

Original Article

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Hypofractionated stereotactic radiotherapy for large vestibular schwannomas and the impact of pre-radiation debulking surgery on dosimetry and clinical outcomes

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Abstract

Introduction: This study was aimed to evaluate the outcomes of patients with large (>2 cm in great diameter) vestibular schwannomas (VSs) treated with hypofractionated stereotactic radiotherapy (HFSRT) compared to small (<2 cm) ones and the impact of debulking surgery prior to radiation for large VSs.

Methods: Fifty-nine patients with VSs treated with HFSRT (25 Gy in 5 fractions) were evaluated by tumour size and surgical status. Patients were divided based on tumour size: small VSs ($n = 42$) and large VSs ($n = 17$). The large group was further divided into the groups of pre-treatment debulking surgery ($n = 8$) and no surgery ($n = 9$). Rates of tumour control, brainstem necrosis and neurologic dysfunction were assessed following treatment. Pre-surgical magnetic resonance imaging (MRI) were used to generate hypothetical HFSRT plans to compare the effect of debulking surgery on dosimetry. Normal tissue complication probability (NTCP) modelling was performed to compare toxicity probabilities with and without surgical debulking in large VSs.

Results: There was no statistical difference of tumour control rate between small and large VSs with 100% for small tumours and 94.1% for large tumours ($p = 0.12$), respectively. In large VSs patient, the tumour control rate of HFSRT was 100% (8/8) for surgically debulked patients and 89% (8/9) for non-surgically debulked patients ($p = 0.35$). There were no patients who experienced brainstem necrosis or progression of facial and trigeminal nerve symptoms after HFSRT in the entire groups of patients. Surgical debulking large VSs did not change the maximum point dose of brainstem ($p = 0.98$), but significantly decreased volumes of VSs and changed the minimum dose to the hottest 0.5 cc of tumour ($p = 0.016$) as well as the volume receiving at least 23 Gy ($p = 0.023$). NTCP modelling revealed very low rates (average < 1%) of brainstem toxicity with or without surgical debulking, but there was a significant difference favoring surgery ($p < 0.05$).

Conclusions: HFSRT is a safe and effective treatment for both small and large VSs and is a viable option for patients with large VSs who cannot undergo surgery, if NTCP of pre-debulking HFSRT dosimetry is lower.

Introduction

Vestibular schwannomas (VS), also known as acoustic neuromas, are benign slow-growing neoplasms that arise from Schwann cells in the vestibulocochlear nerve.^{1,2} Patients commonly present with hearing loss and/or balance problems and left untreated these tumours can grow and cause cranial nerve impairment and brainstem compression.^{3,4} VSs are usually managed with surgery and/or radiotherapy with the goal of controlling tumour growth while attempting to preserve auditory, cranial nerve and brainstem functions.

Stereotactic radiosurgery (SRS) has become an attractive and non-invasive alternative to microsurgery for VSs.^{5–10} Radiosurgery can either be delivered in a single fraction, referred to in this article as SRS, or delivered in a fractionated manner and referred to here as hypofractionated stereotactic radiotherapy (HFSRT). Conventionally fractionated radiotherapy (CFRT) is non-stereotactic and involves smaller daily doses (e.g., 28–30 fractions to total doses of 50–54 Gy). HFSRT is particularly attractive for treating larger lesions as it minimises toxicity by spreading the dose out. HFSRT, which is typically given in 5–10 fractions to a total dose of 25–35 Gy, has been favoured over CFRT because of fewer treatment visits and comparable

Table 1. Patient characteristics and dosimetric parameters

	Small tumours (Koos stage 1–2)	Large tumours (Koos stage 3–4)
Patients	42	17
Sex (M/F)	11/31 (26%/74%)	8/9 (47%/53%)
Laterality (Left/Right)	19/23 (45%/55%)	8/9 (47%/30%)
Number undergoing debulking surgery	2 (4.8%)	8 (47%)
Median Age (years)	61.5 (29–83)	67.5 (16–88)
Median Follow-up (months)	33.5 (range 5–76)	15 (2–49)
Median PTV	0.9 cc (0.1 – 3.4 cc)	4.9 cc (1.4 – 22.6 cc)
Median Brainstem D_{max}	16.5 Gy (1.1 – 28.4 Gy)	26.1 (21.7 – 30.4 Gy)
Median Brainstem $D_{0.5cc}$	4.75 Gy (0 – 21.7 Gy)	20.5 Gy (9 – 23.8 Gy)
Median Brainstem V_{23}	0 cc (0 – 0.33 cc)	0.175 cc (0 – 0.62 cc)

tumour control without increased complication rates. Despite its recent use in treating larger VSs, the clinical outcomes and safety of HFSRT are difficult to assess from studies because of varied dosing patterns and fractionation regimens.^{11–13}

Numerous retrospective series have demonstrated excellent outcomes for small tumours treated with SRS alone.^{14–22} SRS for tumours larger than 2.5 cm in anterior–posterior diameter is more controversial with conflicting morbidity data reported.^{15,17,23,24} Complete resection of larger tumours usually carries unacceptable morbidity risk, and subtotal debulking surgeries are often performed instead.^{25,26} There have been sporadic reports of malignant transformation after SRS for larger tumours, and control rates have been demonstrated to be lower.^{20,27,28} Given these concerns, SRS for larger tumours is commonly reserved for inoperable patients, and subtotal resection followed by SRS for enlarging tumours is a frequently done to minimise target volume.^{29–31} While there are numerous series of single fraction regimens for both large and small VSs reported in the literature, as well as reports of HFSRT for small VSs, there is a lack of HFSRT data for large VSs.^{20,21,32,33}

There remains a need to evaluate HFSRT outcomes based on a consistent fractionation regimen. In order to discern the safety and efficacy of five-fraction HFSRT treatments, we performed this institutional retrospective study specifically focusing on tumour control rate and cranial nerve and brainstem toxicities on VSs treated with a 5 Gy \times 5 fractionations scheme. We then examined the role of surgical debulking followed by HFSRT in management of large VSs.

Materials and methods

Patient population and study design

A chart review at our institution revealed 69 VS patients treated with stereotactic radiation between 2009 and 2016. Of these, 59 were treated with HFSRT to a dose of 25 Gy in 5 fractions. The remaining 10 patients had tumours that were very small and were treated with SRS to a dose of 12 Gy. Patients included in this study were those with: (1) a new diagnosis of VS with hearing loss, (2) an enlarging VS on imaging, (3) worsening hearing loss on a surveillance audiogram or (4) a large tumour at diagnosis not amenable to gross total resection and (5) patients treated with HFSRT. Patients were divided into large (>2 cm or causing brainstem compression) and small tumour groups

(<2 cm) based on Koos stage (Figure 1).³⁴ There were 42 patients in the small tumour group and 17 in the large tumour group. There were eight patients in the large tumour group who had surgical debulking before HFSRT (Table 1).

Patient simulation and treatment

All patients were simulated on a 16 slice Phillips Brilliance Big Bore computerized tomography (CT) Scanner (Phillips Healthcare, Andover, Massachusetts, USA) using a thermoplastic immobilisation mask. CT images were imported into the Brainlab iPlan system (Brainlab iPlan, Feldkirchen, Germany) for treatment planning. Magnetic resonance imaging (MRI) images were obtained using our institutional protocol for the internal auditory canal and were fused to the simulation CT images for target and organ-at-risk (OAR) delineation. The gross tumour volume (GTV) was contoured on the T1-post contrast fat suppression MRI sequence and was expanded by 1 mm to create the planning target volume (PTV). HFSRT plans were generated using non-coplanar arcs or mixed with steady intensity-modulated radiation therapy beams with conformal indices of 1–1.5. All patients were treated with 25 Gy in 5 fractions on a Novalis TX linear accelerator using 6 MV beams (600 MU/min) with a high definition multileaf collimator (2.5 mm leaves) (Varian, Palo Alto, CA). The ExacTrac 6-degree-of-freedom robotic couch alignment system and cone beam CT were used for daily image guidance.

Data collection and statistical analysis

Patient demographics were collected including sex, age, laterality and treated (PTV) volume. Pre- and post-treatment cranial nerve status was collected from clinical documentation at the follow-up visits (6 months interval for the first two years and then yearly) including trigeminal nerve function (normal, hypoesthesia or paresthesia) and facial nerve function (House–Brackmann grade). Dosimetric data for the PTV and brainstem were collected from the treatment planning system. Dose to the brainstem was evaluated with the maximum delivered point dose (D_{max}), the minimum dose to the hottest 0.5 cc ($D_{0.5cc}$) and the volume receiving at least 23 Gy (V_{23}) (Table 1). Rates of post-radiotherapy tumour control were measured using follow-up MRIs to determine if there was true progression. Pseudo-progression defined as temporary enlargement and cystic change of tumour on follow-up MRIs was not counted against tumour control.

Patients with large VSs who underwent surgery were separately analysed to compare the improvement of brainstem dosimetry before and after surgery. These patients either received radiation right after surgery or were observed and treated when the tumour started growing. Hypothetical treatment plans were created using pre-surgical MRI images for target volume and brainstem delineations, and the same tumour and brainstem dosimetric data were collected in order to quantify the effect of debulking on GTV volume and brainstem dose (Table 2).

The cox regression model was used to relate demographics and dosimetry to clinical outcomes of tumour control (tumour appearance on MRI), cranial nerve toxicity and brainstem toxicity (hyperdense FLAIR signal and necrosis on MRI images). The Wilcoxon signed ranked test was used to determine if there was a difference of tumour control, cranial nerve and brainstem toxicities between small and large VSs groups and the pre- and post-surgical plans on large VSs (Table 3).

Normal tissue complication probability modelling (NTCP) for brainstem toxicity

Normal tissue complication probability (NTCP) modelling was performed to compare the probabilities of brainstem toxicity between the treated post-surgical plans and the hypothetical pre-surgical plans (Table 2). This model incorporates dose-response relationships for tumours and adjacent normal tissues.³⁵⁻³⁸ The mathematical expression for this model is

Equation 1:

$$NTCP = \left[1 - \prod_{i=1}^M (1 - P(D_i)^s)^{\Delta v_i} \right]^{1/s}$$

where,

Equation 2:

$$P(D_i) = \exp \left[-e^{-e^{\gamma - \left(\frac{EQD_{2Gy}}{D_{50}} \right)^{\gamma}} * (\gamma - \ln(\ln(2)))} \right]$$

where $P(D_i)$ is the probability when irradiating with D_i , M is the total number of voxels in the organ, s is the relative seriality parameter based on the functional subunit of the organ, $\Delta v_i (= \Delta V_i / V_{ref})$ is the relative volume of an organ that is irradiated with D_i and V_{ref} is the volume of the OAR.³⁹ D_{50} and γ are the physical parameters of the sigmoid curve that represent the complication probability vs delivered dose. D_{50} is the dose at which there will be a 50% complication probability, and γ is the steepness of the curve. EQD_{2Gy} is the dose delivered in 2 Gy fractions that will produce the same biological effects as a different fractionation scheme. EQD_{2Gy} is calculated as

Equation 3:

$$EQD_{2Gy} = D * \left(\frac{1 + \frac{\alpha}{\beta} d}{1 + \frac{\alpha}{\beta} \frac{2}{d}} \right),$$

where the numerator is the biologically effective dose for a fractionation scheme with a dose per fraction of d , and the denominator is the relative effectiveness on the specific tissue $\left(\frac{\alpha}{\beta} \right)$ at 2 Gy/fraction.

MATLAB (Matlab, Natick Massachusetts, USA) 2017b was used to create an algorithm for the relative seriality model.

Table 2. Tumour volume, brainstem dosimetric and NTCP comparison between pre- and post-surgical debulking HFSRT plans in patients with large tumours who underwent debulking surgery prior to radiation

Patient	Pre-Op					Post-Op				
	Vol. (cc)	D _{max} (Gy)	D _{0.5cc} (Gy)	V ₂₃ (cc)	Pre- NTCP (%)	Vol. (cc)	D _{max} (Gy)	D _{0.5cc} (Gy)	V ₂₃ (cc)	Post-NTCP (%)
1	21.552	26.64	23.0	0.5	0.41	3.1	25.5	19.3	0.07	0.35
2	4.424	26.79	22.3	0.38	0.88	3.1	25.9	17.1	0.09	0.49
3	22.36	26.07	20.6	0.24	0.70	22.6	29.5	11.3	0	0.30
4	12.723	25.14	22.9	0.42	0.36	7.2	30.4	23.8	0.62	0.00
5	33.544	28.12	27.6	6.82	0.96	3.9	21.7	21.0	0.26	0.19
6	9.177	25.65	23.3	0.57	0.86	4.0	26.0	20.2	0.16	0.05
7	29.656	28.06	24.7	1.43	2.70	11.9	27.6	21.2	0.22	0.32
8	41.36	25.51	22.8	0.34	0.68	21.0	26.4	21.8	0.23	0.27
Median	21.96	26.36	22.95	0.46	0.78	5.60	26.20	20.60	0.19	0.29
Mean	21.85	26.50	23.40	1.34	0.94	9.60	26.63	19.46	0.21	0.25

Table 3. Clinical outcomes between small tumour group and large tumour group

	Small tumours (n = 42) (%)	Large tumours (n = 17) (%)	p-value
Tumour control	100	94.1	0.12
Rate of new trigeminal neuropathy	0	0	N/A
Rate of new facial neuropathy	2.4	0	0.99
Rate of brainstem toxicity	0	0	N/A
Rate of pseudo-progression	4.8	11.8	0.34

The DVHs for the OARs were used as input arguments into the algorithm along with the physical parameters. Once the NTCPs for the brainstem were calculated for both pre- and post-surgical treatment plans, the Wilcoxon signed ranked test was used to determine if there was a significant difference.

Results

Tumour control

The median follow-up for the entire group was 49 months (range 4–98 months). The median follow-up for the small tumour group and the large tumour group were 33.5 (range 5–76 months) and 15 (range 2–49 months) months, respectively. The tumour control rate was 100% in the small tumour group and 94.1% in the large tumour group (no significant difference with $p = 0.12$), respectively. Only one patient with a very large VS (PTV = 21 cc) had a recurrence; his tumour could not be debulked initially due to intraoperative bleeding and was instead treated with HFSRT only. The tumour grew on follow-up imaging ultimately requiring surgery 5 years after HFSRT.

In the large tumour group, 8 of 17 patients had surgical debulking before HFSRT. The tumour control rate of HFSRT was 100% (8/8) for surgically debulked patients and 89% (8/9) for non-surgically debulked patients ($p = 0.35$). The median tumour volume and brainstem V_{23} were significantly reduced by debulking (Table 2).

From regression analysis, no association was identified between the patient demographics, dosimetric parameters and tumour control rates. The tumour control rates were excellent for both groups (Tables 3 and 4).

Tumour volume reduction and brainstem dosimetry improvement after surgical debulking

The median tumour volumes in large and small tumour groups were 4.9 cc and 0.9 cc, respectively. The median brainstem D_{max} was 26.1 Gy for large tumours and 16.5 Gy for small tumours. The median $D_{0.5cc}$ was 20.5 Gy for large tumours and 4.75 Gy for small tumours. The median V_{23} was 0.18 cc for large tumours and 0 cc for small tumours.

There were eight patients in the large tumour group who underwent debulking before radiotherapy with follow-up available for analysis. HFSRT was delivered either following surgery (5/8) or when tumour growth was identified on follow-up MRI (3/8). Three of eight (37.5%) patients with large tumours undergoing

Table 4. Clinical outcomes between large, debulked tumour group and large, non-debulked tumour group

	Large, debulked tumours (n = 8) (%)	Large, non-debulked tumours (n = 9) (%)	p-value
Tumour control	100	88.9	0.35
Rate of new trigeminal neuropathy	0	0	N/A
Rate of new facial neuropathy	0	0	N/A
Rate of brainstem toxicity	0	0	N/A
Rate of pseudo-progression	25	0	0.12

surgery had cranial nerve V and/or VII damage (Table 4). These cranial nerve symptoms did not worsen following radiation. Debulking significantly reduced target volume and brainstem doses. The average post-operative tumour volume was 9.6 cc compared to 21.8 cc pre-surgery ($p = 0.01455$), respectively. Compared to the hypothetical pre-surgical treatment plans, the post-surgical plans resulted in an average brainstem D_{max} of 26.2 Gy vs. 26.5 Gy ($p = 0.9844$), an average brainstem $D_{0.5cc}$ of 19.46 Gy vs. 23.4 Gy ($p = 0.0156$), and an average brainstem V_{23} of 0.21 cc vs. 1.34 cc ($p = 0.0234$) (Table 2). There was no brainstem toxicity in any patient in this study (Tables 3 and 4).

Normal tissue complication probability (NTCP) modelling for brainstem

Although the calculated brainstem toxicity using NTCP modelling was very low in both pre- and post-surgical debulking scenarios, there was a statistically significant improvement of NTCP with debulking. The median NTCP was 0.78% before surgical debulking and 0.29% afterward ($P < 0.05$). A single patient had a brainstem NTCP of 2.7% without debulking, while the other seven patients were all under 1% (Table 2).

Brainstem necrosis

No patients in this series experienced any clinical symptoms or radiographic evidence of brainstem necrosis. Although brainstem dosimetric analysis demonstrated difference of tumour volume, V_{23} volumes and NTCP between debulked and non-debulked large tumours, they were all remained in tolerant ranges as recommended from TG 101 (D_{max} and V_{23}),⁴⁰ and NTCPs were very low (0.0 to 2.7%) (Table 2).

Cranial nerve Dysfunction

No patients in this series experienced trigeminal neuropathy based on follow-up clinical assessments. Freedom from new facial neuropathy was 97.6% in the small group vs. 100% in the large group ($p = 0.99$). One patient in the small group with a pre-treatment House-Brackmann score of 1 (no symptoms) experienced new facial neuropathy (House-Brackmann score of 2).

Pseudo-Progression

Pseudo-progression is a transient enlargement in tumour size after radiotherapy and is distinct from true treatment failure.⁴¹ It was defined here as a slight increase in the size of tumour volume with significant central necrosis seen on follow-up MRIs. Pseudo-progression rates were 4·8% in the small tumour group vs. 11·8% in the large tumour group ($p = 0\cdot34$). For patients in the large group, there was no statistically significant difference between pseudo-progression rates in those who received surgery and those who received radiation alone (25% vs. 0%, $p = 0\cdot12$).

Discussion

In this study, we have demonstrated excellent outcomes with HFSRT for both small and large VSs. The usual practice at our institution has been to treat Koos stage 1–2 tumours with radiation alone, typically HFSRT at a dose of 25 Gy in five fractions for potential hearing preservation if patients had serviceable hearing. Larger tumours are often debulked for symptom relief and dosimetric improvement. Patients who undergo debulking are either treated shortly after surgery or are observed and treated with HFSRT when residual tumour progression is identified. The primary objectives of this study were to examine the clinical outcomes of small and large VS patients treated with HFSRT and to evaluate the role of upfront debulking in improving tumour control and dose to the brainstem.

There is a large body of literature supporting SRS for small VSs; however, the optimal management for larger tumours is less clear.^{14–22} Numerous treatment strategies have been described for Koos stage 3–4 tumours including maximal possible resection followed by observation, debulking followed by adjuvant radiation in a variety of fractionation schemes and radiation alone.^{26,42–44} Primary concerns with radiation to the internal auditory canal, especially with hypofractionated radiation, include tumour control, hearing preservation and brainstem and cranial nerve toxicity.^{14,16,17,19,22,32,45,46}

For small VSs, numerous studies have demonstrated an advantage of either Gamma Knife or LINAC-based SRS over microsurgery in terms of tumour control and neurologic toxicity.^{14,16,17,24,44} A recently published systematic review by Perrson et al. revealed excellent control rates with both SRS and HFSRT; however, there was a lack of long-term follow-up for patients treated with HFSRT.⁴⁷ While there were actually worse rates of facial and trigeminal toxicity after HFSRT vs. SRS in this review (only two HFSRT studies were included), our results show excellent tumour control rate and neurologic outcomes for patients treated with HFSRT with no trigeminal toxicity and only a single new case of facial neuropathy.

Larger tumours have historically been managed initially with surgery. Talfer et al. have reported on the necessity of definitive surgery for large VSs with a tumour control rate of 86% with surgery alone, but at the cost of 37% of patients experiencing poor facial function measured by a House–Brackmann score of 3 or greater.⁴⁸ These results are consistent with other surgical series for large VSs.^{26,42,43,49–53} Although perioperative mortality for this surgery is near zero, there are small risks for other peri-operative complications including CSF leak, infection, bleeding and stroke.⁴⁸ Given the high percentage of patients experiencing facial dysfunction from surgery, investigation into alternative strategies for reducing cranial nerve toxicity was warranted.

There are less data for primary management of large VSs with radiation alone. Milligan et al reported their results of 22 large VS patients treated with Gamma Knife SRS (median dose 12 Gy) and found a tumour control rate of 82% at 5 years. However, functional hearing was preserved in 28% of patients, and freedom from new facial neuropathy was very good at 85%.⁴⁶ While these results are comparable to other surgical series in terms of tumour control, patients who are able to achieve a gross total resection have the lowest recurrence rates of around 3%; however, attempts at complete resection carry a higher risk of neurologic toxicity.^{25,29,31,54} Cranial nerve toxicity was lower with Gamma Knife compared to typically reported rates with microsurgery.^{14,16,17,24,44} While Gamma Knife was highly effective for the large VS patients, the rates of tumour control and facial function preservation were worse compared to small VSs.^{14–16,19,22,46} In our study, we have demonstrated excellent tumour control rates with minimal brainstem and cranial nerve toxicity for both small and large tumour groups treated with HFSRT. To our knowledge, this study represents the first reported series of HFSRT for large VSs with excellent tumour control (94·1%) and no incidence of brainstem and cranial nerve toxicity.

Although the excellent outcome of radiotherapy for large VSs in this study, the treatment paradigm of debulking surgery followed by SRS is still an attractive treatment strategy for large VSs, especially for patients who present with symptoms of brainstem compression.^{25,26,44} The theoretical advantage of reducing tumour volume by debulking is to stave off radiation by allowing for a period of observation and/or reducing dose to the brainstem as large VSs commonly about the brainstem.^{3,4} We sought to evaluate the dosimetric and clinical benefits of surgery in the management of large VSs. By re-planning eight patients in our series, who underwent upfront debulking, we found significant improvements in brainstem $D_{0\cdot5cc}$ and V_{23} , but not the D_{max} . As expected, the target PTV was significantly reduced with debulking. Pre-surgical plans of three patients did not meet the TG-101 V_{23} brainstem dose constraint, but median pre-surgical brainstem dosimetry was still within commonly referenced brainstem tolerance criteria ($D_{max} < 31$ Gy, $V_{23} < 0\cdot5$ cc).⁴⁰ Given that none of the patients in our series experienced any brainstem toxicity, the clinical relevance of this lower brainstem dose finding is questionable. To further clarify this issue of clinical relevance, we used NTCP models, which revealed very low probabilities of brainstem toxicity with or without surgery; however, there was a small but statistically significant probability difference favouring debulking.

While this study has shown that at the very least, HFSRT alone appears to be an attractive option for selected patients who cannot undergo or otherwise refuse surgery with the advantages of avoiding possible surgical complications while retaining excellent neurologic outcomes, we do acknowledge some of its limitations of the small sample size of 59 patients and relative short follow-up, which may not have been adequate to fully characterize the clinical impact of HFSRT as a treatment for VSs as well as delineate any potential toxicities. We recommend further investigation by other institutions on their VS patients treated in a similar manner as well as studies into determining whether the timing of HFSRT after surgical debulking impacts clinical outcomes.

Conclusions

HFSRT to a dose of 25 Gy in five fractions appears safe and effective treatment option for both small and large VSs including

tumours with significant brainstem compression in our study. The optimum management of large VSs is still unclear as there is a lack of randomised data; however, HFSRT alone appears to be a viable option for selected patients with large VSs, who cannot undergo surgery or are unwilling to have surgery. While this paper does not definitively recommend HFSRT as a treatment option, it does warrant further investigation as stated above.

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