head and shoulder thermoplastic mask, fitted to a carbon-fibre S-frame. Daily online orthogonal 2D-2D MV advanced image matching was performed, with automatic repositioning of patients in the longitudinal, lateral and vertical directions to ensure geometric accuracy of treatment delivery.

Data analysis and statistical considerations

Demographics, clinical information and tumour characteristics were descriptive, and the analysis of data displayed using tables and charts expressed as means and percentages.

Hearing was scored by Gardner-Robertson classification, using available clinical and audiogram information. Facial nerve dysfunction was scored using the House-Brackman grading. Frequency of clinical symptoms pre- and post treatment was expressed as percentages and analysis was descriptive.

Tumour progression was defined as ≥20% increase from baseline GTV, and tumour control was depicted on a Kaplan-Meier curve. Events were determined from time of time of treatment to confirmed tumour growth as seen on MRI. Patients were censored at time of their last MRI.

The Spearman correlation was used to correlate radiologist MLD and calculated TV.

For statistical tests performed, a p-value of <0.05 was considered significant. Graph Pad Prism version 7.0 was used for data evaluation.

Ethical consideration

Approval for the study was obtained from the University of Cape Town's Faculty of Health Sciences Human Research Ethics Committee (HREC REF: 385/2018)

Results

Patient and tumour characteristics

The mean age of the 13 patients included was 60.4years (range 45-79 years), with 4 (30.8%) being female. Demographics and tumour characteristics are shown in table 1. Most patients were considered to be well at their initial visit, having an ECOG performance status of 1(92.3%) or 2 (7.7%). Seven patients (53.8%) had left sided tumours and median tumour size was 1.15cm^3 (mean 1.59 cm^3 and range 0.62-3.35 cm^3). Nine patients (69.2%) had Koos stage 2 ANs, 3 (23.1%) had stage 3 tumours and 1 (7.7%) had a stage I tumour.

Two patients had NF2, one of whom (patient 1) had surgical debulking of her tumour 11 months prior to her SRT. She was also found to have a contralateral AN which is being managed with observation.

The median follow-up time was 29 months (range 0-50 months). Five deaths occurred during follow-up; 3 died of other illnesses, 1 folder (patient 12) was lost and her cause of death is unknown and one patient likely demised of advanced age. These are discussed below.

The median BTV, as calculated by the treatment planning system (TPS), was 1.15 cm^3 (mean 1.59 cm^3 with range 0.62-3.35 cm^3).

Table 1.*Patient and tumour characteristics*

	N (%)
Gender	
Female	4 (30.8%)
Male	9 (69.2%)
Age (y) at initial visit	
Mean	60.4y
	Range 45-79y
Tumour location	
Left	7 (53.8%)
Right	6 (46.2%)

Koos classification	
Stage I (intracanalicular)	1 (7.7%)
Stage II (CPA)	9 (69.2%)
Stage III (CPA reaching pons)	3 (23.1%)
Stage IV (deforming pons shifting 4th ventricle)	0
Alive	
Yes	8 (61.5%)
No	5 (38.5%)
Previous surgery	
Yes	2 (15.4%)
No	11 (84.6%)
Tumour size (MLD)	
<10mm	0
11-20mm	12 (92.3%)
21-30mm	1 (7.7%)
31-40mm	0
>41mm	0
ECOG	
0	0
1	12 (92.3%)
2	1 (7.7%)
3/4	0
Neurofibromatosis type II	2 (15.4%)

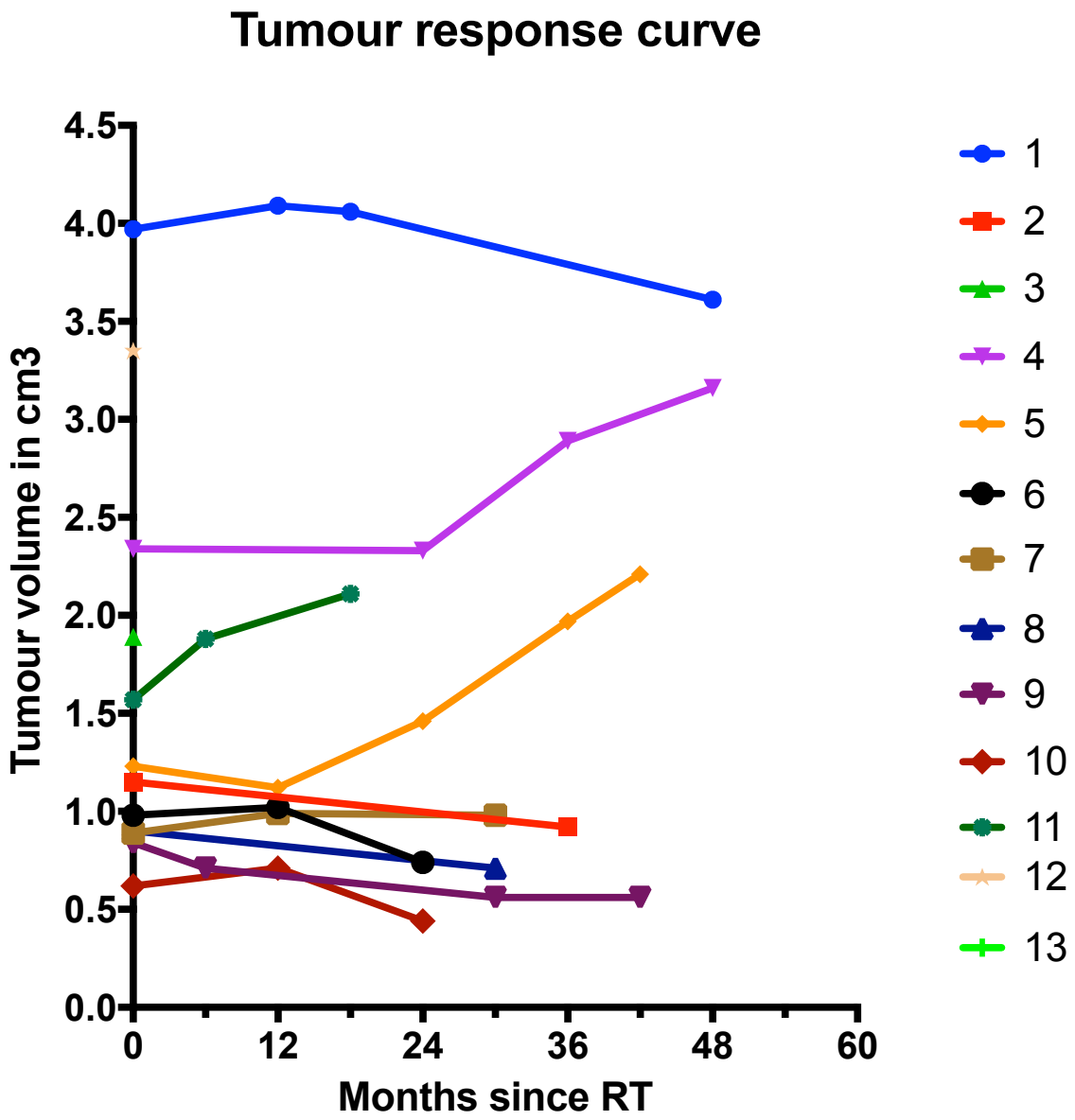

Figure 1.*Individual tumour response trend after SRT*

Figure 1 graphically shows individual tumour control after SRT over time. Transient tumour growth is noted in patients 1, 6 and 10 in their early scans (months 12, 11 and 12 respectively). Growth is also noted in early scans for patient 11 (month 18), but in the absence of surveillance imaging it's not clear if this is transient or true growth. Sustained growth is seen in patients 4 and 5.

Tumour control

Three patients did not have follow-up imaging. The mean MRI follow-up time for the remaining 10 patients was 35.1 months (range 18-50 months).

Three patients had radiological progression (≥20% increase) in TV post RT: one (patient 11) exhibited growth of 34.4% at his 18month MRI. He is due for a subsequent scan and retains useful hearing.

The other 2 patients who progressed (patients 4 and 5) had increases in their calculated TV of 23.5% at 38 months and 60.16% at 36 months respectively. Their last MRIs showed ongoing growth of 35.04% and 79.67% at 50 and 43 months respectively.

Multidisciplinary discussion regarding further intervention for both patients is ongoing (discussed below). None of these 3 patients who progressed had NF2.

The remaining 7 patients had stable lesions, with 4 exhibiting ≥20% tumour regression.

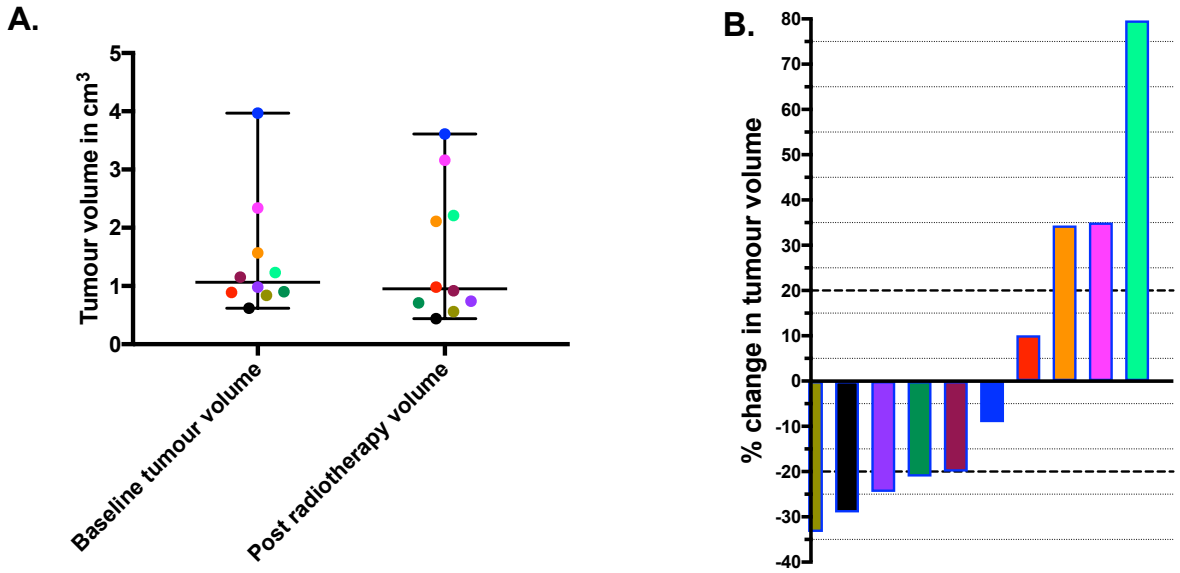

***Figure 2**. Changes in tumour volume from Baseline*

C. Wilcoxon plot depicting pre- and post-RT volumes for 10 patients , at time of last imaging (range 18- 50 months) . Maximum, minumum and median TV are depicted by the superior, inferior and middle lines.

D. Waterfall plot showing post treatment volumes. Stable disease is between the dashed lines (-20% and +20% change in tumour volume).Tumour

progression can be seen in 3 patients, stable disease in 3 patients, and regression in 4 patients.

Tumour control was depicted on a Kaplan Meier curve (fig 2). Tumour control at 36 months was 74%. Three patients had progression, showing an increase of TV of 34.4%, 60.16% and 23.5% at 18, 36 and 38 months respectively.

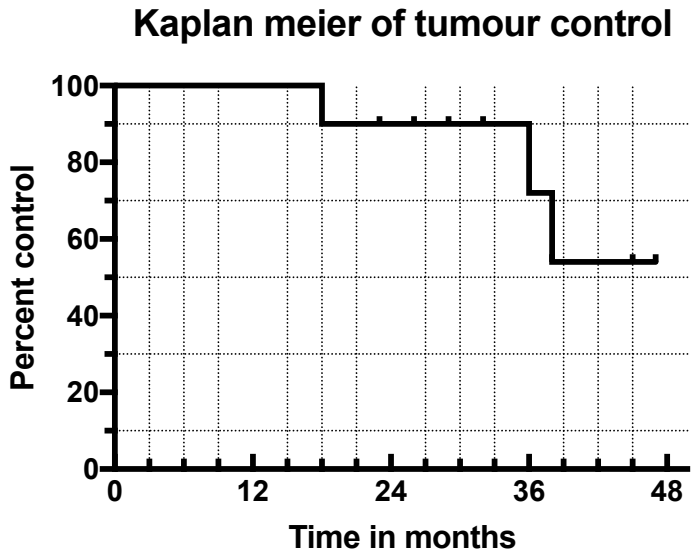

Figure 3. *Kaplan-Meier curve showing radiological tumour control after hypofractionated SRT*

Symptom outcomes

Baseline symptoms

Symptoms at baseline included vestibular-cochlear (VIII) related symptoms, namely tinnitus in 8 (61.5%), non-serviceable hearing (Gardner Robertson grade III-V) in 10 (76.9%) and ataxia in 7 of 13 patients (53.8%). Facial nerve (CN VII) dysfunction (House-Brackman grade II) was noted in one patient (7.7%) and trigeminal neuralgia (CN V) in 2 patients (15.4%). One patient (patient 12) had a facial nerve palsy (House-Brackmann grade VI) prior to her initial visit and SRT. This resolved after attempted biopsy and debulking of the lesion, which was found to be attached to the facial nerve (see discussion).

CN VIII outcomes

Non-hearing symptoms

Of the 8 patients experiencing tinnitus prior to RT, one case resolved after RT, 3 had persistent symptoms and 4 patients had no documentation of the presence or absence of tinnitus. There was one new case of tinnitus patient 1 with NF2 in the contralateral ear in which a new AN was seen on follow-up imaging.

Ataxia was present at baseline in 7 patients: 4 patients' symptoms resolved, 3 persisted. One patient had new onset imbalance post RT.

Hearing symptoms

Of the 3 patients with serviceable hearing pre RT, one became non-serviceable after treatment while the remaining 2(67%) continued to have serviceable hearing (Gardner Robertson grade II). Of the other 10 patients, 1 died (patient 20) and 9 did not recover serviceable hearing after treatment.

CN V and VII outcomes

The 2 patients (15.4%) with pre-treatment trigeminal neuralgia experienced persistent symptoms post treatment, and there were no apparent new RT-induced CN V symptoms.

Mild CN VII dysfunction (House-Brackmann grade II) present in one of 13 patients (7.7%) resolved to normal function post therapy. Patient 11, who lives out of town and whose tumour had shown growth at his 18 month MRI, telephonically reported facial paralysis post RT. His GP reported it as a Bell's palsy which resolved over some months. He has not seen

in our clinic after his treatment due to financial constraints, and sends his imaging for review by mail.

Other symptoms

Headaches that were reported by 2 patients(15.4%) prior to treatment resolved in both cases.

No-one experienced nausea or vomiting prior to or after radiotherapy. Dizziness was seen in 2 (15.4%) patients before treatment and this has persisted. New onset dizziness was also reported in a further 2 patients post-RT.

Correlation of radiologist reported 2D TV versus calculated TV

Radiologist reported axial measurements were plotted against calculated TV for MRIs (fig 4).

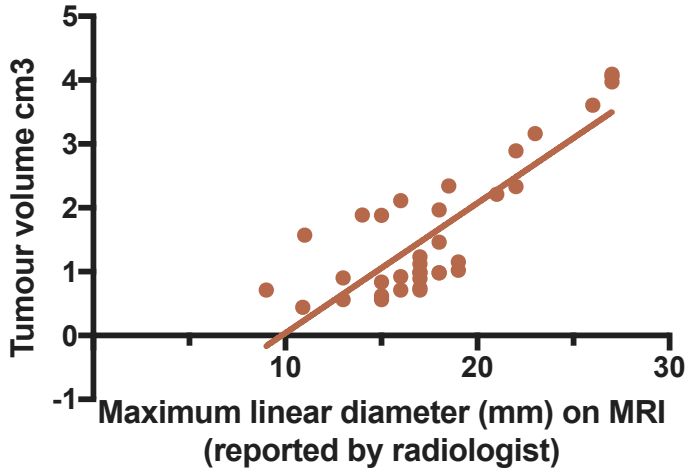

Figure 4. *Radiology correlation*

Spearman's rank test showed good correlation between MLD and calculated TV (Spearman's r=0.7394 p=<0.0001 (CI 0.5317 to 0.8632).

When comparing radiologist reported increase in MLD (*i.e.* ≥2mm from baseline MRI) with calculated TV (i.e. change ≥20% from baseline volume), we looked at a total at 23 follow-up MRIs in ten patients. There was concordance between 18 of the 23 scans. Of the 5 scans where there was discordance between radiologist reported change and change in calculated TV (i.e. false positives), there was no instance where the radiologist underreported growth (i.e. no false negatives). In fact, in all 5 cases, MLD was reported as increased while

calculated TV was unchanged or decreased; in 2 cases, stable disease was reported where calculated TV showed decrease in TV and one case where MLD was smaller and calculated TV was stable.

The sensitivity (positive predictive value) of the radiologist correctly identifying growth in tumour volume after treatment was 100% and specificity (negative predictive value) was 77.3%. The accuracy of the radiologists' assessment of whether there was a change in tumour volume was 82.1%.

Discussion

Since the advent of the Gamma Knife, SRS has become the gold standard for management of symptomatic small and medium sized ANs(2, 4, 10, 17, 18). Dose de-escalation over time has seen the reduction of marginal dose from 10-22.5 Gy to 12-14 Gy(19-21) with excellent local control of 89-99%(2), varying degrees of preservation of auditory nerve function and less morbidity of facial and trigeminal cranial nerves.

With no access to SRS in our resource constrained setting, we piloted a hypofractionated IGRT DCA regimen for treatment of ANs using 6.4Gy/fraction to a total dose of 19.2Gy. Recent publication on this data has shown this method to be dosimetrically acceptable (15), and we retrospectively describe radiological tumour control and symptom outcomes for this cohort.

Three patients in the initial cohort had only baseline imaging, and were thus excluded from the imaging follow up analysis for tumour volume. Of these 3, one patient is well and declines follow up. The other 2 demised- one patient (patient 13) died 13 months post treatment at 80 years after an emergency cardiac bypass. The second patient (Patient 12) demised 6 months post RT; her hospital folder was not found and it is unclear how she ultimately demised. At time of surgery, prior to her radiotherapy, she had a facial nerve palsy (House-Brackmann grade II/III) which resolved completely post debulking and biopsy. Biopsies of her small intracanalicular tumour prior to RT, showed only chronic inflammation. Intra-operatively the lesion was thought morphologically to be a schwannoma and was adherent to the facial nerve with extensive destruction of the cochlea and surrounding sphenoid bone. It is thus possible that she had a facial nerve or a cochlear schwannoma.

Three further patients demised during their follow-up of causes unrelated to their tumour or treatment: Patient 6 was 77, and likely died of age related illness 2y and 6months after RT. Patient 7 died after a cardiac arrest and patient 10 demised from renal failure secondary to

sepsis, 3years and 2.5 years post RT respectively. The high number of deaths, proportional to the low numbers in our cohort contribute to the poor outcomes reported.

ANs are asymmetrical “ice-cream cone” shaped tumours with different growth patterns depending on whether they are purely intra-canalicular or involve the CPA. This makes accurate measurement challenging, especially considering that tumour growth typically is estimated based on MLD on MRI. A small increase would be associated with a far greater volumetric expansion. Recent studies have highlighted the inaccuracies of 2D measurement, and proposed actual delineation of tumour volume as the preferred method(19, 22). In addition, tumour measurement is also variable across studies: some use MLD to assess growth (2mm being widely accepted), while more recent series use volumetric measurements. There is also much inter- and intra-radiologist variation in 2D tumour measurement, and it has been reported that variations of <2mm cannot be accurately measured (23). In our unit, most AN MRIs are reported on by experienced neuro-radiologists who see relatively high numbers of these tumours. However, some imaging is done elsewhere with non-standardised protocols and results may vary. For this reason, we wished to correlate radiologist 2D measurements and tumour volumetric expansion. Contrary to the literature, in our small study we found radiologist interpretation of change in tumour size was an accurate (82.1%) surrogate for the more accurate volumetric measure, with sensitivity of 100% and specificity of 77.3%. However, our numbers are small and results may therefore be skewed.

Tumour control for ANs after RT is not well defined on review of the literature, with some authors defining the endpoint for LC as being the lack of need for further intervention and others using radiological non-progression (19, 24, 25). Patel et al describes radiological response in their cohort, but ultimately defines LC as the “lack of need for surgical intervention”(24). Flickinger et al also reported LC as resection-free survival (97.1%) as well as neuroimaging control (91.0%).

Various authors have compared 2D and volumetric modalities, and propose a change in TV of 19.7-20% as being significant for growth (26, 27). Similar to small series reported by Vivas et al and Okunaga (27, 28) we defined radiological progression as >20% growth in TV from baseline. A recent literature review by Apicella et al quoted local control rates of >92% in series’ of patients with small ANs treated with radiotherapy (4). In this series there were 3 studies using hypofractionated regimens similar to ours: 3 of 4 used 18Gy/3 fractions using photons while Vernimmen et al described their outcomes using protons (26CGyE/3 fractions). All but one reported local control rates of >97%: in his cohort, Vivas et al describe reported LC rate of 83%, but specifies this is for radiological control; when reporting LC as the lack of need for further intervention in this group, this translates to 95%(28). Our small

series showed LC of 72% at 36 months which is significantly lower than that quoted in the literature with SRS and SRT. We postulate this may be partly attributable to very small patient numbers, several unrelated deaths and short follow up time in this study, as well as our definition of LC as radiological non-progression while some other studies quote LC as lack of intervention.

In addition to the lack of consensus in the literature on the precise definition of AN growth after radiotherapy, it is also unclear which of these patients whose tumours enlarge indeed require additional intervention (microsurgery or repeat SRT). In his 2006 analysis of ANs that grew after SRS, Pollock quotes enlargement in as many as 14% of 208 patients treated with SRS between 1990 and 2001. Median tumour volume increase was 70%. He describes 3 "types" of enlargement Type 1 tumours initially enlarge and then shrink back to a similar pre-treatment size; type 2 tumours enlarge and remain larger than their original volume, but do not progress and type 3 tumours are characterised by progressive growth on serial imaging(22). He postulates that it is only type 3 tumours who may benefit from further intervention. In our cohort, we saw growth in 3 of 10 patients (30%) , which is double that seen in Pollock's cohort and other studies (2, 29). At least 2 of these appear to fall into Type 3 of Pollock's classification (patients 4 and 5) and they have been discussed in the multidisciplinary meeting whether surgery should be planned. Neither patient was known to have NF2. This decision is complicated, and must consider change in imaging characteristics (e.g. increasing enhancement to suggest growth), patients choice and risk-benefit ratio of further treatment. Patients 4's calculated TV has increase by 35.04% at 50 months; however his tumour showed less enhancement and more necrosis at his last 2 MRIs compared with baseline. He is also not amenable to surgery, and so is being followed with serial MRIs.

Patient 5, although exhibiting significant tumour growth post SRT (79.67% at 43months post SRT) remains otherwise stable from her tumour symptoms. She is being managed with neuroleptics for trigeminal neuralgia that preceded her SRT, but has multiple health issues that makes decisions for further intervention complex.

Hearing loss was present in all of our patients, with only 3 having serviceable hearing (Gardner Robertson Grades1/2) at baseline. This may be a function of the delay in diagnosis from presentation to the patient's primary health care facility, as well as resource constraints on our radiology services. Hearing preservation rates for SRS historically were 51% (17, 30) but with dose de-escalation and current marginal doses of 12-14Gy large series report hearing preservation rates of between 41-79% for Gamma knife (2). Multiple studies such as Meijer et al and Collen et al have directly compared single fraction SRS with SRT and found no significant benefit for hearing preservation using fractionated RT.

In terms of other cranial nerve function, high rates of preservation of facial nerve (95-100%) (2)and trigeminal nerve (99-100%)(25, 31) function is reported for SRS and SRT. No significant differences have been described in studies comparing hypofractionated regimens with SRS (2, 32). Similarly, in our cohort, facial nerve preservation was 100% although, longer follow up is required to assess late toxicity. It is noted that older series using doses >13Gy for SRS had more cranial nerve toxicity and hearing preservation was not as high as in current series(33). Fully fractionated regimens of 5-6 weeks may theoretically further preserve remaining CN function by allowing repair of normal tissue, but has not translated to clinically significant differences in comparative studies (21, 32, 34, 35)However, lengthy treatment may not always be logistically desirable to patients, or possible in resource constrained settings with long waiting times.

Our study has several limitations which may affect interpretation of results. This is a retrospective study, with a small cohort, and therefore may not reflect statistically significant differences in data. Some clinical and imaging data is missing, which may skew results and imaging was reported by various radiologists which may contribute to inter-reporter variability.

Conclusion

This is the first study looking at hypofractionated SRT in a local South African setting. While our cohort showed lower LC rates compared with similar published international hypofractionated cohorts, our numbers are small with relatively short follow up time and high attrition rates. No unexpected acute treatment toxicities were noted, but long term follow-up is needed to assess late RT effects. A prospective study in our centre using this method of treatment would better define LC.

Acknowledgements

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Authors' contributions

Data collection and analysis, statistics and article composition was done by AR and AH. Supervision and review were done by JDP and HB.

Conflict of interest

There are no competing interests to declare.

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7. Appendices

A. REDCAP data capture sheets

B. Ethics approval

C. South African Journal of Oncology instructions to the author

A. ETHICS APPROVAL

UNIVERSITY OF CAPE TOWN
Faculty of Health Sciences
Human Research Ethics Committee

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06 June 2018

HREC REF: 385/2018

Prof J Parkes
Radiation Oncology
L-Block
GSH

Dear Prof Parkes

PROJECT TITLE: CLINICAL SYMPTOMS AND VOLUMETRIC RADIOLOGICAL RESPONSES OF ACOUSTIC NEUROMA PATIENTS, TREATED WITH HYPO-FRACTIONATED IMAGE GUIDED RADIOTHERAPY (IGRT) AT GROOTE SCHUUR HOSPITAL BETWEEN 2013 AND 2016 -(MMeD candidate-Dr A Riddick)

Thank you for submitting your study to the Faculty of Health Sciences Human Research Ethics Committee (HREC) for review.

It is a pleasure to inform you that the HREC has **formally approved** the above-mentioned study.

Approval is granted for one year until the 30 May 2019.

Please submit a progress form, using the standardised Annual Report Form if the study continues beyond the approval period. Please submit a Standard Closure form if the study is completed within the approval period.
(Forms can be found on our website: www.health.uct.ac.za/fhs/research/humanethics/forms)

We acknowledge that the student: Dr Alison Riddick will also be involved in this study.

Please quote the HREC REF in all your correspondence.

Please note that the ongoing ethical conduct of the study remains the responsibility of the principal investigator.

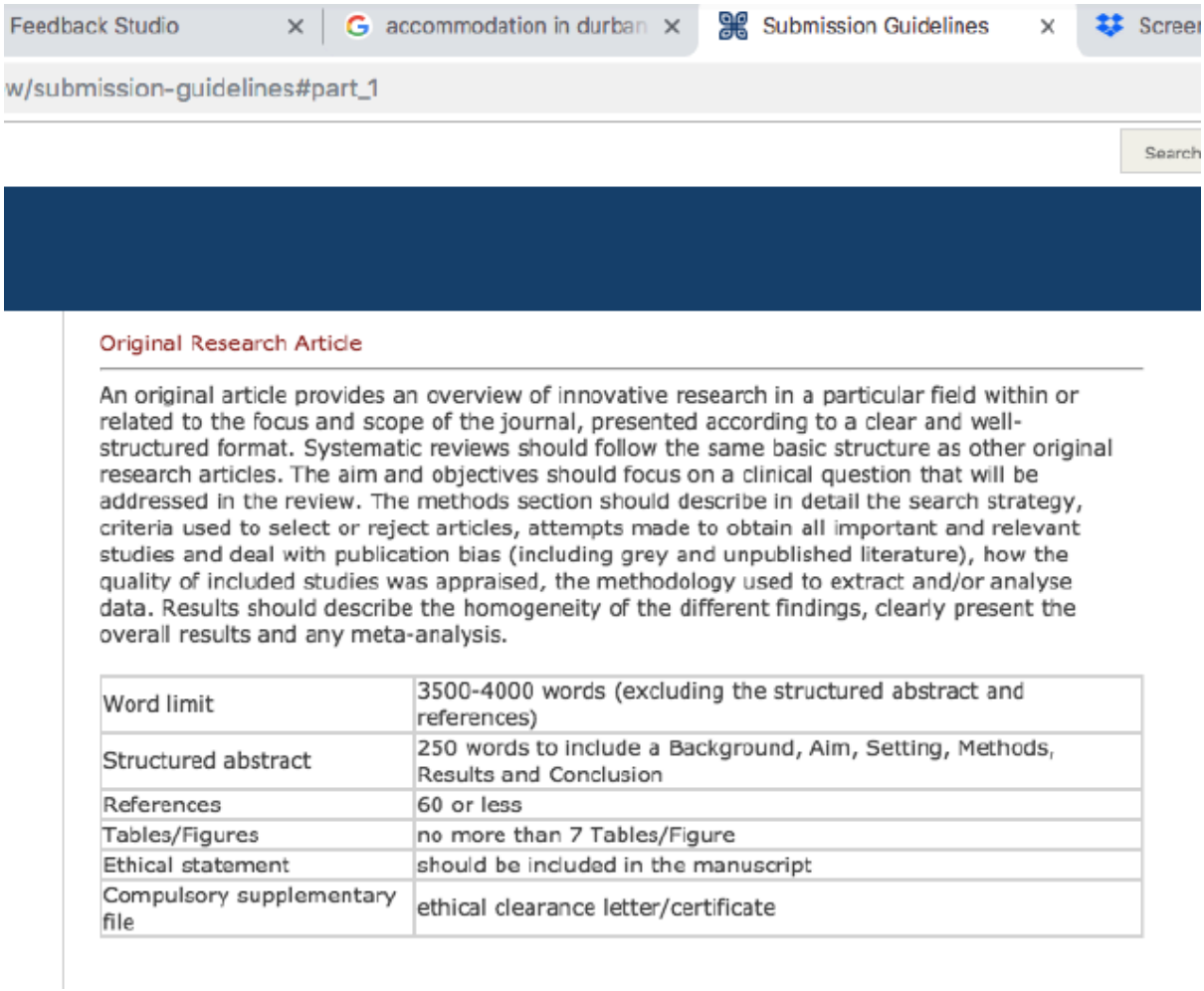
Please note that for all studies approved by the HREC, the principal investigator **must** obtain appropriate institutional approval before the research may occur.
Yours sincerely

TBurgess

PROFESSOR M BLOCKMAN
CHAIRPERSON, FHS HUMAN RESEARCH ETHICS COMMITTEE

Federal Wide Assurance Number: FWA00001637.
Institutional Review Board (IRB) number: IRB00001938

B. SA Journal of Oncology instruction to Authors



C. REDCAP data capture sheets

Confidential

Demographics

RT number	_____
Folder number	_____
Gender	◯ Female ◯ Male
Date of birth	_____
Age (years)	_____
Is patient dead	◯ yes ◯ no ◯ unknown
Date of death	_____
age at death	_____
Position of tumour	◯ Internal auditory meatus ◯ Cerebro-pontine angle ◯ OTHER
Side of tumour	◯ Left ◯ Right

Baseline visit

Date of 1st visit	_____
Neurofibromatosis 2	○ Yes ○ No ○ Unknown
ECOG score	○ 0 - Asymptomatic (Fully active, able to carry on all predisease activities without restriction) ○ 1 - Symptomatic but completely ambulatory (Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature. For example, light housework, office work) ○ 2 - Symptomatic, < 50% in bed during the day (Ambulatory and capable of all self care but unable to carry out any work activities. Up and about more than 50% of waking hours) ○ 3 - Symptomatic, >50% in bed, but not bedbound (Capable of only limited self-care, confined to bed or chair 50% or more of waking hours) ○ 4 - Bedbound (Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair) ○ 5 - Death
Previous treatment for AN	○ Yes ○ No

	Surgery	Radiation
Intervention	○	○

Date of intervention	_____

		yes	no	unknown
1	VIII Sx: Vest-cochlear symptoms	☐	☐	☐
2	VII Sx: Facial nerve fallout	☐	☐	☐
3	V Sx: Trigeminal nerve fallout	☐	☐	☐
4	Neurology besides cranial nerves above	☐	☐	☐

Tinnitus	○ Yes ○ No ○ Unknown
Ataxia	○ Yes ○ No ○ Unknown
Hearing loss	○ Yes ○ No ○ Unknown

	I - Good	II - Serviceable	III - non-serviceable	IV - Poor	V - Deaf
Gardner-Robertson grade hearing loss	○	○	○	○	○

Facial numbness	☐ V1 distribution ☐ V2 distribution ☐ V3 distribution
House-Brackman grading facial nerve	○ I - normal ○ II - mild dysfunction ○ III - moderate dysfunction ○ IV - moderately severe dysfunction ○ V - severe dysfunction ○ VI - total facial n paralysis
Other neurological symptoms	☐ Headaches ☐ Dizziness ☐ Vomiting ☐ Other
Comments	

Baseline MRI

29) Date of baseline MRI _____

30) Radiologist _____

31) AP diameter (mm) _____

32) TV diameter (mm) _____

33) Volume of lesion (calculated on TPS) in cm3 _____

Other radiological findings	Yes	No	Unknown
34) Contralateral AN	○	○	○
35) Extension out of auditory meatus	○	○	○
36) Brainstem compression	○	○	○
37) Hydrocephalus	○	○	○
38) Trigeminal nerve involved	○	○	○
39) Facial nerve involved	○	○	○
40) Central tumour necrosis	○	○	○
41) Enhancement of tumour	○	○	○

Post RT clinical check

Date of visit	_____
Is this the last visit?	○ Yes ○ No
ECOG	○ 0 - Asymptomatic (Fully active, able to carry on all predisease activities without restriction) ○ 1 - Symptomatic but completely ambulatory (Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature. For example, light housework, office work) ○ 2 - Symptomatic, < 50% in bed during the day (Ambulatory and capable of all self care but unable to carry out any work activities. Up and about more than 50% of waking hours) ○ 3 - Symptomatic, >50% in bed, but not bedbound (Capable of only limited self-care, confined to bed or chair 50% or more of waking hours) ○ 4 - Bedbound (Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair) ○ 5 - Death
Interim Radiotherapy delivered	○ yes ○ no
Dose of RT	○ 6.0Gy/fraction to TD of 18.0Gy ○ 6.4Gy/fraction to TD of 19.2Gy
Date of last fraction	_____
Time since RT (Mnths)	_____
Interim surgical intervention	○ yes ○ no
Sugical intervention	○ VP shunt hydrocephalus ○ Microsurgery to AN ○ Other
Date of surgery	_____

Symptoms at visit

		yes	no	unknown
1	VIII Sx: Vest-cochlear symptoms	○	○	○
2	VII Sx: Facial nerve fallout	○	○	○
3	V Sx: Trigeminal nerve fallout	○	○	○
4	Neurology besides cranial nerves above	○	○	○

Tinnitus
- ○ Yes
- ○ No
- ○ Unknown

Ataxia
- ○ Yes
- ○ No
- ○ Unknown

Hearing loss
- ○ Yes
- ○ No
- ○ Unknown

	I - Good	II - Serviceable	III - non-serviceable	IV - Poor	V - Deaf
Gardner-Robertson grade hearing loss	○	○	○	○	○

Facial numbness
- ☐ V1 distribution
- ☐ V2 distribution
- ☐ V3 distribution

House-Brackman grading facial nerve
- ○ I - normal
- ○ II - mild dysfunction
- ○ III - moderate dysfunction
- ○ IV - moderately severe dysfunction
- ○ V - severe dysfunction
- ○ VI - total facial n paralysis

Other neurological symptoms
- ☐ Headaches
- ☐ Dizziness
- ☐ Vomiting
- ☐ Other

Comments

Post RT MRI

Date of follow-up MRI	_____
Radiologist	_____
Date of last fraction	_____
Time since last fraction RT	_____
AP diameter (mm)	_____
TV diameter (mm)	_____
Change in max diam >=2mm	○ Yes - increase size >=2mm ○ Yes - decease size >=2mm ○ No change
Radiologist reported change?	○ No-unchanged ○ Yes-increased ○ Yes-decreased
Volume (calculated on TPS) in cm3	_____

Change in radiological findings from pre-RT MRI

	Yes	No	Unknown
Contralateral AN	○	○	○
Extension out of auditory meatus	○	○	○
Brainstem compression	○	○	○
Hydrocephalus	○	○	○
Trigeminal nerve involved	○	○	○
Facial nerve involved	○	○	○
Central necrosis	○	○	○
Enhancement of tumour	○	○	○

Change in enhancement	○ unchanged ○ More ○ Less
Change in necrosis	○ unchanged ○ more ○ less

Clinical Follow-up form

Date of visit	_____
Is this the last visit?	○ yes ○ no
ECOG	○ 0 - Asymptomatic (Fully active, able to carry on all predisease activities without restriction) ○ 1 - Symptomatic but completely ambulatory (Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature. For example, light housework, office work) ○ 2 - Symptomatic, < 50% in bed during the day (Ambulatory and capable of all self care but unable to carry out any work activities. Up and about more than 50% of waking hours) ○ 3 - Symptomatic, >50% in bed, but not bedbound (Capable of only limited self-care, confined to bed or chair 50% or more of waking hours) ○ 4 - Bedbound (Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair) ○ 5 - Death
Time since RT (Mnths)	_____
Interim surgical intervention	○ yes ○ no
Sugical intervention	○ VP shunt hydrocephalus ○ Microsurgery to AN ○ Other
Date of surgery	_____

		yes	no	unknown
1	VIII Sx: Vest-cochlear symptoms	○	○	○
2	VII Sx: Facial nerve fallout	○	○	○
3	V Sx: Trigeminal nerve fallout	○	○	○
4	Neurology besides cranial nerves above	○	○	○

Tinnitus	○ Yes ○ No ○ Unknown
Ataxia	○ Yes ○ No ○ Unknown

Hearing loss	○ Yes ○ No ○ Unknown

	I - Good	II - Serviceable	III - non-serviceable	IV - Poor	V - Deaf
Gardner-Robertson grade hearing loss	○	○	○	○	○

Facial numbness	☐ V1 distribution ☐ V2 distribution ☐ V3 distribution
House-Brackman grading facial nerve	○ I - normal ○ II - mild dysfunction ○ III - moderate dysfunction ○ IV - moderately severe dysfunction ○ V - severe dysfunction ○ VI - total facial n paralysis
Other neurological symptoms	☐ Headaches ☐ Dizziness ☐ Vomiting ☐ Other
Comments	_____

Follow-up MRI

Date of follow-up MRI	_____
Radiologist	_____
Time since last fraction RT	_____
AP diameter(mm)	_____
TV diameter (mm)	_____
Change in max diam >=2mm	○ Yes - increase size >=2mm ○ Yes - decease size >=2mm ○ No change
Radiologist reported change?	○ No-unchanged ○ Yes-increased ○ Yes-decreased
Volume (calculated on TPS) in mm3	_____

Other radiological findings

	Yes	No	Unknown
Contralateral AN	○	○	○
Extension out of auditory meatus	○	○	○
Brainstem compression	○	○	○
Hydrocephalus	○	○	○
Trigeminal nerve involved	○	○	○
Facial nerve involved	○	○	○

Change in enhancement since prev MRI	○ Unchanged ○ More ○ Less
Change in necrosis since prev MRI	○ Unchanged ○ More ○ Less