Long-term clinical outcomes of stereotactic radiotherapy for bilateral vestibular schwannomas in neurofibromatosis type 2 patients

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Abstract

Purpose

The evidence for treating patients with neurofibromatosis 2-related vestibular schwannoma (VS-NF2) using hypofractionated stereotactic radiation therapy (HSRT) is limited. This study aimed to investigate clinical outcomes in patients with VS-NF2 treated with CyberKnife HSRT.

Methods

We retrospectively analyzed 25 NF2 patients with 48 VSs who were treated using CyberKnife HSRT at Ramathibodi Hospital from January 2009 to January 2020.

Results

Median follow-up was 98 months (range, 24–155). Median tumor volume was 2.3 cm³ (range, 0.04–28.3). Median prescribed dose was 18 Gy (range, 18–25) in three fractions (range, 3–5). The 5- and 10-year progression free survival rates were 87% and 80%, respectively. The 5- and 10-year hearing preservation rates were 59% and 35%, respectively. Three patients developed new symptoms associated with transient volume expansion after treatment: hydrocephalus in one, facial weakness in one, and ataxia in one. No patient developed worsening of trigeminal nerve function. No malignant transformation occurred.

Conclusions

CyberKnife HSRT demonstrated excellent long-term tumor control with a low non-auditory complication rate in patients with VS-NF2. However, preservation of hearing remains a major concern.

Introduction

Neurofibromatosis type 2 (NF2) is a rare autosomal dominant disorder caused by mutations in the NF2 gene [1–2]. Bilateral vestibular schwannomas (VSs) are a hallmark, but NF2 is also associated with other benign schwannomas as well as meningiomas and ependymomas. Patients with NF2-related VS (VS-NF2) commonly present with progressive hearing loss and deafness. There are several different options to treat VS-NF2, including observation, radiotherapy, bevacizumab administration [3], and surgical resection; however, the optimal treatment remains controversial.

Although stereotactic single-fraction radiosurgery (SRS) and fractionated stereotactic radiotherapy have been frequently cited as successful treatments for sporadic VS, their effectiveness for VS-NF2 is debatable because studies have reported worse outcomes for VS-NF2. Additionally, they may be
associated with malignant transformation and radiation-induced secondary tumors. Delivery of hypofractionated stereotactic radiotherapy (HSRT) with the CyberKnife frameless robotic radiosurgery system has recently emerged as an option for treatment of benign intracranial tumors. However, data regarding HSRT for patients with VS-NF2 is limited. This study aimed to investigate clinical outcomes of CyberKnife HSRT treatment of VS-NF2, with a focus on tumor control, hearing preservation, and long-term treatment toxicity.

Materials and Methods

Patients

This retrospective study examined consecutive patients diagnosed with NF2 who harbored unilateral or bilateral VSs treated using CyberKnife HSRT at Ramathibodi Hospital, Mahidol University in Bangkok, Thailand from January 2009 to December 2014. Patients with VS-NF2 are managed in our institution using a team-based approach. Treatment decisions are mainly based on symptoms and Koos classification \[4\]. The Koos classification divides tumors into four grades determined on magnetic resonance imaging (MRI) of the brain. Koos I tumors are completely contained within the meatus; Koos II tumors have intra- and extra-meatal components but do not contact the brainstem; Koos III tumors have direct contact with the brainstem; and Koos IV tumors contact with mass effect on the brainstem.

For Asymptomatic Koos I tumors, observation is generally recommended. Symptomatic patient with Koos grade I-III tumors are typically treated with HSRT. Koos grade IV tumors are typically resected with or without postoperative HSRT. However, some patients with Koos grade IV tumors and contraindications for surgery may be treated using HSRT. All patients provided informed consent for treatment. The study was approved by the institutional review board of Ramathibodi Hospital.

HSRT

HSRT was delivered using a CyberKnife G4 system (Accuray, Inc., Sunnyvale, CA, USA), which uses a 6 MV light-weight linear accelerator that is mounted on an articulated robotic arm. Multiplan Treatment Planning Software (Accuray, Inc.) was used for inverse treatment planning. Real-time 6D skull tracking was applied for image-guidance to visualize and engage the intracranial lesion. A thermoplastic facemask was individually constructed for patients to wear while lying in the supine position. Computed tomography simulation was performed with the mask applied using 1.25 mm slice thickness. Simulation images and gadolinium-enhanced magnetic resonance images were transferred to the treatment planning workstation. Gross tumor volume (GTV) and critical structures were delineated at the workstation. No additional margin was added to the GTV to obtain the clinical target volume (CTV) and planning target volume (PTV).

HSRT was delivered in three to five fractions. Total dose ranged from 18 to 25 Gy and was prescribed to the periphery of the lesion. Prescribed isodoses were selected individually for each patient to cover more than 95% of the GTV Selection of total tumor dose, number of fractions, and prescribed isodose varied
among patients according to tumor size and treating physician preference. Eighteen Gy delivered in three fractions was a commonly used regimen. Radiation was administered once a day for 3 to 5 consecutive days. Treatment planning (Fig. 1) was determined and finalized by a radiosurgery team comprising neurosurgeons, radiation oncologists, and medical physicists.

**Assessment of treatment response and toxicity**

Patients were followed clinically and with magnetic resonance imaging (MRI) to evaluate treatment outcomes. Hearing function was evaluated using patient-reported hearing ability and audiometric testing. Hearing function was classified using the Gardner–Roberson (GR) system [5]; class I and II hearing was defined as serviceable. Trigeminal and facial nerve function were assessed using the Barrow Numbness Index and House–Brackman score [6], respectively. New trigeminal or facial nerve symptoms or worsening of pre-existing ones were defined as nonauditory complications.

MRI was performed annually or biannually for the first 5 years, and then every 2 to 3 years thereafter. Radiologic response was reported using the standard RECIST criteria [7]. Complete disappearance of the tumor was defined as complete response (CR). Diameter reduction > 30% from baseline was considered partial response (PR). Diameter increase > 20% was considered progressive disease (PD). Any response that did not meet the definitions of CR, PR, or PD was considered stable disease (SD). Tumor control was defined as the absence of radiologic tumor progression. Tumor growth with or without alterations in the tumor enhancement pattern followed by a size decrease to pretreatment size or smaller was classified as transient volume expansion (TVE). Tumors exhibiting TVE were considered controlled unless symptoms worsened and further treatment was required; these tumors were considered progressive. Hearing preservation was defined as the presence of serviceable hearing (GR class I or II) at last follow up.

**Statistical analysis**

Categorical data are expressed as numbers with and percentage. Continuous data are expressed as medians with range. Survival was determined using the Kaplan–Meier method. Univariate and multivariate survival analysis were performed using the log-rank test and Cox proportional hazard regression, respectively. Statistical analyses were performed using SPSS software version 18 (IBM Corp., Armonk, NY, USA)

**Results**

Twenty-five NF2 patients with bilateral VSs were included for analysis. Twenty-three (92%) underwent HSRT simultaneously on both sides and two (8%) underwent it on only one side because of small tumor size or asymptomatic nature. Therefore, 48 tumors were analyzed. Median age was 25 years (range, 30–54). Eight patients were men (32%) and 17 were women (68%). Sixteen patients (64%) had previously undergone surgery. No patient was treated with bevacizumab. Prior to HSRT, 18 patients (37%) had serviceable hearing in the treated ear. Median prescribed radiation dose was 18 Gy (range, 18–25) in three fractions (range, 3–5). Median isodose was 71% (range, 60–82). Most tumors were Koos grade II
(38%) and grade I (31%). Median tumor volume was 2.3 cm$^3$ (range, 0.04–28.3). Patient, tumor, and treatment characteristics are summarized in Table 1

Table 1. Patient, tumor, and treatment characteristics
<table>
<thead>
<tr>
<th>Characteristic</th>
<th>N (%) or median (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>25 (30-54)</td>
</tr>
<tr>
<td>Follow-up (months)</td>
<td>98 (24-155)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>8 (32)</td>
</tr>
<tr>
<td>Female</td>
<td>17 (68)</td>
</tr>
<tr>
<td>Presenting symptom</td>
<td></td>
</tr>
<tr>
<td>Hearing loss</td>
<td>15 (60)</td>
</tr>
<tr>
<td>Hemiparesis</td>
<td>5 (20)</td>
</tr>
<tr>
<td>Ataxia</td>
<td>2 (8)</td>
</tr>
<tr>
<td>Hydrocephalus</td>
<td>2 (8)</td>
</tr>
<tr>
<td>Facial pain</td>
<td>1 (4)</td>
</tr>
<tr>
<td>Previous surgery</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>16 (64)</td>
</tr>
<tr>
<td>No</td>
<td>9 (36)</td>
</tr>
<tr>
<td>Location</td>
<td></td>
</tr>
<tr>
<td>Right</td>
<td>25 (52)</td>
</tr>
<tr>
<td>Left</td>
<td>23 (48)</td>
</tr>
<tr>
<td>GR hearing class before treatment</td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>13 (27)</td>
</tr>
<tr>
<td>II</td>
<td>5 (10)</td>
</tr>
<tr>
<td>III</td>
<td>9 (19)</td>
</tr>
<tr>
<td>IV</td>
<td>15 (31)</td>
</tr>
<tr>
<td>V</td>
<td>6 (13)</td>
</tr>
<tr>
<td>Hearing status before treatment</td>
<td></td>
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<tr>
<td>Serviceable</td>
<td>18 (38)</td>
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<tr>
<td>Non-serviceable</td>
<td>30 (62)</td>
</tr>
<tr>
<td>Tumor volume (cm³)</td>
<td>2.3 (0.04-28.3)</td>
</tr>
</tbody>
</table>
Tumor response and progression-free survival (PFS)

Median clinical follow-up was 98 months (range; 24–155). TVE occurred after treatment in 13 tumors (27%) in 13 patients. These tumors appeared more bulbous and heterogeneous on the initial follow-up MRI (median, 6 months (range, 4–45), indicative of TVE. Ten of these patients were asymptomatic and had tumors that appeared stable or smaller on subsequent MRI (median follow-up, 12 months [range, 5–30]). Three patients developed new symptoms in conjunction with TVE, including one with hearing decrease and facial weakness that improved with dexamethasone treatment; the other two had progressive ataxia and required surgical intervention. At last follow up, the tumor response was classified as stable in 30 (63%), PR in 11 (23%), and PD in 7 (14%).

In six patients with seven tumors classified as PD, two developed symptoms in conjunction with TVE; the other four had progressive tumors. Four of these six required surgical intervention, including tumor resection in three (two with a progressive tumor and one with TVE) and ventriculoperitoneal shunt placement in one patient who developed hydrocephalus because of TVE. The two other patients with progressive tumors did not undergo surgery because of extensive simultaneous bilateral tumor progression and poor performance status. One died because of the tumor and the other was still alive at last follow-up. The 5- and 10-year PFS rates for the entire cohort were 87% and 80%, respectively (Figure 2A). The median time to progression was 42 months (range, 10–83). Several factors were analyzed for association with PFS, including prior surgery, Koos classification, and radiation dose; Koos grade III/IV tumors (compared to Koos grade I/II tumors) was the only factor significantly associated with disease progression (Figure 2B). Figure 3 presented case of bilateral VS treated with HSRT and showed different response in each tumor.

Hearing preservation

Seventeen patients with 18 tumors had serviceable hearing in the affected ear before treatment: GR class I in 13 (72%) and class II in 5 (28%). One patient with bilateral VSs presented with GR class 1 hearing on both sides and maintained serviceable hearing in both throughout follow-up. Nine patients (53%)
developed worsening of hearing in the treated ear. The 5- and 10-year hearing preservation rates were 59% and 35%, respectively (Figure 4). Median time to hearing deterioration was 59 months (range, 5–146). Serviceable hearing was maintained in 62% of patients with GR class I hearing before treatment; in patients with class II hearing, serviceable hearing was maintained in only 20%. In univariate analysis, no factor was significantly associated with hearing preservation.

Non-auditory complications

No patient developed new or worsening facial numbness after HSRT. No radiation-induced malignancy occurred.

Discussion

Management of VS-NF2 remains challenging because these tumors are frequently bilateral and they occur in young patients. Moreover, the risks of malignant transformation and radiation-induced tumors are a particular concern in young patients [8, 9]. Based on the European Association of Neuro-Oncology guidelines for treatment of patients with VS-NF2 [10], observation with surveillance imaging every 6 to 12 months is recommended for asymptomatic small tumors. Surgical decompression is mandatory for large tumors compressing the brainstem. For tumors that are incompletely resected to preserve hearing and/or facial nerve function, the residual may be treated using SRS. SRS may also be used to treat smaller tumors to preserve hearing and facial nerve function. Bevacizumab is also recommended in NF2 patients because of its effects on hearing and VS growth [3].

Image-guided robotic radiosurgery performed using the CyberKnife allows delivery of fractionated radiation without the use of a rigid fixed frame attached to the skull. Fractionated dosing is theoretically safer for the vestibulocochlear nerve and cochlea than a single large radiosurgical dose and might improve treatment outcomes, particularly hearing and facial/trigeminal nerve function outcomes. Although treatment of sporadic VSs using HSRT has been previously reported [11], the role of HSRT for treating VS-NF2 is unclear. To the best of our knowledge, this is the first study to report long-term clinical outcomes of HSRT treatment of VS-NF2.

In previous studies of SRS in VS-NF2, 10-year tumor control rates varied between 41% and 87% [12–20]. The large difference in rates might be due to interstudy differences in design, definition of tumor control, and length of follow-up. PFS at 10 years in our study was 80%, which is comparable with the above rates and the 88% rate reported in a meta-analysis of SRS for NF2-VS [14]. Based on our results, HSRT appears to provide excellent tumor control comparable with that of SRS.

Although various factors have been associated with tumor control, such as Wishart phenotype, age, marginal dose, and tumor volume [19, 21, 22], independent factors have not been definitively established. We graded tumor bulkiness using the Koos classification and found that Koos grade III/IV was the only factor significantly associated with progression, which agrees with two previous reports [17, 21]. In contrast, another previous study reported no correlation between tumor size and outcome [17]. However,
tumor size cutoffs varied between studies, which makes interpretation and comparison of studies difficult. Future studies are warranted to better define tumors that are appropriate to treat using SRS or HSRT.

Thirteen tumors (27%) transiently enlarged after treatment and then stabilized or decreased in size. This TVE is common in benign tumors treated using SRS/SRT. Most patients in our study who experienced TVE (85%) did not require treatment; only two patients (15%) required surgical intervention because of symptomatic progression and both harbored Koos grade IV tumors. This suggests that surgical intervention is not necessarily required if TVE is encountered, especially in asymptomatic patients. However, those with Koos grade IV tumors should be informed that TVE is possible after HSRT, which may cause brainstem and/or cranial nerve compression that requires surgical intervention.

Hearing preservation is a critical challenge in NF2 patients with VSs. In previous SRS studies, the 5-year serviceable hearing preservation rates ranged from 10–50%; at 10 years, the rates decreased to between 25% and 30% [13, 15, 17–21]. The reasons these rates are so low in NF2 patients are multifactorial and remain unclear. Although fractionation is theoretically better for preserving hearing, our 5- and 10-year hearing preservation rates were 59% and 35%, respectively, which are similar to those in the SRS studies. HSRT therefore did not improve hearing preservation as we had anticipated. We now avoid using radiation therapy in patients with VS-NF2 who have serviceable hearing.

Trigeminal and facial neuropathy are also concerning potential complications of SRS in patients with VS-NF2; reported rates of facial neuropathy range from 16–50% [20, 22]. Such high rates may be due to the less sophisticated treatment plans and higher SRS doses used in the old era of SRS treatment. Recent advances in radiosurgery technique along with the use of lower SRS doses and fractionation has reduced these rates to between zero and 5% [14, 18, 21]. No patient in our study experienced facial or trigeminal neuropathy as a complication.

Despite their efficacy and low complication rate, SRS and SRT have not been widely used to treat patients with VS-NF2, probably because of concerns about malignant transformation and radiation-induced tumors. The true incidence rates of these potential complications are unknown and reported rates vary. No patient in our study developed a secondary tumor or experienced malignant transformation, which is consistent with previous reports [14–22]. However, a recent study of NF2 patients in the UK reported a 6% long-term risk of malignancy/malignant progression in those treated with radiation; in contrast, the risk was < 1% in non-irradiated patients [23]. The study concluded that radiation therapy should not be the first-line option for treating benign tumors in NF2 patients. Nonetheless, radiation therapy will still have a role, especially for inoperable tumors and in older patients and those with comorbidities.

**Conclusion**

HSRT is effective for tumor control in patients with VS-NF2 and associated with a low non-auditory complication rate; however, hearing preservation, radiation-induced tumors, and malignant transformation remain concerns. HSRT should be recommended for growing tumors in older patients,
patients with comorbidities, and those with inoperable tumors. HSRT should not be recommended in patients with VS-NF2 if hearing preservation is a goal. Although development of radiation-induced tumor and malignant transformation did not occur in our study, they are known risks that must be clearly disclosed to patients prior to HSRT.

**Declarations**

**Funding**

The authors declare that no funds, grants or other support were received during the preparation of this manuscript

**Competing Interests**

The authors have no relevant financial or non-financial interests to disclose

**Author Contributions**

All authors contributed to the study conception and design. PP, MD, RR, KB, AH, KS and PY designed study, Material preparation, data collection and analysis were performed by PP, MD, RR, KB, AH, KS and PY. The first draft of the manuscript was written by PP and all authors commented of the manuscript. All authors read and approved the final manuscript.

**Data Availability**

The datasets generated and/or analyzed during the current study are available from the corresponding author on reasonable request.

**Ethics approval**

The study was performed in the line with the principles of the Declaration of Helsinki. Approval was grant by the institutional review board of Ramathibodi Hospital.

**References**


**Figures**
Figure 1

Treatment planning with the CyberKnife.
Figure 2

Kaplan–Meier survival curves in (A) all patients and (B) patients stratified according to Koos grade I/II and III/IV groups.)
Figure 3

Bilateral vestibular schwannomas are shown (A) before, (B) 6 months after, and (C) 12 months after hypofractionated stereotactic radiotherapy. The tumors showed different responses. The tumor on the right appeared more bulbous initially with an altered enhancement pattern; then it decreased to the pretreatment volume, suggestive of transient volume expansion. In contrast, the one on the left continuously enlarged and required resection. Postoperative imaging is shown in panel D. Sequential follow-up scans (E and F) showed bilateral tumor regression over time.
Figure 4

Hearing preservation in the entire cohort.