



# Fractionated Proton Beam Therapy for Acoustic Neuromas: Tumor Control and Hearing Preservation

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## Abstract

**Purpose:** This prospective cohort evaluated patients with acoustic neuroma treated with proton irradiation at Loma Linda University Medical Center. A dose of 50.4 Gy in 28 fractions was given to improve hearing preservation while maintaining tumor control.

**Patients and Methods:** Ninety-five patients were treated from March 1991 to March 2008. Fractionated proton radiotherapy at daily doses of 1.8 Gy was employed. Patients were treated to 1 of 3 total doses: 59.4 Gy, used initially for patients without serviceable hearing; 54 Gy, used for patients with serviceable hearing through October 2000; and 50.4 Gy used since 2001 for patients with serviceable hearing. Survival and local control were calculated using the Kaplan-Meier method. Logistic regression analysis was performed comparing dose, tumor size, and tumor location with hearing preservation.

**Results:** Ninety-four patients were assessable; the median follow-up was 64 months. Five-year local control rates for the 59.4 Gy, 54 Gy, and 50.4 Gy groups were 95%, 97%, and 92%, respectively ( $P = .80$ ); the overall 10-year actuarial control rate was 90%. Cranial nerve injuries occurred in <5% in all groups. Four-year actuarial rates of hearing preservation were maintained in 44% of patients treated with 54 Gy and 64% treated with 50.4 Gy ( $P = .284$ ). On multivariate analysis, initial tumor diameter ( $\leq 1.5$  cm) was found to be a prognostic factor for maintaining serviceable hearing in both groups ( $P = .011$ ).

**Conclusions:** Fractionated proton therapy of 50.4 Gy offers excellent local control and minimal cranial nerve toxicities. Improved rates of hearing preservation that are comparable with radiosurgery were seen with 50.4 Gy compared with higher doses, although this did not reach significance. Maintaining hearing was found to be associated with smaller initial tumor size.

**Keywords:** acoustic neuroma; proton therapy; tumor control; hearing preservation

## Introduction

Acoustic neuromas (or vestibular schwannomas) are benign tumors that arise from the Schwann cells lining the VIIIth cranial nerve at the internal auditory meatus. Patients often present with unilateral sensorineural hearing loss, associated vertigo, and/or tinnitus, or the tumors may be found incidentally on imaging examinations.

The diagnosis is typically made with imaging techniques such as contrast-enhanced magnetic resonance imaging (MRI), and the use of this examination has been increasing

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in the last few decades. The increased use of MRI imaging has also led to an increase in diagnosis of smaller acoustic neuromas [1]. The incidence in the last 25 years increased from an estimated 5 tumors per 1 million people annually in 1976 to 19.3 tumors per 1 million in 2001. [1, 2]

Options for managing acoustic neuromas have included observation, surgical resection, and radiotherapy. Surgical resection offers excellent local tumor control but has been associated with significant risk of injury to the Vth, VIIth, and VIIIth cranial nerves [3]. More recently, stereotactic radiosurgery (SRS) has been used as a noninvasive approach for definitive treatment for small to medium-sized tumors as it offers excellent rates of local control and, with long-term follow-up, the range of hearing preservation from single-institution reports has been 32% to 71% [4].

Charged-particle beams, such as protons, have physical properties that allow tumor irradiation with maximal sparing of normal tissues by depositing energy along the Bragg peak. The dose is minimal on entry and reaches a maximum at the stopping region, which is planned to occur in the target volume [5]. These characteristics have made it theoretically possible to maximize tumor local control while sparing adjacent tissues from the negative effects of radiation. The treatment of acoustic neuromas using photon-based techniques has been well studied, but data analyzing patients with fractionated proton-beam radiotherapy are limited.

In a previous trial at this institution, a dose of 54 Gy in 30 fractions offered excellent local control and minimal cranial nerve deficits but resulted in suboptimal rates of hearing preservation [6]. This study now examines patients treated with a decreased dose of 50.4 Gy in 28 fractions in an attempt to maximize serviceable hearing while still offering excellent tumor control rates. It will also update the rates of local control, treatment toxicity, and hearing preservation in all patients previously treated.

## Patients and Methods

Under institutional review board approval, we analyzed 96 acoustic neuromas in 95 patients treated with proton-beam therapy between March 1991 and March 2008. Pretreatment workup included a neurological examination, brain MRI with gadolinium, and audiometric evaluation. Fractionated proton therapy was used at daily doses of 1.8 Gy to 1 of 3 doses: 59.4 Gy was used initially for patients without serviceable hearing; up to October 2000, 54 Gy was used for patients with serviceable hearing; thereafter, the dose was reduced to 50.4 Gy. Patients were classified as having serviceable hearing by being designated grade 1 or 2 according to the Gardner-Robertson Hearing Scale. Hearing was deemed unserviceable if the pure tone average and speech reception threshold showed more than a 50 decibel hearing loss or if the patient had <50% speech discrimination. If the grade of hearing preservation did not correlate between the 2 groups (pure tone average/speech reception threshold or <50% speech discrimination), the poorer of the 2 was used to determine the overall grade [7].

All patients were treated at the hospital-based proton treatment facility at Loma Linda University Medical Center. Patients were immobilized with a thermoplastic mask and treatment planning was done via 3-dimensional-based contrast enhanced computed tomography with magnetic resonance imaging registration. The gross tumor volume was contoured as seen on the contrast enhanced imaging with no additional clinical target volume margin. Software specifically designed for proton beams was used in planning, and the appropriate apertures and tissue compensators were fabricated. Most patients were treated with passively scattered proton beams using 2 to 3 fields; typically 2 fields were treated daily. An appropriate planning target volume margin of 2 to 3 mm was added to account for penumbra and immobilization uncertainty, and the dose equivalent (in relation to photons) was done with a relative biological effectiveness volume value of 1.1. For tumors smaller than 1 cm, field-specific calibration measurements were required for accurate field-specific dosimetric calculations.

After treatment, local control and hearing preservation were monitored with biannual brain MRI and audiometry for the first 5 years. The same tests were done yearly thereafter.

Local control was determined by contrast-enhanced MRI. If a patient could not receive an MRI, a computed tomography scan of the head with contrast was used for comparison. Disease progression was documented by radiologic evidence of tumor growth as confirmed by a neuroradiologist at Loma Linda University Medical Center, using Response Evaluation Criteria In Solid Tumors criteria or by clinical evidence of progression leading to surgical removal of the tumor. Cranial nerve deficits or other neurologic injury were determined with routine clinical history and physicals.

Univariate and multivariate statistical analyses were performed to compare hearing preservation with radiation dose, tumor location, and size. Tumor location was organized as either being solely confined to the internal auditory canal or tumor that also had a component in the cerebellopontine angle. The size of the tumor was classified as either medium to large (maximum tumor diameter >1.5 cm) or small (maximum tumor diameter ≤1.5 cm).

**Table 1.** Patient characteristics.

Number treated	96
50.4 Gy	43
54.0 Gy	34
59.4 Gy	19
Male:female	45:50
Median age (y)	56
Range	21–80
Serviceable hearing	44 (46%)
Tumor size	
Mean (cm)	1.4
Range	0.7–3.7
Nonhearing	
Tumor size	
Mean (cm)	1.6
Range (cm)	0.3–3.8
Bilateral tumors	5
Previous surgery	14

Univariate analysis was done by either a Pearson's  $\chi^2$  test or a Fisher 2-sided exact test. Multivariate analysis was done by logistic regression and linear regression generated Kaplan-Meier curves. Actuarial hearing preservation and local control rates were determined from these data. A Mann-Whitney U test was used to assess a difference in patient characteristics.

## Results

Of the 96 patients that were treated in all 3 groups, 94 were assessable for local control. One patient died of a myocardial infarction 2 months after treatment and was deemed unassessable; another was lost to follow-up. Forty-four patients treated had serviceable hearing; all of these patients were assessable for radiation effects. Patient characteristics of all patients are shown in **Table 1**, and characteristics of the hearing preservation cohorts are shown in **Table 2**. Fourteen patients were treated with surgical resection initially; 12 of them were treated in the 59.4 Gy group.

### Local Control

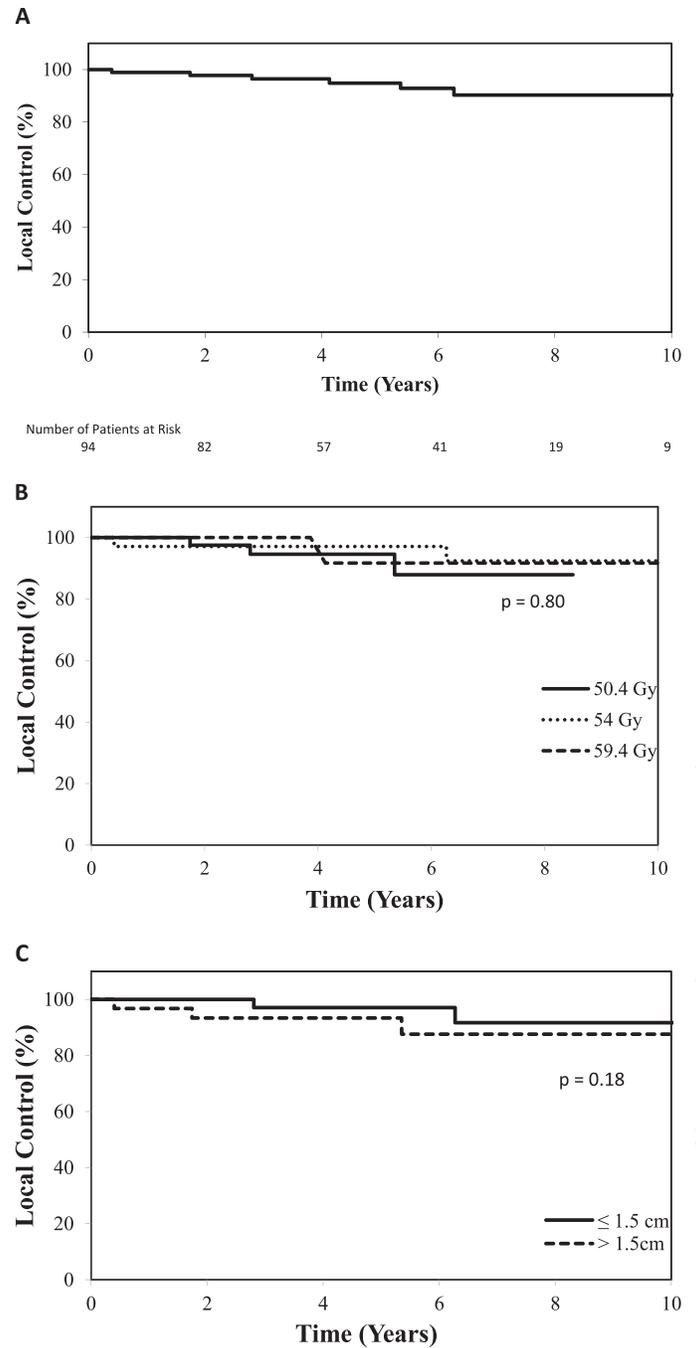
Radiologic follow-up ranged from 0.6 years to 16 years in the entire case series; median follow-up periods were 4.3, 7.4, and 6.6 years in the 50.4 Gy, 54 Gy, and 59.4 Gy groups, respectively. Local tumor control for the entire group is shown in **Figure 1A**. Tumor progression was documented in 6 patients, and surgical resection was required in 4 patients (**Table 3**). Radiologic disease regression, however, was noted in 39%, 44%, and 50% of patients treated to 50.4 Gy, 54 Gy, and 59.4 Gy, respectively. Five-year local control rates were found to be 95%, 97%, and 92% in these respective groups (**Figure 1B**). A trend for improved local control was seen in tumors  $\leq 1.5$  cm in diameter ( $P = .18$ ). (**Figure 1C**).

**Table 2.** Characteristics of patients with serviceable hearing.

	50.4 Gy	54.0 Gy
Median age (y)	54	56
Median tumor diameter (cm)*	1.1	1.6
No. with serviceable hearing	28	16
Gardner-Robertson Scale		
1	17	10
2	11	6

\* $P = .225$ .

**Figure 1.** Kaplan Meier curves to assess for local control. (A) All patients treated, (B) local control by dose group, and (C) local control by tumor diameter. Patients treated with previous surgery were excluded in the size analysis.



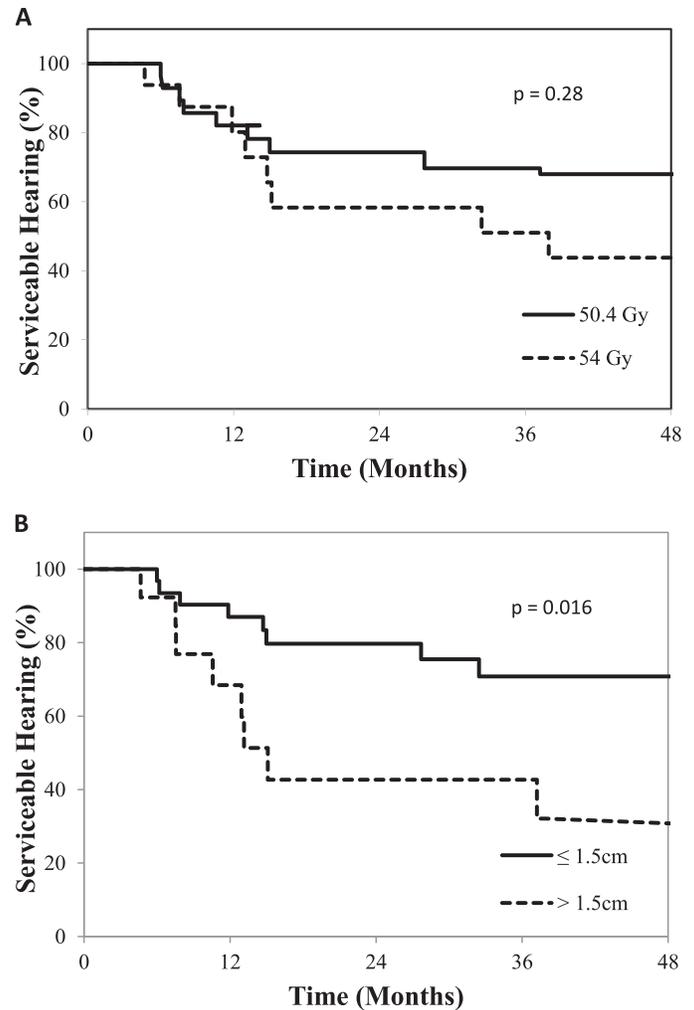
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**Table 3.** Tumor recurrence characteristics.

	No. (%) with progression <sup>a</sup>	Mean time to disease progression (range)	Mean tumor diameter (cm)
50.4 Gy	3 (7%)	3.4 y	2.0
	2 (5%)	(12 mo to 5.35 y)	
54.0 Gy	2 (6%)	3.3 y	2.4
	2 (6%)	(5 mo to 6.27 y)	
59.4 Gy	1 (5%)	4.1 y	3.8
	0 (0)		

<sup>a</sup>Italics indicate surgery required.

**Figure 2.** Kaplan Meier estimates of hearing preservation by (A) dose and (B) tumor diameter.



### Cranial Nerve Injuries

Major cranial nerve toxicities were minimal and were seen in 2 patients, or 2.1% of the total patient population. One of these patients had a 3.7-cm diameter tumor treated to 54 Gy and developed facial paralysis with difficulty in swallowing; the other had prior surgical resection, treated to a dose of 59.4 Gy, and then developed partial facial paralysis with decreased sensation. One patients in the 50.4-Gy group had only facial twitching, which was controlled with anticonvulsant medication, and 1 patient in the 54-Gy group developed a peritumor cyst requiring surgical intervention but without cranial nerve deficits. Seven subjects (7.4%) had transient facial and/or trigeminal nerve dysfunction following treatment. There were no secondary malignancies within the treatment region encountered during this follow-up period.

### Hearing Preservation

Audiometric follow-up ranged from 8.7 months to 10.2 years in those with serviceable hearing. Of the 16 patients with serviceable hearing treated in the 54-Gy group, 43% maintained useful hearing with a median follow-up time of 58.2 months. The median time to observe patients decreasing from a Garden-Robinson scale of 1 or 2 to an unserviceable hearing status of at least 3 took 14.8 months (range, 4.7 to 49 months). Of the 28 patients treated in the 50.4-Gy cohort, 64% maintained useful hearing with a median follow-up time of 42.7 months. Of the patients who did not maintain useful hearing, the median time to hearing loss was 12 months (range, 6 to 61 months). The difference in serviceable hearing between the 50.4-Gy and 54-Gy groups at 24 months and 48 months was not statistically significant ( $P = .362$  and  $P = .284$  respectively). The Kaplan-Meier curves of the 50.4-Gy and 54-Gy groups are shown in **Figure 2**.

To account for other possible reasons of improved hearing preservation between the latter 2 groups, univariate analysis was also done (**Table 4**). Factors included tumor location (intracanalicular or extending into the cerebellopontine angle) and

**Table 4.** Univariate analysis of hearing preservation variables

All Patients	Variable	No.	Preserved hearing	P value <sup>a</sup>
Dose	50.4 Gy vs 54.0 Gy	44	64% vs 43%	.185
Diameter	≤1.5cm vs. >1.5cm	44	68% vs 23%	.007 <sup>b</sup>
Location	IAC vs CPA	44	64% vs 42%	.149
50.4 Gy				
Diameter	≤1.5 cm vs >1.5 cm	28	74% vs 20%	.041
54.0 Gy				
Diameter	≤1.5 cm vs >1.5 cm	16	50% vs 38%	1.000
≤ 1.5 cm				
Dose	50.4 Gy vs 54.0 Gy	31	74% vs 50%	.341

**Abbreviations:** IAC, internal auditory canal; CPA, cerebellopontine angle.

<sup>a</sup>P values were determined by  $\chi^2$  and Fisher exact tests.

<sup>b</sup>Remained significant on multivariate analysis.

maximal tumor diameter (>1.5 cm or ≤1.5 cm). The rate of hearing preservation of small versus large tumors was 68% versus 23% ( $P = .007$ ) in both radiation groups combined; and this significance was also seen within the low dose group ( $P = .041$ ). On multivariate analysis, the tumor's initial size (≤1.5 cm in diameter) was the only significant predictor of hearing preservation ( $P = .011$ ).

## Discussion

Proton beam radiotherapy offers radiation treatment delivery that improves normal tissue sparing that surpasses what can be achieved with photon base techniques, including tumors located near the base of skull, such as acoustic neuroma [8]. Although there are no published randomized comparisons between these modalities, Arvold et.al compared treatment plans with proton beam and intensity-modulated radiation therapy and predicted fewer secondary tumors and cranial nerve toxicities with the use of proton beam [9]. The low rate of significant cranial nerve toxicities in our series using fractionated proton therapy provides data that appears to support the use of proton therapy for acoustic neuroma as predicted by these reports.

Fractionated proton-beam therapy to a decreased dose of 50.4 Gy yielded minimal cranial nerve toxicities while still maintaining a level of local control similar to the 54-Gy group. Our evaluation of the low-dose group produced a local control rate of 93% with a median follow-up of 4.14 years and an actuarial 5-year control rate of 92%. This was not found to be statistically different from the local control rates of 95% to 97% seen in the higher-dose groups ( $P = .80$ ). The overall 5-year actuarial control rate is 95%, and the 10-year rates were 90%, which is consistent with 5-year local control rates published for stereotactic radiosurgery [4, 10–16].

Actuarial hearing preservation at 48 months was found to be 64% versus 44% for the 50.4-Gy and 54-Gy groups, respectively ( $P = .284$ ). When comparing similarly sized small tumors, the rates of hearing preservation with median follow up times of 58 and 42 months were 74% versus 50%, respectively ( $P = .341$ ). There may be a trend for improved hearing in the low-dose cohort, but the sample size for this comparison remain small and continued follow-up will be needed to confirm this finding. The 64% rate of hearing preservation in the 50.4-Gy cohort compares favorably with published results utilizing stereotactic radiosurgery. **Table 5** summarizes hearing preservation with radiosurgery producing a mean hearing preservation rate of 54%. It is possible that use of proton beam combined with fractionated therapy to lower doses improves hearing preservation, although more data is needed to confirm this conclusion. In our study, tumor diameter was the salient predictor of hearing preservation; tumors smaller than or equal to 1.5 cm had a 68% hearing-preservation rate, compared with 23% for larger tumors ( $P = .007$ ). The suboptimal hearing preservation rates of 31% published at this institution 10 years ago [6] at a higher dose of 54 Gy may be attributed to the larger tumor diameters commonly treated in the past. Patients who are now diagnosed with acoustic neuromas tend to have smaller tumors compared with those diagnosed 10 years ago; this trend is likely the result of increased use of MRI, which has allowed an earlier diagnosis [15]. Caution should, therefore, be exercised when comparing hearing preservation rates across studies and modalities of treatment because there is a significant bias favoring smaller-sized tumors. The rates of hearing preservation in this study are comparable to photon stereotactic radiosurgery modalities (**Table 5**). Hearing preservation rates of 59% to 75% are reported in the stereotactic radiosurgery literature with a reduced dose of 11-14 Gy and when using the same Gardner-Robertson Scale for assessment [10–22].

**Table 5** Comparison of hearing outcomes.

Trial	Patients (n) with serviceable hearing <sup>a</sup>	Dose (Gy/No. of fractions)	Hearing preservation rate (%)
Loma Linda University Medical Center	28	50.4/28	64
Protons	16	54.0/30	44
Komaki <sup>12</sup>	16	>13/1	13
GKRS	74	≤13/1	68
Royal Hallamshire <sup>24</sup>	49	14.6/1 (mean) <sup>b</sup>	76
GKRS			
Pittsburg <sup>25</sup>	28	14/1 (mean) <sup>b</sup>	56
GKRS			
Charlottesville <sup>26</sup>	36	13.3/1 (mean) <sup>b</sup>	58
GKRS			

**Abbreviation:** GKRS, gamma knife radiosurgery, peripheral dose.

<sup>a</sup>Serviceable hearing defined as grade I or II on the Gardner-Robertson Hearing Scale

<sup>b</sup>Mean denotes average dose used; actual dose varied in these studies.

In support of these findings, Milligan also reported a 28% hearing preservation rate when large tumors ( $\geq 2.5$  cm in diameter) were treated with modern SRS techniques [21]. Despite what this study shows, however, the effect of tumor size still remains controversial in the literature, as a large meta-analysis by Yang et al found no difference in improved hearing preservation when comparing tumor volumes [22].

Additional attempts have been made to improve proton planning techniques. Stereotactic radiosurgery with proton-beam therapy has been explored and published, but investigators reported suboptimal rates of useful hearing when using doses of 13 to 17 Gy prescribed in a single fraction [16]. The rate of hearing preservation was only 33.3% (7 of 21 patients), and the investigators consequently concluded that fractionated stereotactic radiotherapy should be utilized to improve future results.

Fractionated radiotherapy is well known for reducing normal-tissue damage and has been shown in original acoustic neuroma data to reduce cranial nerve toxicity and enhance hearing preservation [19, 20]. Andrews et al studied local control and hearing preservation rates with fractionated photon doses of 50.4 Gy and 46.8 Gy. Both groups had a 100% local control rate and patients treated with doses of 46.8 Gy had a greater likelihood of maintaining GR level 2 hearing ( $P < .0001$ ; log-rank test) [23]. Rates of hearing preservation, then, may be further improved by dose optimization.

## Conclusion

A high degree of local control, hearing preservation, and minimal cranial nerve toxicities were seen with fractionated proton radiotherapy delivering a reduced dose of 50.4 Gy. Improved rates of hearing were also seen in patients with small tumors and lower doses. Further dose optimization should be explored in future clinical trials to identify the optimal dosing regimen.

## ADDITIONAL INFORMATION AND DECLARATIONS

**Conflict of Interest Statement:** Actual or potential conflicts of interest do not exist for any of the listed authors.

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