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# Hypofractionated CyberKnife stereotactic radiosurgery for acoustic neuromas with and without association to neurofibromatosis Type 2

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## Summary

CyberKnife stereotactic radiosurgery (CKSRS) has been proved effective in treating intra-cranial lesions. To treat acoustic neuroma (AN) patients with or without neurofibromatosis Type 2 (NF2) associations, the functional preservation of hearing, trigeminal nerve, and facial nerve are important.

Twenty-one patients were treated with hypofractionated CKSRS. Fourteen non-NF2 and seven NF2 patients were enrolled. Cranial nerve function, audiograms, and magnetic resonance images (MRI) were monitored.

Mean follow-up was 15 month. Tumors with volumes ranging from 0.13 to 24.8 $cm^3$ (mean 5.4 $cm^3$) were irradiated with the marginal dose 1800–2000 cGy/3 fractions. Tumors were treated with an 80 to 89% isodose line (mean 83%) and mean 97.9% tumor coverage. Two patients experienced hearing deterioration (16.7%) in the non-NF2 group, and 3 patients (50%) in the NF2 group. No facial or trigeminal dysfunction, brain stem toxicity, or cerebellar edema occurred. Tumor regression was seen in 9 patients (43%) and stable in 12 patients (57%). 100% tumor control rate was achieved.

Hypofractionated CKSRS was not only effective in tumor control but also excellent in hearing preservation for non-NF2 AN. But for NF2 patients, although the tumor control was remarkable, hearing preservation was modest as in non-NF2 patients.

*Keywords:* Acoustic neuroma; neurofibromatosis Type 2 (NF2); hypofraction; CyberKnife (CK); stereotactic radiosurgery.

## Introduction

Acoustic neuroma (AN) is a slow-growing tumor, which occurs in adults with age ranging between 40 and 70 years. This tumor comprises 8–10% of intracranial tumor. Association with neurofibromatosis Type 2 (NF2) is seen in 2–4% [11]. NF2 typically presents with bilateral acoustic neuromas and mainly involves younger patients [18]. Whether non-NF2 or NF2 in type, AN always tends to infiltrate into, or compress on adjacent cranial nerves, such as the 5th, 7th and 8th cranial nerves. Treatment modalities available for AN, including surgical resection, stereotactic radiotherapy (SRT), and stereotactic radiosurgery (SRS) are aimed not only at controlling tumor volume but also at preserving function of adjacent cranial nerves [1, 8, 10, 14, 18]. Many publications report that surgical intervention for tumor resection always comes with high morbidity, such as hearing loss, facial nerve dysfunction, and brain stem insult [1, 6, 10, 16, 18]. However, SRT can provide only moderate tumor control, even though this treatment choice offers a better chance to preserve hearing function.

SRS has recently been proved effective for tumor control and functional preservation in patients with ANs [1, 7, 8]. Published radiobiological articles show that single-stage radiosurgery can control the tumor quite well but hearing can be maintained in only 50–73% of the AN patients [1, 7, 17]. In comparison, hypofractionated treatment modality, such as CyberKnife (CK) therapy, can mitigate cranial nerve deterioration [20]. By delivering a few fractions of smaller radiation doses, CK

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SRS can provide 74 to 78% hearing preservation for non-NF2 patient [1]. However, for NF2 patients with AN, the hearing preservation is not as ideal as for patients with non-NF2 AN. In this study, we applied CK SRS to the treatment of non-NF2 and NF2 patients with ANs and analyzed the therapeutic results and side effects of this treatment modality in both the non-NF2 and NF2 groups.

## Materials and methods

*Patients*

From 2005 September to 2007 October, 21 patients with ANs (13 right: 8 left) were treated. Among them, 7 patients were diagnosed to have NF2, and images showed bilateral ANs in 6 patients. For the 6 NF2 patients with bilateral ANs, only one target with the major symptom was treated in this period of time. One patient had had surgical treatment before and the tumor recurrence was identified during the follow-up period, and the other 20 patients received CKSRS as the primary treatment. Eleven patients were females (55%) and 10 patients (45%) were males. The mean age was 54 years (range: 27 to 79 yrs). Tumor volume ranged from 0.13 to 24.8 $cm^3$ (mean 5.4 $cm^3$). The post-treatment follow-up duration for these 21 patients ranged from 6 to 25 months (mean: 15 months). Basic patient information is listed in Table 1.

Table 1. *Patients' clinical data*

| | |
|---|---|
| Number of patients | 21 |
| Male | 10 |
| Female | 11 |
| Mean age (year) | 54 (range: 27–79) |
| Association with NF-2 | 7 |
| non NF-2 | 14 |
| Mean follow up time (months) | 15 (range: 6–25) |
| Mean tumor volume ($cm^3$) | 5.4 (range: 0.13–24.8) |
| Prescribed marginal dose (cGy) | 1800–2000 |
| Fractions | 3 |
| Mean isodose (%) | 83 (range: 83–89) |
| Coverage (%) | 97.9 (range: 94.8–99.4) |
| CI | 1.27 (range: 1.14–1.59) |
| HI | 1.19 (range: 1.12–1.27) |
| NCI | 1.38 (range: 1.16–1.67) |

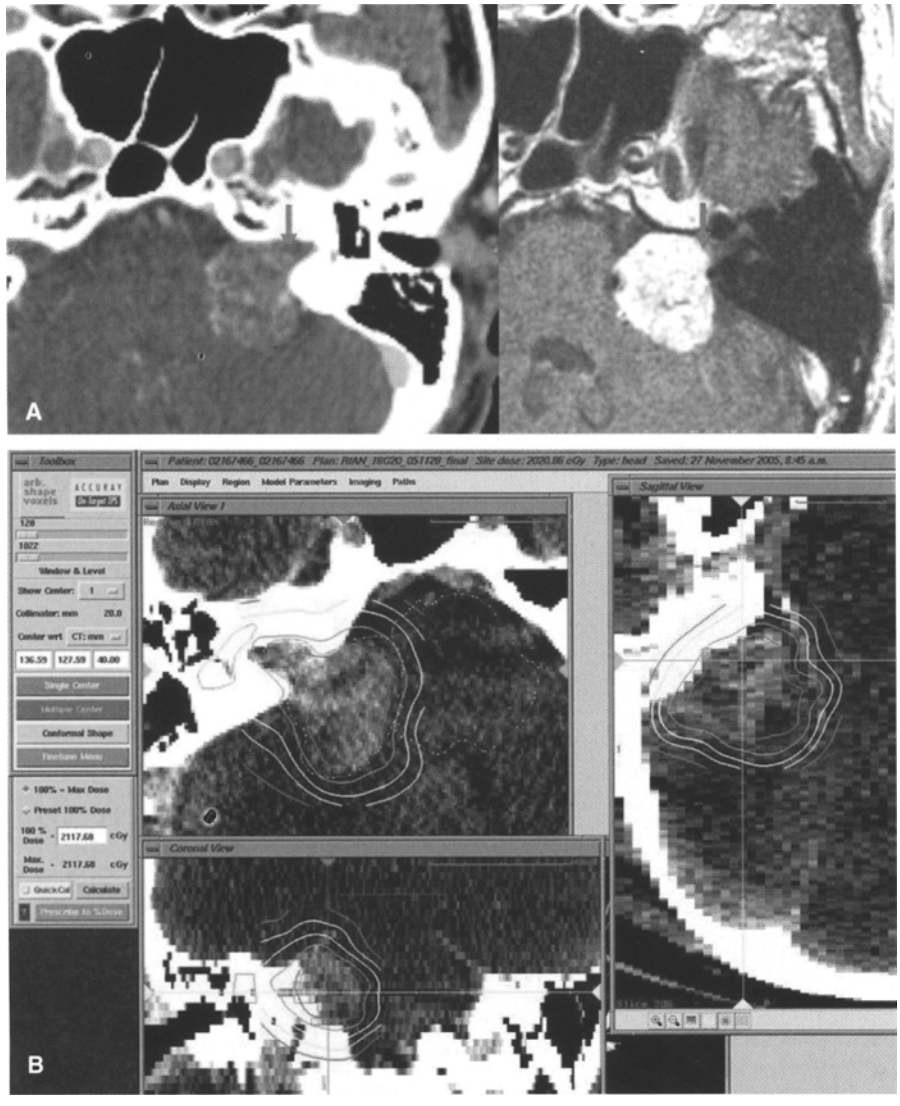


Fig. 1. (A) Comparison of contrast-enhanced axial CT scans (*left*) with enhanced T1W MRI (*right*) of same patient harboring acoustic neuroma with intra-canacular extension. MRI was superior in identification of tumor margin in IAC (*arrow*), facilitating protection of vital organs, such as cochlear, in IAC from irradiation. (B) Non-isocentric inverse planning: no hot or cold spot could be identified; isodose line runs along adjacent border between tumor and brain stem ideally for irradiation delivery

*Clinical evaluation*

All the patients were evaluated routinely with neurological examination, audiogram, and MRI, which were taken as a baseline reference. Hearing and functions of the facial trigeminal nerves were graded according to the Gardner-Robertson classification system (GR), House-Brackmann grading system (HB), and semi-quantitative scale [1]. MRI T1W image with enhancement was used to evaluate the tumor size, and T2 flair image was used to evaluate perifocal edema of the brain stem and cerebellum before and after the CKSRS. Among 7 AN patients associated with NF2, the major symptoms before CKSRS were hearing impairment ($n=7$; 100%) and tinnitus ($n=6$; 86%). As to the patients without NF2, the following manifestations were seen in some: trigeminal neuralgia ($n=1$; 7.1%), facial palsy ($n=3$; 21.4%), tinnitus ($n=11$; 78.6%), and hearing impairment ($n=13$; 92.9%). After the CKSRS, all above image studies and clinical evaluation were repeated 3, 6, 12, 18, and 24 months after the treatment.

*Tumor size measurement*

Tumors shown in MRI were measured in three orthogonal dimensions. Tumor volume (Vol) was calculated as: Vol ($mm^3$) $= \pi (a \times b \times c)/6$, where a, b, and c represent width, height, and thickness, respectively [13]. For each patient, the last follow-up MRI was compared with MRI before treatment [1].

*Image fusion, tumor delineation, and treatment planning*

Thin-sliced (1.25 mm) high-resolution CT images were obtained for tumor delineation after intravenous administration of 125 ml of Omnipaque contrast (iohexol, 350 mg I/ml; Nycomed Inc., Princeton, NJ). If the tumor involved the internal auditory canal (IAC) and IAC dilatation was confirmed, MRI image was then arranged for image fusion in order to prevent an unnecessary dose on CNVII and CNVIII in the IAC (Fig 1A).

A conformal inverse planning method with non-isocenteric technique was used for all cases (Fig 1B). The treatments for all patients were given with 3 equal dose fractions. The total dose was 18 Gy for patients with hearing GR1–4 to reduce the risk of hearing impairment. For patients with hearing GR5 before the SRS, we prescribed 20 Gy for better tumor control. All planning was evaluated with dosimetry indices for optimal results, including tumor coverage percentage, homogeneity index (HI), conformality index (CI), and new conformality index (NCI). The data for these indices are summarized in Table 1.

## Results

### *Tumor response on MRI image*

During an average of 15-month follow-up, there was no patient who suffered from tumor recurrence. For the

Table 2. *Tumor control after CKSRS*

| | Stable | Regression | Total | |
|---|---|---|---|---|
| Non-NF2 | 7 (50.0%) | 7 (50.0%) | 14 (100.0%) | |
| NF2 | 5 (71.4%) | 2 (28.6%) | 7 (100.0%) | |
| Total | 12 (57.1%) | 9 (42.9%) | 21 (100.0%) | OR = 2.5 |

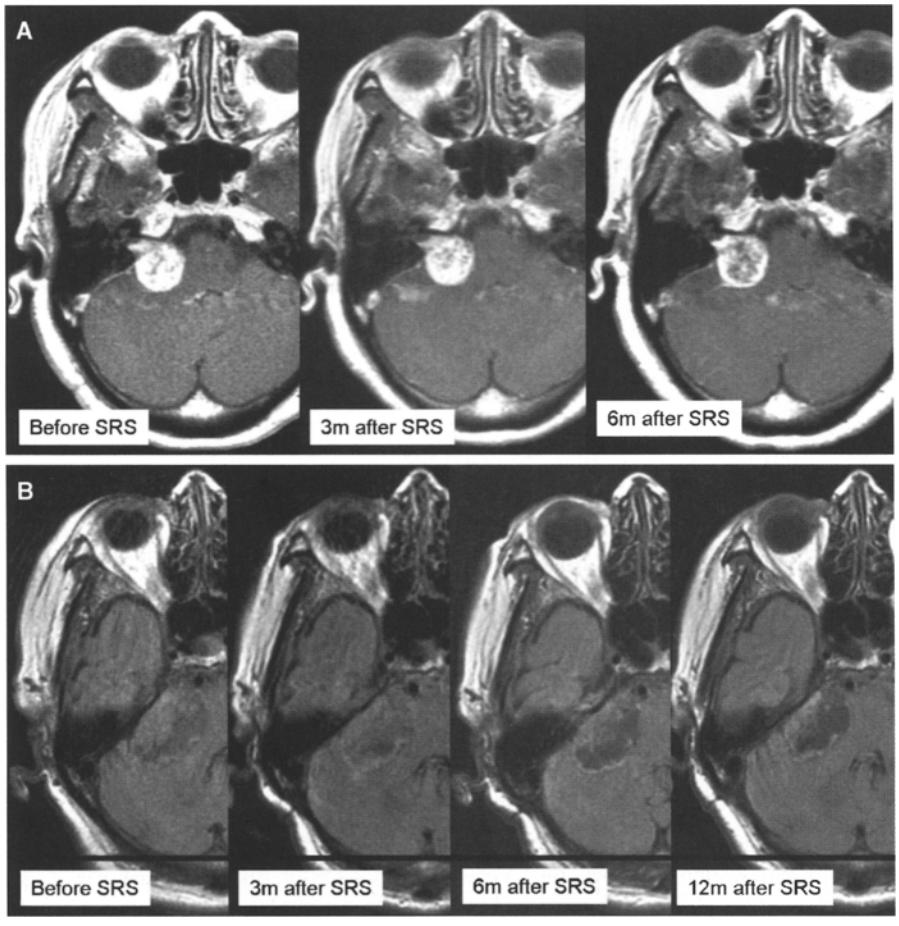


Fig. 2. (A) Series Gd-enhanced T1W MRI: gradually loss of central enhancement 6 months after CK SRS. (B) Series T2W flair image for 12 months follow up: no evidence of new perifocal edema around brain stem or cerebellum even though tumor diameter was around 4.2 cm in diameter

Table 3. *Hearing preservation after CKSRS*

| | Deterioration | Preserved | Total | |
|---|---|---|---|---|
| Non-NF2* | 2 (16.7%) | 10 (83.3%)# | 12 (100.0%) | |
| NF2$ | 3 (50.0%) | 3 (50.0%) | 6 (100.0%) | |
| Total | 5 (27.8%) | 13 (72.2%) | 18 (100.0%) | OR = 5.0 |

* Two patients excluded from non-NF2 group and $1 patient excluded from NF2 group because of GR5 hearing.
# One patient in non-NF2 group not only preserved but also got some improvement about the hearing function (from GR3 to GR2).

NF2 patient, 5 tumors (71.4%) were under stable condition and 2 patients (28.6%) had tumor regression. Among the non-NF2 patients, 7 tumors (50%) were stable and 7 tumors (50%) shrunk (Table 2). The response in non-NF2 patients seems better than in NF2 patients (OR = 2.5).

Loss of enhancement inside the tumor was observed on MRI images 6 months after the SRS (Fig. 2A), and there was no correlation with tumor regression. For all the patients followed up for more than 1 year, the series of MRI T2 flair images showed no evidence of perifocal edema within the adjacent brain stem or cerebellum (Fig. 2B).

### *Preservation and improvement of cranial nerve functions*

#### Hearing in non-NF2

For the 14 non-NF-2 patients, 2 patients did not have detectable hearing (GR5) and were excluded. The remaining 12 patients had GR1 to 4 hearing before treatment. Two patients showed hearing deterioration, from GR2 to 3 in one and from GR3 to 4 in the other. The remaining 10 patients preserved their original hearing after the SRS (83.3%). One of these 10 patients even showed improvement from GR3 to GR2 (Table 3).

#### *Hearing in NF2*

For the 7 patients associated with NF-2, 1 patient had hearing impairment with GR5 before treatment. Three of other 6 patients with hearing GR1 to 4 (50%) retained their hearing at the last follow-up. None showed improvement in the follow-up period. Our results are comparable with those in the currently papers, which show an average of 40–50% of hearing preservation in NF-2 patients [5, 11, 18] (Table 3).

#### *Trigeminal and facial nerve*

One patient suffering from trigeminal neuralgia before treatment had improvement with decreased pain frequency and intensity (from VAS 9 to 3 without medication). Three patients with facial palsy (House-Brackmann grading 2 before treatment) kept the same condition without any deterioration after the SRS. No new facial and trigeminal dysfunction developed in any patients. No patients experienced brain stem toxicity or cerebellar edema.

## Discussion

Nowadays, the management of AN has been well established. Available strategies of ANs include surgery and non-surgical treatment, such as SRT and SRS. In some instances, a larger tumor causes prominent compression on the brain stem or cerebellum and an invasive treatment procedure for decompression, such as microsurgery, is still needed. However, many publications have reported significant morbidity of microsurgery, which includes cranial nerve dysfunction [9, 16] and low hearing preservation (50–60% overall, decreased to 16% if the tumor size is larger than 1.5 cm) [1, 14, 15]. Therefore, non-invasive treatment, such as SRS, has become an alternative option for ANs.

Single staged SRS has proved to have high conformality, and its tumor-control rate reaches about 95%, with 50–73% hearing preservation after long term follow-up [7, 15, 17, 19]. Such a result is not good enough for a functional preservation-oriented treatment option. Hypofractionated CKSRS is theoretically and clinically proved to be effective in reducing irradiation damage to normal vital structures and producing significant hearing preservation in AN treatment [1, 2, 4, 14]. Furthermore, if AN is treated with single fraction SRS and the tumor size is larger than 3 cm or the tumor volume more than 27 ml, there may be some delayed radiation effect on the adjacent structure [1]. Not only tumor swelling but also perifocal edema will compress on the brain stem and result in severe adverse neurological deficits. But in our experience there was no such rigid limitation for CKSRS. In Fig. 2B, there is no evidence of new-onset perifocal edema around the AN during the 12-month follow-up period, though the tumor was large (4.2 cm in longest diameter). Clinically there was also no brain stem toxicity or cerebellar edema in our 2-year experience.

Our report would strongly support that hypofractionated CKSRS provides an ideal tumor control rate, as in other single-staged SRS systems. In our small series and limited follow up duration (mean 15 m), a 100% control rate was achieved (42.9% regression and 57.1% stationary). Furthermore, with regard to hearing protection, our results were comparable with those from other larger series: 72.2% for overall and 83.3% and 50% for non-

NF-2 and NF-2 patients, respectively. We prescribed the marginal dose for 18–20 Gy/3 fractions, and this hypofractionated dose is equivalent equal to 12, 13 Gy/single fraction ($\alpha/\beta = 2$ Gy). According to previous reports, using single-stage dose of less than 14 Gy can retain 71–73% of useful hearing. This may also explain the low risk for hearing impairment [1].

For the CKSRS system, all the tumor delineation and treatment planning were based on the CT scan images. If the tumors have involved the IAC and the IAC is enlarged by the tumor invasion, then MRI with enhancement has higher sensitivity than an enhanced CT scan on identifying the real tumor contour, cranial nerve, and IAC [3]. Fused image with MRI will then be necessary.

Data of our dosimetry indices, 97.9% tumor coverage, 1.3 mean CI, 1.2 mean HI, and 1.4 mean NCI, have demonstrated ideal conformality, homogeneity, and accuracy, which may be the basis of hearing preservation. Two of patients in the non-NF2 group suffered from hearing deterioration, and both the CI and NCI for these two patients were larger than 1.5. This might be the reason why the patients could not keep their original hearing function.

Finally, AN is a complex disease and it can be present with both the sporadic AN and genetically transmitted pattern (NF2, chromosome 22 abnormality) [11, 18]. ANs associated with NF2 tend to involve the cochlear nerve more invasively, and result in significant hearing impairment [12, 18]. The outcome of SRS treatment on NF2 patients is also undesirable, with only around 50% of hearing preservation [11, 18]. In our result present series, only 50% of NF2 patients preserved original hearing function. This result was not superior that in other single-staged SRS systems.

As almost all the SRS can achieve a very good tumor control rate (more than 95%), the choice for different SRS systems should rely on the ability of hearing preservation and lesser toxicity to the brain stem and cerebellum. Our 2-year experience strongly suggests that hypofractionated SRS be an ideal modality to provide excellent hearing preservation and adjacent vital nerve protection for ANs.

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