

Title: Hypofractionated stereotactic radiotherapy for acoustic neuromas: safety and effectiveness over 8-year experience

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Abstract

Background: Little information is available about long-term outcomes of hypofractionated stereotactic radiotherapy (hypo-FSRT) for acoustic neuromas. In this study, the safety and effectiveness of hypo-FSRT for unilateral acoustic neuroma were reviewed over 8-year experience of our institution.

Methods: Between May 1998 and October 2006, 27 patients were consecutively treated by linear accelerator-based hypo-FSRT. Two patients were excluded from this study because they were lost to follow-up within 12 months. The median follow-up period for the rest was 59 months (range, 24-133). Two types of treatment schedule were adopted. Thirteen patients received 30-39 Gy, given in 10-13 fractions (regimen A), while after July 2003, twelve patients received 20-24 Gy, given in 5-6 fractions at the tumor periphery (regimen B). These treatments were scheduled to be delivered in three fractions per week (Monday, Wednesday, Friday). The median planning target volume was 2.0 mL, 1.7 mL (range, 0.7-10.6) in regimen A and 5.2 mL (range, 0.9-9.3) in regimen B. Seven patients had serviceable hearing (Gardner-Robertson Class 1-2) in the pre-treatment audiogram; two patients in regimen A and five in regimen B.

Results: Local control rates were 100% with regimen A and 92% with regimen B, respectively. Serviceable hearing was preserved in four of five patients in regimen B but no patients in regimen A at the last follow-up. No permanent facial and trigeminal nerve morbidity were newly observed. No salvage surgery was needed.

Conclusions: Hypo-FSRT for acoustic neuromas achieved a high local control rate with minimal facial and trigeminal nerve morbidity.

Mini-abstract

Hypofractionated stereotactic radiotherapy for acoustic neuromas achieved a high local control rate with minimal facial and trigeminal nerve morbidity.

Key words: acoustic neuroma, stereotaxic techniques, radiotherapy, dose fractionation.

Introduction

Acoustic neuroma is a benign intracranial tumor, commonly arising from the vestibular portion of the 8th cranial nerve. They are typically slow growing, but can cause several symptoms, such as hearing loss, facial paresis, facial numbness, and hydrocephalus^{1,2}.

Surgery has been the main treatment option for small-to-large acoustic neuromas, but the morbidity rates can not be ignored, even with an experienced team³. As an alternative, stereotactic radiosurgery (SRS) has been adopted, but initial reports failed to achieve favorable cranial nerve preservation rates. To improve cranial nerve morbidities with a high local control rate, two different radiotherapeutic strategies have been developed; dose-reduced SRS and stereotactic radiotherapy (SRT). Dose-reduced SRS had shown excellent local control rates and minimal morbidity in the treatment of small-to-medium acoustic neuromas in long-term follow-up^{4,5}. Conventionally fractionated SRT has also demonstrated high hearing preservation rates and local control, with relatively short follow-up periods⁶⁻⁸.

Our institution started to treat acoustic neuromas with hypofractionated stereotactic radiotherapy (hypo-FSRT) in May 1998. Various schedules of hypofractionation have been developed not only for the intracranial lesions but also the extracranial lesions⁹⁻¹¹. The merits of hypo-FSRT are that it should reduce normal tissue damage, versus SRS and is more convenient than conventionally fractionated SRT, because it involves fewer irradiation sessions. Recent studies have reported that hypo-FSRT provides a high local control rate and acceptable morbidity for small and even large acoustic neuromas¹²⁻¹⁵. However, little information is available as to whether high tumor control rates and minimal morbidity are maintained for an extended period with a hypofractionated

regimen. The aim of this study was to review the safety and effectiveness of linear accelerator-based hypo-FSRT for acoustic neuroma over 8-year experience.

Materials and Methods

Between May 1998 and October 2006, 27 patients (27 tumors) with acoustic neuroma underwent hypo-FSRT at Kyoto University Hospital. Two patients who were lost to follow-up within 12 months were excluded from the analysis. For hypo-FSRT, we sought patients with continuously enlarging tumors who were not candidates for surgery. All patients gave informed consent for the treatment. Eleven patients had previously undergone at least one surgical tumor resection and were histologically confirmed to have acoustic neuroma; the median interval between the last surgical procedure and hypo-FSRT was 45 months (range, 4-120). The remaining 14 patients who were diagnosed with acoustic neuroma by imaging studies received hypo-FSRT as an initial treatment. No patient suffered from neurofibromatosis type 2. Patients were regularly followed by physical examination, audiometric testing, and contrast-enhanced MR imaging studies, every 3-6 months for 3 years and every 12 months thereafter.

All tumors were treated by linear accelerator-based hypo-FSRT, using 6 MV X-ray beams generated by a Clinac-2300c linear accelerator (Varian Inc., Palo Alto, CA) with head immobilization using a Gill-Thomas-Cosman relocatable stereotactic frame. Treatment planning was carried out using the X-knife system (Radionics Inc., Burlington, MA). In this study, all patients were treated with not using multi-leaf collimator, but using collimating cylinder. From May 1998 to May 2003, twelve patients were treated with a regimen of 39 Gy in 13 fractions at the edge of the PTV (3.2-3.75 Gy per fraction at the isocenter). One patient was treated with 30 Gy in 10 fractions (3.75 Gy per fraction at the isocenter). Starting in July 2003, the regimen was changed by reference to the other institutional report¹³, and 11 patients received 20 Gy in five fractions (5 Gy per fraction at the isocenter). One patient was treated with 24 Gy

in six fractions (5 Gy per fraction at the isocenter). We define the regimen of 30-39 Gy in 10-13 fractions as regimen A and 20-24 Gy in 5-6 fractions as regimen B. The median diameter of extrameatal portion was 15 mm: 13 mm (range, 5-34) in regimen A and 19 mm (range, 5-27) in regimen B. The planning target volume (PTV) was defined as the contrast-enhancing area of the tumor with a 2 mm margin in helical CT images of 2.5 mm slice thickness, fused with previously generated MR images. The median PTV was 2.0 mL: 1.7 mL (range, 0.7-10.6) in regimen A and 5.2 mL (range, 0.9-9.3) in regimen B. All patients were treated with a single isocenter and the collimator diameter ranged from 17.5 to 32.5 mm.

Three-dimensional multiple arc therapy, with a median arc number of five (range, 4-7), was used. These treatments were scheduled to be delivered in three fractions per week (Monday, Wednesday, Friday). The median follow-up period was 59 months; 87 months (range, 24-133) in regimen A and 39.5 months (range, 24-64) in regimen B.

In this study, local tumor control was defined as no continuous tumor enlargement on serial MR images. Tumor size was estimated according to the Committee of Hearing and Equilibrium guidelines for the evaluation of hearing preservation in acoustic neuroma, in which the diameter of the tumor is defined as the square root of (long diameter $\times$ short diameter)¹⁶.

The Gardner-Robertson class system was used to classify the hearing¹⁷ (Table 2). Seven patients with serviceable hearing (Gardner-Robertson class I-II) in the pre-treatment audiogram were included for the evaluation of hearing preservation. The median pure tone average before hypo-FSRT was 32 dB (range, 31-33) in regimen A and 18 dB (range, 13-26) in regimen B respectively. The median audiometric follow-up period was 43 months (range, 30-52): 37 months (range, 30-44) in regimen A and 43

months (range, 34-52) in regimen B. Facial nerve dysfunction was scored by using House-Brackmann grading system¹⁸ (Table 3). The characteristics of 25 patients are outlined in Table 1.

Results

Local control rates in the follow-up period were 100% (13/13) in regimen A and 92% (11/12) in regimen B. The transient tumor increase was seen in 48% (12/25) of treated tumors but the continuous tumor enlargement was observed in the only one case (Figure. 1). Six tumors, the diameters of the extrameatal portion of which were larger than 25 mm, were well-controlled. The median time when the tumor was maximally enlarged after hypo-FSRT was 13 months (range, 8-35). No patient needed salvage surgery within the follow-up period.

The changes of pure tone average after hypo-FSRT in patients with serviceable hearing are shown in Figure 2. The deterioration of pure tone average by more than 20 dB was observed in 5 of 7 patients during the follow-up period. The median pure tone average at the last follow-up was 59.5 dB (range, 59-60) in regimen A and 40 dB (range, 9-65) in regimen B. Serviceable hearing (Gardner-Robertson class I- II) was preserved in 4 of 5 patients in regimen B but no patients in regimen A at the last follow-up.

No early toxicity requiring medication occurred. Late toxicity (3 months after hypo-FSRT) requiring treatment was seen in two patients (8%): one with temporary facial paresis (House-Brackmann grade IV) 5 months after the hypo-FSRT in regimen A and one with transient symptomatic non-communicating hydrocephalus 12 months after hypo-FSRT in regimen B. Facial paresis was resolved in 12 months with oral steroid medication. Symptoms related with non-communicating hydrocephalus disappeared in a month with intravenous steroid and glycerol, without permanent cerebrospinal fluid shunting or operative resection of tumor. No patient developed trigeminal nerve

dysfunction or dysequilibrium requiring medication in the acute or late period. No radiation-induced secondary tumor was observed.

Discussion

We found that hypo-FSRT for acoustic neuromas had the excellent rate of local control without severe cranial nerve morbidity over 8-year experience. The findings of this study support the growing body of literature of hypo-FSRT regarding safety and effectiveness. In previous studies, the rate of local control and severe cranial nerve morbidity were reported as 94-100% and 0-3%, respectively¹²⁻¹⁵ (Table 4) and comparable to this data.

In this study, the transient enlargement of tumor volume was observed in 48% of treated tumors but the continuous enlargement of tumor volume was observed in only one case over a follow-up period. The reasons for the transitional enlargement remain unclear but were supposed to associate with intratumoral hemorrhages or increased vascular permeability induced by radiotherapy^{19, 20}. The rate of the transient tumor enlargement after SRS was reported as 14 to 45.2%²¹⁻²³ and the time when the transient enlargement occurred was said to be within 2 years after radiotherapy^{21, 22}. Pollock suggested that surgical resection should be delayed until continuous enlargement was confirmed with serial imaging over 2 or more years²³. In this study, all patients were followed for more than 2 years and our data was compatible with those reports. Cautious follow-up could be helpful to distinguish the transient or progressive enlargement and to avoid an unnecessary operation due to a misinterpretation of natural history of tumor after radiotherapy. The salvage surgery for an irradiated tumor could cause the poor patient outcomes^{24, 25}. Hypo-FSRT was effective to control tumor growth over a long-term follow-up period. Watch and wait policy is important in the follow-up of irradiated acoustic neuromas.

Six tumors, the diameters of the extrameatal portion of which were larger than 25 mm, were well-controlled locally with minimal morbidity in this study. Previously favorable outcomes of radiotherapy for large acoustic neuromas were reported in a short follow-up. Fourteen patients with tumors greater than or equal to 3.0 cm, received 30 Gy given in 10 fractions. No patient had growth of acoustic neuromas or developed facial weakness with the median clinical follow-up 1.8 years¹³. In another report, tumors greater than or equal to 3 cm (16 patients) received 20 Gy in 5 fractions. All tumors were controlled with median radiographic follow-up 20 months. No patient developed trigeminal nerve symptoms after treatment nor did any patient require surgery for treatment failure²⁶. In the treatment of large acoustic neuroma, a high local control rate with minimal morbidity was achieved by maximal removal and adjuvant radiotherapy^{27, 28}, however we believe that the treatment by radiotherapy alone is still needed for some patients who are unfit for a surgical treatment due to medical reasons. This study suggests that radiotherapy alone with hypo-FSRT is one of the acceptable treatment options in the treatment for large acoustic neuromas.

It is reported that the annual rate of hearing loss was slower than accelerated after radiotherapy but the tendency of deterioration in hearing level was observed even after radiotherapy^{29 30}. In this study, the continuous deterioration of hearing was observed after hypo-FSRT; serviceable hearing was preserved in all patients one year after hypo-FSRT but 4 of 7 in 2-year after hypo-FSRT. The similar type of deterioration was seen after SRS and therefore the rates of hearing preservation were lower in the long-term follow-up reports; $44.5\% \pm 10.5\%$ at 10 years³¹ and 55% at 9 years in the reports of SRS³². The wide range of the rates of hearing preservation from 66 to 100% was reported in hypo-FSRT. Those results may not reflect the change of continuous

deterioration of hearing level after radiotherapy because those reports suffered from a relatively short follow-up period ¹²⁻¹⁵. The length of time required for stabilization of hearing after radiotherapy is unclear. The number of literatures of hypo-FSRT was growing but their follow-up period was short yet. The longer follow-up study is required for evaluating the rates of hearing of hypo-FSRT, to reflect the delayed change of hearing level.

The rate of facial nerve preservation and severe trigeminal nerve morbidity were reported as 97 to 100% and 0 to 3% in hypo-FSRT ¹²⁻¹⁵ (Table 4). The rate of cranial nerve morbidity was comparable to those of other radiotherapeutic techniques: gamma knife ^{31, 33}, linac-based SRS ^{32, 34}, and conventionally fractionated SRT ^{8, 35}. The findings in this study substantiated the safety of hypo-FSRT for acoustic neuromas.

The local control rate for small-to-medium-sized acoustic neuromas is approaching satisfactory, but the rate of hearing preservation is not. From the rationale of a linear-quadratic model, fractionated SRT is expected to have radiobiological benefits for normal tissue, versus SRS. From clinical experience, fractionated SRT did lead to a higher rate of serviceable hearing preservation than SRS ⁷. Hypo-FSRT has the possibility of being less time-consuming than conventionally fractionated SRT and of better radiobiological benefit to adjacent normal tissues, compared with SRS. Excellent local control with minimal morbidity were demonstrated in this study, however our data weren't far from adequate. This study was retrospective in nature; the population was heterogeneous with regard to initial treatment, recurrence, tumor size, and hearing ability. Additional studies are needed to evaluate the effectiveness of hypo-FSRT especially for hearing preservation.

In conclusion, hypo-FSRT for acoustic neuromas achieved a high local control rate with minimal facial and trigeminal nerve morbidity.

Conflict of Interest Statement

Katsuyuki Sakanaka, Takashi Mizowaki, Yoshiki Arakawa, Norio Araki, Natsuo Oya, Jun A. Takahashi, Nobuhiro Mikuni, Susumu Miyamoto, Nobuo Hashimoto and Masahiro Hiraoka have no conflict of interest.

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Figure Legends

Figure 1: Transitions of the tumor size after hypo-FSRT in two types of the regimens

a: Alterations of the tumor size after hypo-FSRT in 13 patients with regimen A (30-39 Gy in 10-13 fractions at the margin of planning target volume).

b: Alterations of the tumor size after hypo-FSRT in 12 patients with regimen B (20-24 Gy in 5-6 fractions at the margin of planning target volume). In this study, the size of tumor was estimated using the Committee of Hearing and Equilibrium guideline¹⁶ and the size of the intracanalicular tumor was described as 0 mm. Each regimen included one patient with the intracanalicular tumor which didn't enlarge in the follow-up period.

Figure 2: The alterations of pure tone average after hypo-FSRT in seven patients with serviceable hearing. Dashed and solid lines represent regimen A (30-39 Gy in 10-13 fractions at the margin of planning target volume) and regimen B (20-24 Gy in 5-6 fractions at the margin of planning target volume), respectively.

Tables

Table 1. Patient characteristics

	Regimen A	Regimen B
Patients (<i>n</i>)	13	12
Gender (<i>n</i>)		
Male	6	6
Female	7	6
Median age (years)	52 (range, 32-73)	51.5 (range, 30-75)
Tumor diameter (mm)		
0-19	9	8
20-24	2	0
25-	2	4
Median planning target volume (mL)	1.7 (range, 0.7-10.6)	5.2 (range, 0.9-9.3)
Prior surgery (<i>n</i>)	7	4
Gardner-Robertson grade		
1-2 (<i>n</i>)	2	5
3-5 (<i>n</i>)	11	7
Median audiometric follow-up (months)	37 (range, 30-44)	43 (range, 34-52)
Median follow-up (months)	87 (range, 24-133)	39.5 (range 24-64)

Regimen A: 30-39 Gy in 10-13 fractions at the margin of planning target volume

Regimen B: 20-24 Gy in 5-6 fractions at the margin of planning target volume

Tumor diameter = the diameter of extrameatal portion.

Table 2. Gardner-Robertson class system

Class	Description of hearing	Pure tone average (dB)	Speech discrimination (%)
I	serviceable	0-30	70-100
II		31-50	50-69
III		51-90	5-49
IV		90-100	1-4
V		0	0

Table 3. House-Brackmann grading system

Grade	Characteristics
I. Normal	Normal function in all areas
II. Mild dysfunction	Gross Slight weakness noticeable on close inspection May have slight synkinesis Normal symmetry and tone at rest Motion Forehead: Moderate to good function Eye: Complete closure with minimal effort Mouth: Slight asymmetry
III. Moderate dysfunction	Gross Obvious but not disfiguring difference between the two sides Noticeable but not severe synkinesis, contracture, or hemifacial spasm Normal symmetry and tone at rest Motion Forehead: Slight to moderate movement Eye: Complete closure with effort Mouth: Slightly weak with maximum effort
IV. Moderately severe dysfunction	Gross Obvious weakness and/or disfiguring asymmetry Normal symmetry and tone at rest Motion Forehead: None Eye: Incomplete closure Mouth: Asymmetric with maximum effort
V. Severe dysfunction	Gross Only barely perceptible motion Asymmetry at rest Motion Forehead: None Eye: Incomplete closure Mouth: Slight movement
VI. Total paralysis	No movement

Table 4. Previous reports of hypo-FSRT for acoustic neuroma

	Tumor size (mm)*	Tumors (n)	Dose Prescription (Gy/fraction)	Follow-up period	Local control rate	Permanent facial and trigeminal nerve dysfunction after hypo-FSRT
Poen et al. (12)	<15	4	21/3	2 years	97%	3% and ND
	16-30	27				
	30<	3				
Williams (13)	<30	111	25/5	1.8 years	100%	0%
	30≤	14	30/10		100%	
Meijer et al. (14)	25 (range: 8-38)	80	20/5 or 25/5	33 months	94%	ND
Chang et al. (15)	18.5 (range: 5-32)	61	18/3 or 21/3	48 months	98%	0%
Sakanaka et al	<25	19	20/5 or 39/13	60 months	96%	0%
	25≤	6				

Abbreviations: ND = not described, hypo-FSRT = hypofractionated stereotactic radiotherapy

Figure 1

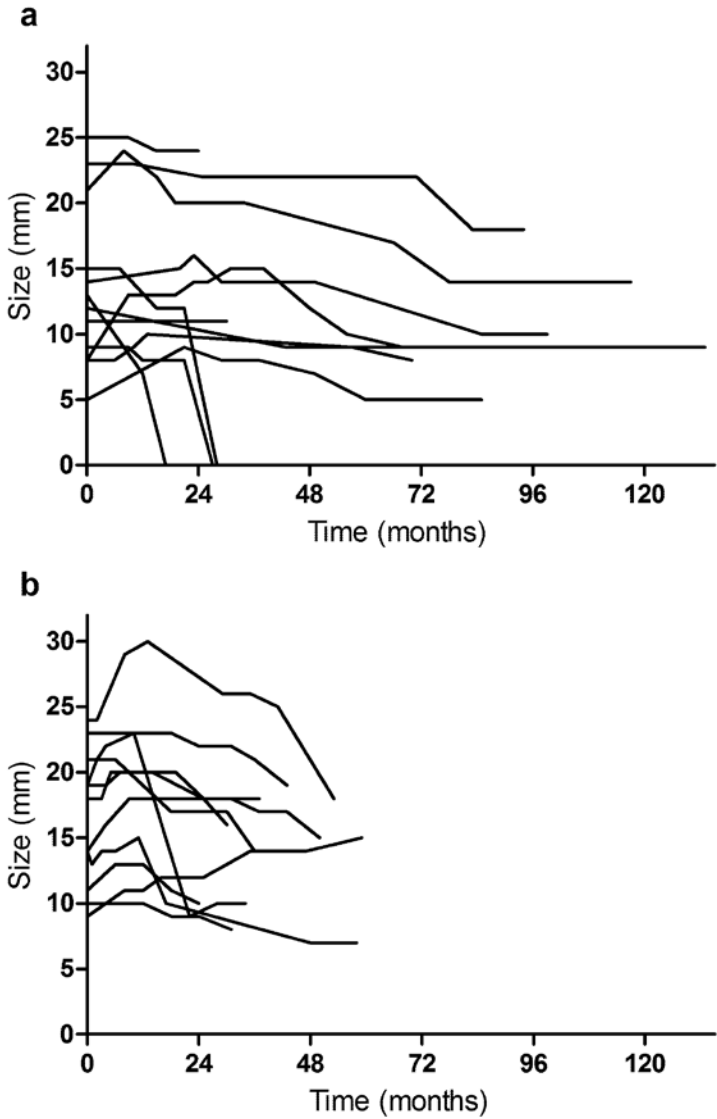


Figure 2

