Optimal dose of stereotactic radiosurgery for acoustic neuromas: a systematic review

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Abbreviations
AN Acoustic Neuroma, Gy Gray, GK Gamma knife, LINAC linear accelerator, NF2 Neurofibromatosis type 2, PFS Progression-Free Survival,

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Abstract

Purpose: Radiosurgery is increasingly employed in the treatment of acoustic neuroma but the optimal dose in terms of long-term tumour control and minimal adverse effects has not been established. We performed a systematic review of the published literature of radiosurgery of acoustic neuroma to assess whether the use of low dose radiosurgery is as effective as high dose treatment.

Methods and Materials: Reports of radiosurgery for acoustic neuroma were identified through a Medline search. Studies with at least 15 patients and a median follow-up longer than 12 months were included. The relationship between actuarial 5 year progression-free survival (PFS) and tumour and treatment parameters was examined.

Results: 42 studies were included. Tumour control following lower radiosurgery doses was similar to that reported following high doses. Only 12 studies reported actuarial outcomes at 5 years. There was no relationship between PFS at five years and dose to the tumour margin. Radiosurgery of larger tumours was associated with lower 5 year PFS ($p < 0.05$).

Conclusion: Although on initial inspection radiosurgery of acoustic neuroma with doses of 12-13 Gy seems to be as effective as higher dose treatment, the available reports are subject to a number of confounding factors, are not sufficiently statistically powered and there is only limited long-term actuarial outcome data. Currently, available studies do not provide sufficient confidence to support the claim that low dose radiosurgery is equally effective as higher doses in the long term control of acoustic neuroma.

Acoustic neuroma, vestibular schwannoma, radiosurgery
Introduction

The treatment options for patients with acoustic neuroma (AN) are microsurgical resection, radiotherapy, expectant observation or any combination of these modalities. Surgical resection, including sub-occipital, trans-labyrinthine and middle fossa approaches, allows for the removal of the AN in most cases. However, even with recent technological advances, considerable morbidity remains, including hearing loss and facial nerve weakness, particularly in patients with large tumours \(^1\). Furthermore, almost half the tumours that are incompletely excised recur \(^2\).

Conservative management was initially reserved for patients unsuitable for surgery. As imaging has improved and understanding of this slow-growing tumour has increased, expectant observation has become accepted as an initial treatment option for selected patients \(^3\). However, many untreated AN will progress within 2 years \(^4\) and even in those without radiological progression, hearing has been shown to deteriorate \(^5\).

Focal irradiation as either single fraction radiosurgery or fractionated stereotactic radiotherapy is increasingly employed as an alternative to microsurgery for the treatment of acoustic neuromas. It produces excellent local control rates with enhanced preservation of function \(^6\)-\(^8\).

Over the past two decades, treatment planning techniques have improved. Magnetic resonance imaging and sophisticated 3D radiation planning, combined with increasingly conformal treatment delivery, allow radiation to be given in a more localised manner achieving good tumour control. Alongside definitive tumour management, preservation of cranial nerve function has also become a significant aim. Larger radiotherapy doses are associated with higher risk of hearing loss and other cranial nerve damage \(^9\). This damage increases with proximity of each nerve to the region of high dose radiation. Toxicity has also been shown to be associated with increasing length of cranial nerve irradiated \(^10\).

Initial reports of radiosurgery in the 1980s used a marginal dose of more than 20Gy \(^11\). More recent studies with doses of 16-18 Gy were associated with high rates of facial nerve palsy and hearing loss \(^12\). Since these preliminary results, lower doses were
used with documented reduction in complication rates, particularly in terms of cranial nerve dysfunction and a lower incidence of hearing loss. Although dose reduction results in fewer side effects, there is limited data to show that such low radiation doses are as effective in achieving long-term disease control as higher doses. Despite this, reassuring statements have been made about the efficacy of low dose radiosurgery. To ascertain whether low dose radiosurgery is indeed effective, we performed a systematic review of the published literature to examine the long term tumour control in patients treated with stereotactic radiosurgery in differing doses. We also examined whether other variables affect outcome after radiosurgery.

**Materials and Methods**

*Search strategy and inclusion criteria*

A MEDLINE literature search was conducted using PubMed from 1966 to March 2005. The search used all variations and combinations of the keywords “acoustic neuroma” and “vestibular schwannoma”. This was combined with a search of all variations of the keywords “radiosurgery”, “gamma knife” and “LINAC”. The search was limited to English language journals and those concerned with human subjects. The abstracts of all articles were examined, and those reporting trials or case series of patients treated with radiosurgery for acoustic neuromas were included. Reports from abstracts or conference proceedings were excluded. Case series of less than 15 patients and those with a median follow-up of 12 months or less were not included as they did not provide sufficient data to assess long term outcome. To avoid duplication of data, earlier reports and overlapping patient subsets from the same centre were also excluded.

*Data analysis*

The number of patients in the study and the number followed up for the stated time period were extracted from full publications. Patient population characteristics including age, the number of patients with type 2 Neurofibromatosis (NF2), the proportion who had undergone previous surgery and the size of the tumour (median volume and diameter) were recorded. Radiosurgery doses to the tumour margin (minimum,
maximum and median) were noted. Where median doses were not reported, the mean was recorded or calculated from the available data. As a summary figure, the mean of the reported median values was calculated.

Outcome data was recorded as percentage tumour control and as progression-free survival (PFS) if available. If outcomes were reported as resection free survival (RFS) and PFS on imaging, only the radiological PFS was used for analysis as other factors may have influenced the decision to surgically resect a progressing tumour. Duration of follow-up from radiosurgery was noted. As a summary figure, the mean of the reported median follow-up, corrected for the number of patients in each study was calculated. Relationship between dose to tumour margin, tumour control and and 5 year PFS were analysed using linear regression. Other comparisons were made on actuarial data only. Factors affecting PFS were analysed using linear regression or t-tests as appropriate. In all tests, p < 0.05 indicated significance.

Results

Study characteristics

42 studies from 32 centres were identified. These were published between 1993 and 2005. Ten studies were from one centre. There were no prospective controlled trials. Full details of the studies are shown in Table 1.

Patient characteristics

3721 patients were included in the 42 studies, although the actual number is likely to be less due to multiple reporting (Table 1). The number of patients in individual reports ranged from 20 to 313 with a median of 69 patients per study. Patients were aged from 7 to 92 years with a corrected summary median of 58 years. Twelve studies excluded patients with NF2 and three studies looked exclusively at the radiosurgical management of patients with NF2. Fifteen reports included a mix of patients with and without NF2 and 12 studies did not provide details of NF2 status. The studies differed in the proportion of patients who had undergone previous surgery. One
reported only patients with tumours recurrent after previous surgery\textsuperscript{26}, while others\textsuperscript{6} excluded such patients.

\textit{Tumour Characteristics}

Where tumour volume was reported, the tumours varied in size from a minimum volume of 0.02cm\textsuperscript{3} \textsuperscript{27,28} to a maximum of 36.7 cm\textsuperscript{3} \textsuperscript{29}. 23 out of 42 studies reported median volumes and the summary median tumour volume was 2.96 cm\textsuperscript{3}. 12 studies reported median diameters of tumours which ranged from 3mm \textsuperscript{15} to 50mm \textsuperscript{15} with a summary median of 21 mm. One study reported only intracanalicular tumours \textsuperscript{30}.

\textit{Radiosurgery}

7 studies reported linear accelerator (LINAC) based radiosurgery \textsuperscript{21,31,32,33,34,35,12} and 35 reported gamma knife radiosurgery. The dose to the tumour margin ranged from 7.5Gy \textsuperscript{15} to 25 Gy \textsuperscript{24,36}. The summary median marginal dose was 13.6 Gy and the weighted mean dose was 14.1Gy.

\textit{Follow-up data}

Follow-up ranged from 1.2 months \textsuperscript{16} to 154 months \textsuperscript{24}. Only 16 of 24 studies had a median follow-up greater than 3 years, with only 6 studies having a median follow-up of 5 years or more. \textsuperscript{27,13,29,37,38,39}. The summary weighted mean of the median follow-up was 42 months.

Many reports quoted a larger number of patients treated than were included in the follow-up of the study, suggesting exclusions and loss to follow-up \textsuperscript{40,41,23,42,43}.

\textit{Outcome data}

All studies reported “tumour control”, defined as lack of progression on neuroimaging without information on the duration of follow-up. Tumour control, as assessed by neuroimaging, ranged from 86\% \textsuperscript{13} to 100\% \textsuperscript{18,20,21,30}. The summary weighted median tumour control was 94.7\%. Relationship of “tumour control” at an unspecified time and dose for all studies is shown in Figure 1. There was no correlation between tumour control and median dose to tumour margin.
Only 13 of the studies (33%) reported actuarial outcome. Of these, only 12 reported progression-free survival at 5 years or more (Table 2). In these studies, five year progression-free survival ranged from 87% \(^{29,32}\) to 100% \(^{31}\) with a weighted mean of 92%. There was no correlation between 5 year PFS and median dose, median age, gender, NF2, previous surgery and treatment technique (GK or LINAC).

The relationship between dose to the tumour margin and 5 year PFS is shown in Figure 2 for the twelve studies where this information was available. Only seven studies reported both five year PFS and tumour volumes (Table 2). For these studies, median tumour volume was negatively correlated with 5 year PFS \((r^2 = 0.74, p< 0.05)\). For every 1 \(cm^3\) increase in tumour volume, 5 year PFS fell by 1.52% (95% confidence interval 1.11-1.93%) (Figure 3).

**Discussion**

We report a systematic review of the published literature of radiosurgery for acoustic neuroma reported in the past 39 years in English language journals. All published experience of radiosurgical treatment of acoustic neuroma is from retrospective data with no prospectively designed Phase I, II or III clinical trials. Only 42 studies were published reporting series of patients who have undergone radiosurgery for AN with a median follow-up of more than 12 months and at least 15 patients. The original series describing early experience with radiosurgery in acoustic neuroma were excluded due to the small numbers of patients involved. A quarter of the studies stem from one centre. As they contain large numbers of patients, it is likely that this may have disproportionately influenced the opinion and practice of radiosurgery.

We have not evaluated hearing preservation in radiosurgery as this has been done in other reports \(^44,45\) and is beyond the scope of this review.

*Neurofibromatosis type II*

Comparison between reports is difficult due to considerable heterogeneity in the acoustic neuroma patient population, radiosurgery details and reporting of results.
In particular, patients with NF2 are likely to represent a sub-group which is particularly difficult to treat. They are at increased risk of complete deafness due to bilateral tumours, many patients also have other intracranial neoplasms, which may complicate radiosurgical regimens and the concern of malignant transformation is greater. These patients are more likely to suffer cranial nerve damage as well as other complications during radiosurgical treatment, than patients with sporadic AN. Tumour control rates are also recognised to be lower in all treatment modalities in patients with NF2, with an estimated local tumour control rate of 50% at 5 years. Furthermore, tumour control is often more difficult to define due to increased loss to follow-up and higher mortality in NF2. It may also be difficult to distinguish recurrence of a previously treated tumour from a new lesion. For these reasons, the assessment of radiosurgery for the treatment of acoustic neuroma should best be carried out separately for patients with and without NF2 and studies combining these patient groups may not reflect the true outcome of either of the groups alone.

*Post-resection studies and differences in tumour size*

Some studies reported post-resection cohorts, where tumours had recurred despite surgery. This could result in selection of patients with unfavourable prognosis. The variation in tumour size between series also makes comparison difficult. Doses of radiosurgery had been adjusted to tumour size, which does not allow for an independent assessment of the influence of dose. Furthermore, we have shown that large tumour volume is associated with a worse outcome, supporting previous findings, which may make it difficult to compare PFS at equivalent doses in cohorts with differing tumour volumes.

*Follow-up data*

Acoustic neuromas are benign, slow growing tumours, where surveillance is considered a reasonable management option. In a recent meta-analysis of conservative management of acoustic neuromas with a mean follow-up of 3.2 years, 57% of tumours showed no growth and some regressed in size. In conditions where more than half of tumours do not progress even without treatment, it is critical that follow-up is of sufficient
duration to identify change in size which may occur over many years. Long term follow-up is also required for assessment of treatment associated morbidity which may take years to manifest.

Many studies suffered from limited follow-up information. More than half the studies had a median follow-up of less than 3 years. Only six reported a median follow-up of five years or more. In addition, a number of studies excluded rather than censored patients lost to follow-up which leads to bias, particularly if the estimates of tumour control are not quoted as actuarial outcome.

**Outcome data**

In the first 12 months following radiosurgery, tumours may transiently increase in size before shrinkage. This occurs most frequently around 6 months after treatment but may be seen for up to 2 years. As the enlargement is temporary, this is likely to represent a reactive process. The incidence of this phenomenon may be related to the dose delivered and could account for early reports of tumour progression associated with high radiation doses. The recognition of this phenomenon may have led to an apparent improvement in tumour control in more recent reports, coinciding with the use of lower radiation doses.

When examining the efficacy of a treatment over time with variable length of follow-up, the only accepted measure of local tumour control is actuarial PFS. Tumour control figures without an indication of the timing of measured outcome provide a highly unreliable outcome measure due to wide variation in the duration of follow-up. Only twelve studies reported PFS at 5 years (Table 2), with values ranging between 87-100% and most studies reporting 5 PFS in the region of 91-96%.

The 5 year PFS seems on initial inspection independent of radiation dose with similar control rates for doses of <14Gy and ≥14Gy. However, results are confounded by potential patient selection, with smaller tumours treated with radiosurgery in more recent years and the recognition that transient increase in tumour size does not reflect tumour progression, both of which lead to apparent improvement in local tumour
control in sequential studies. The small size of patient cohorts and the small proportion of patients at the 5 year time point provide for large confidence intervals with considerable uncertainty about the equivalence of the results. The available retrospective data is not sufficiently powered to reliably detect such a difference. Furthermore, a recent study with longer follow up suggests worse actuarial tumour control in patients treated with a marginal dose less than 12Gy compared to doses ≥12Gy. There is, therefore, insufficient data to substantiate the claim that the use of lower dose radiosurgery in the treatment of AN is as effective as higher doses.

**Technical improvements**

In the time that radiosurgery doses have declined both the technique of radiosurgery and selection criteria for treatment have evolved. Earlier studies were more liberal in selection of patients, essentially treating all who were unsuitable for surgery. More recent series have selected patients with better overall prognosis. The introduction of MRI for the delineation of AN has also been associated with improved outcome and techniques of conformal radiosurgery in the form of multiple isocentre (gamma-knife) and conformal fixed field treatment (linear accelerator) have also progressed. Improved delivery of radiation may have also affected outcome. All such changes influence outcome regardless of radiosurgery dose and may account for unchanged tumour control rates, despite lower doses.

**Fractionated Stereotactic Radiotherapy**

An alternative way to preserve hearing and reduce complication rates whilst achieving comparable local tumour control rates to radiosurgery is to deliver radiation in fractionated manner. A recent study of fractionated stereotactic radiotherapy for AN reported an actuarial 5 year PFS rate of 93% and only mild toxicity with 98% actuarial hearing preservation at 5 years in patients without NF2. Previous studies referred similarly good preservation of cranial nerve function with maintained tumour control. Fractionation which is associated with low risk of irradiation-induced nerve toxicity offers an alternative treatment option for AN of all sizes.
Summary
Radiosurgery as an effective treatment for AN has evolved and improved over the last
decade, leading to a reduction in side effect profile and improvement in outcome. The
toxicity of higher dose radiosurgery has led to dose reduction which has resulted in a
decline in complication rates \(^{13}^{19}\) although a recent study \(^{53}\) using a median marginal
dose of 12Gy showed low rates of hearing preservation. While low dose radiosurgery
may be the correct approach, there is currently insufficient data to substantiate the claim
\(^{17}\) that lower doses are as effective in achieving long-term tumour control as higher
doses. There are too few studies, inadequate follow-up, limited actuarial data and
results are confounded by changing patterns of care and technology. Ideally, a
randomised multi-centre trial with follow-up of at least 8-10 years would provide
sufficient information for an evidence based choice. For the moment, we have to await
the long term follow-up of existing studies reported in an actuarial manner to have full
confidence in the efficacy of the low-dose approach.

Acknowledgment
This work was supported in part by the Neuro-Oncology Research fund, The Royal
Marsden NHS Foundation Trust and Cancer Research UK. The work was undertaken by
the Royal Marsden NHS Trust who received a proportion of its funding from the NHS
Executive; the views expressed are those of the authors and not necessarily those of the
NHS Executive.
Table 1
Characteristics of 42 studies of radiosurgery for acoustic neuroma

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GK- gamma knife, LINAC – linear accelerator  
a 5yr PFS - 5 year Progression-Free Survival  
b Tumour control - percentage of tumours that have not increased in size on neuro-imaging  
* Where median is not reported, the mean was recorded or calculated from the available data  
† All patients underwent this treatment dose  
‡ "Almost all" patients underwent this treatment dose  
"nd" no data available  
In centres reporting more than one study: § Pittsburgh, m Mayo Clinic, mf Mayo Foundation
### Table 2

Characteristics of twelve studies reporting 5 year Progression-Free Survival after stereotactic radiosurgery for acoustic neuroma

<table>
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<tr>
<th>Study (first author)</th>
<th>Number of patients</th>
<th>Patients with NF2 (%)</th>
<th>Median Volume (cm³)</th>
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* Where median is not reported, the mean was recorded or calculated from the available data
Nd – not documented
Figure 1

A scatter plot showing the relationship between Median Dose (Gy) and Tumour Control (%). The x-axis represents the Median Dose (Gy) ranging from 10 to 20, while the y-axis represents Tumour Control (%) ranging from 84 to 100. The data points are plotted as blue diamonds, and a trend line is drawn through the data points, indicating a positive correlation between the Median Dose and Tumour Control.
Figure 2

![Graph showing 5 year PFS (%) vs Dose (Gy)]
Figure 3

![Graph showing the relationship between median volume of tumour (cm³) and 5 year PFS (%). The graph displays a downward trend with decreasing 5 year PFS as the median volume of tumour increases.](image-url)
Figure Legends

Figure 1
Relationship between overall tumour control (at unspecified time point) and median radiosurgery dose to tumour margin in the treatment of acoustic neuroma. 39 studies included; 2 studies reported only PFS, 1 study (Rowe 2003 on NF2) unable to report neuroimaging tumour control due to loss to follow-up and death in patients with NF2. Regression coefficient by linear regression $r^2 = 0.007$, $p = 0.61$. Gy - Gray

Figure 2
Actuarial 5 year Progression-Free Survival following radiosurgery for acoustic neuroma, according to median dose to tumour margin. 12 studies included. The size of the symbol (♦) is scaled to the number of patients in the study. The paler symbols represent two studies (19 61) from the same centre which may have included some overlap of patients. Regression coefficient by linear regression $r^2 = 0.13$ $p = 0.24$. 5 yr PFS - 5 year Progression-Free Survival Gy - Gray

Figure 3
Actuarial 5 year Progression-Free Survival in 7 studies* against median tumour volume. Regression coefficient by linear regression $r^2 = 0.74$ $p = 0.013$ ($< 0.05$).* 5 year Progression-Free Survival and tumour volume data only available for 7 studies.
References:


