Hearing Optimization in Neurofibromatosis type 2: A Systematic Review

Simon Kingsley Wickham Lloyd MBBS, BSc(Hons), MPhil, FRCS(ORL-HNS)*.##.
Andrew Thomas King MBBS, FRCS(SN)†
Scott Alexander Rutherford MBChB, FRCS(Ed)(Neuro.Surg)†
Charlotte Lucy Hammerbeck-Ward MBBS, BSc(Hons), PhD, FRCS(Neuro Surg)†
Simon Richard MacKenzie Freeman MBBS, BSc(Hons), MPhil, FRCS (ORL-HNS)##.
Deborah Jane Mawman MSc~
Martin O’Driscoll PhD~
Dafydd Gareth Evans PhD^

*Department of Otolaryngology, Salford Royal Hospital NHS Foundation Trust, Manchester, M6 8HD, UK
#Department of Otolaryngology, Central Manchester NHS Foundation Trust, Manchester Academic Health Science Centre, Manchester, M13 9WL
^Department of Genomic Medicine, Central Manchester University Hospitals NHS Foundation Trust, Manchester Academic Health Science Centre, Manchester, M13 9WL, UK
+Department of Neurosurgery, Salford Royal Hospital NHS Foundation Trust, Manchester, M6 8HD, UK
~School of Medical Sciences, University of Manchester, M13 9PL
~Richard Ramsden Auditory Implant Centre, Central Manchester NHS Foundation Trust, Manchester, M13 9WL

Address for Correspondence:
Professor Simon Lloyd
University Department of Otolaryngology Head and Neck Surgery
Manchester Royal Infirmary
Oxford Road
Manchester
M20 9WL
Email: sklloyd@me.com
Tel: +44 161 276 3397
Fax: +44 161 276 5003

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/coa.12882
This article is protected by copyright. All rights reserved.
Abstract

Background: It is common for patients with Neurofibromatosis type 2 to develop bilateral profound hearing loss and this is one of the main determinants of quality of life in this patient group.

Objectives: The aim of this systematic review was to review the current literature regarding hearing outcomes of treatments for vestibular schwannomas in neurofibromatosis type 2 including conservative and medical management, radiotherapy, hearing preservation surgery and auditory implantation in order to determine the most effective way of preserving or rehabilitating hearing.

Search Strategy: A MESH search in PubMed using search terms ("Neurofibromatosis 2"[Mesh]) AND "Neuroma, Acoustic"[Mesh]) AND "Hearing Loss"[Mesh] was performed. A search using keywords was also performed. Studies with adequate hearing outcome data were included. With the exception of the cochlear implant studies (cohort size was very small) case studies were excluded.

Evaluation Method: The GRADE system was used to assess quality of publication. Formal statistical analysis of data was not performed because of very heterogenous data reporting.

Results: Conservative management offers the best chance of hearing preservation in stable tumours. The use of Bevacizumab probably improves the likelihood of hearing preservation in growing tumours in the short term and is probably more effective than hearing preservation surgery and radiotherapy in preserving hearing. Of the hearing preservation interventions, hearing preservation surgery probably offers better hearing preservation rates than radiotherapy for small tumours but recurrence rates for hearing preservation surgery were high. For patients with profound hearing loss, cochlear implantation provides significantly better auditory outcomes than auditory brainstem implantation. Patients with untreated stable tumours are likely to achieve the best outcomes from cochlear implantation. Those who have had their tumours treated with surgery or radiotherapy do not gain as much benefit from cochlear implantation than those with untreated tumours.

Conclusions: This review summarises the current literature related to hearing preservation/rehabilitation in patients with NF2. Whilst it provides indicative data, the quality of the data was low and should be interpreted with care. It is also important to consider that the management of vestibular schwannomas in NF2 is complex and decision making is determined by many factors, not just the need to preserve hearing.
Key points

- Conservative management is the best way of preserving hearing in patients with vestibular schwannomas in NF2.
- Treatment with bevacizumab may prolong hearing preservation in tumours with rapidly growing tumours.
- For patients undergoing active treatment of their vestibular schwannoma with the aim of preserving hearing, hearing preservation surgery may provide better outcomes than radiotherapy in selected cases. This needs to be balanced against the risk of recurrence, however.
- Cochlear implantation in the presence of a stable vestibular schwannoma offers effective hearing rehabilitation in most cases.
- Auditory brainstem implantation offers limited hearing rehabilitation in those who do not have a functional cochlear nerve.

Introduction

Hearing loss is almost inevitable in Neurofibromatosis type 2 (NF2) and is one of the main factors influencing quality of life in this condition(1, 2). The hearing loss results from the presence of bilateral vestibular schwannomas or their treatment. Clinicians strive to preserve hearing in at least one ear wherever possible. This can, however, be difficult because of the need to manage the often aggressive behaviour of vestibular schwannomas in NF2. In the past 25 years the options for preserving or rehabilitating hearing loss in NF2 have expanded considerably. This review aims to present the current evidence base for outcomes of hearing preservation or rehabilitation for all the treatment modalities currently available in order to answer the question ‘What is the best way of preserving hearing in Neurofibromatosis type 2?’ In answering this question, it is important to note that hearing preservation is not the only consideration when managing a patient’s vestibular schwannomas and decision making in vestibular schwannoma management in NF2 is, in reality, extremely complex.
Methods

A MESH search in PubMed using the following search terms was performed:

(("Neurofibromatosis 2"[Mesh]) AND "Neuroma, Acoustic"[Mesh]) AND "Hearing Loss"[Mesh]

181 references were identified.


All relevant papers were then back referenced to identify any additional papers of relevance.

Of all the papers identified, 74 were of direct relevance to the question and were included. These were divided up into relevant treatment modalities and each paper was scored according to the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system(3). Papers duplicating results included in other papers were excluded.

A review of the literature relevant to each treatment modality was performed and the outcomes were summarized.

According to the GRADE system, the quality of all evidence was low and the strength of the evidence was weak. The main difficulties with the analysis were:

- Data reporting was very inconsistent
- Duplicate reporting of results between papers
- Retrospective study design in most studies
• No control group in any study and therefore no way of comparing the outcomes of the study with the natural history of hearing loss in NF2.
• Different auditory implant devices were used by different centres at different times
• The type of speech discrimination testing used was very heterogenous
• Limited comparative studies
• Small cohort sizes in some studies
• Absence of raw audiological data in several papers
• Variable use of different hearing classification systems
• Short follow up in some studies

Other than for cochlear implant outcomes, where numbers of patients were very low, case reports were excluded. Papers not reporting hearing outcomes were excluded but all other studies were included even if the study design was felt to be of low quality. With a limited number of studies in the literature very rigorous exclusion criteria would have meant a significant proportion of the data was excluded. Serviceable hearing was generally defined as AAO class A or B or equivalent.

Literature Review
Hearing Change in Conservatively Managed Patients

There were 8 papers in the literature related to hearing loss in conservatively managed patients with vestibular schwannomas secondary to NF2. Only 4 of these contained analyzable data regarding degree of hearing change over time (4-7). A paper by Plotkin et al (8) was not included in the meta-analysis because it did not include data regarding specific changes in threshold or word recognition. It did, however, include data regarding the proportion experiencing hearing decline (defined as an increase in threshold of >6dB). They found that in a cohort of 76 ears, 5%, 13% and 16% of patients experienced hearing decline over 12, 24 and 36 months respectively. 28% of patients had hearing decline over the whole study period of 62 months.
There were 393 ears included amongst the 4 included papers. The mean tumour size was 13.8mm and during the follow up period the mean increase in tumour size was 1.5mm. The mean pure tone average at presentation was 28.4dB and the mean speech discrimination score (SDS) was 87.7%. The mean annual change in pure tone average was 3.6dB and the mean change in SDS was 1.9%. The proportion of patients who had serviceable hearing at presentation who maintained serviceable hearing was 64% over a mean period of 56 months. The proportion of patients with no hearing loss at presentation was surprisingly high in most studies, ranging from 71-85% (6, 8). The population included in these studies had relatively small tumours, were likely to be patients early on in the natural history of their disease and probably tended to have milder phenotypes than the overall NF2 population and this may explain the relatively high proportion of patients with good hearing at presentation and the better than expected hearing preservation rates. The hearing loss may be gradual, stepwise or sudden, with between 5.6 to 15% having sudden hearing loss(7, 9).

Fisher et al(5) and Kontorinis et al found that there was no correlation between change in hearing threshold and tumour growth(5, 7). In contrast, Lalwani et al found that there was a correlation between greater tumour size at presentation and poorer hearing threshold (10). Hearing loss in one ear does not appear to be correlated with hearing loss in the second ear(5).

The Effect of Radiotherapy on Hearing

There were 13 papers related to radiotherapy in NF2 that include hearing outcomes, 9 related to stereotactic radiosurgery (SRS)(11-19), 1 related to hypofractionated radiotherapy(20) and 3 papers related to fractionated radiotherapy(21-23).

The data is summarized in table 1. For stereotactic radiosurgery, 41.1% of patients maintained serviceable hearing over a mean follow up period of 58 months. The dosage varied between series and often varied over time with early patients tending to have received higher doses than more recently treated patients. The dosage was reduced over time because of an awareness of the relatively poor hearing outcomes from higher

This article is protected by copyright. All rights reserved.
doses\((12, 14, 15)\). In some series a significant proportion of patients had had previous surgery on the tumour being treated\((11, 14, 24)\). The SRS results appear to be poorer than those achieved with fractionated radiotherapy (57.3% serviceable hearing preservation) but this conclusion should be interpreted with care because of the low number of patients in the fractionated radiotherapy cohort. No reliable conclusions can be drawn with regards to hearing outcomes with hypofractionated radiotherapy because of the very low numbers of patients treated in this way. It should be noted that there are no studies comparing hearing progression in conservative versus radiotherapy patients and it is likely that some of the hearing loss is due to the natural history of hearing loss in patients with vestibular schwannomas.

The Effect of Chemotherapy on Hearing

There were 7 papers in the literature related to use of bevacizumab (Avastin) that include hearing outcomes\((25-31)\). The results are summarized in table 2. The dose used varied between series but over a mean follow up period of 21 months 38.3% of patients had stable hearing on treatment and 48.3% of patients appear to have an improvement in their hearing. The median improvement in WRS was 10% but the extent of the response was very variable and ranged from -44% to 89%.

Other drugs have also been trialed including Erlotinib (EGFR antagonist)\((32)\), Imatinib, Evorilimus\((33)\), Lapatinib\((34)\) and Pazopanib\((29)\). The numbers of patients treated are too low and follow up too short to draw any conclusions about hearing benefit with these drugs. The use of most have been associated with significant side effects.

Outcomes of Hearing Preservation Surgery

There were 2 papers investigating outcomes of hearing preservation tumour resection surgery via a retrosigmoid approach both of which were published by the Hanover group\((35, 36)\). The 1997 paper included all those patients from the 1995 paper and the 1995 paper was therefore excluded. There were also 5 papers investigating outcomes of tumour
reseption via the middle fossa approach most of which were published by the House group (37-41).

For the retrosigmoid approach studies, there were 81 ears in total. Mean tumour size at surgery was at most 50mm (further detail was not available) and 87.5% of patients had complete tumour removal. Serviceable hearing was maintained in 22% of patients over an unspecified follow up period. Hearing was preserved in some of the very large tumours. There was no data for maintenance of serviceable hearing for small tumours but some hearing was preserved in 57% of tumours smaller than 3cm and 24% of tumours larger than 3cm. Eleven subtotal removals were included and some hearing was preserved in 73% of these patients. 30% of total removals had some hearing preserved.

For the middle fossa approach studies, there were 175 ears in total. The mean tumour size was 10mm but only 63% had total removal. The hearing preservation rate was 65.1% but 59% had residual tumour in the surgical bed at last follow up. Of those that included more than 5 years follow up, at least 7% had a delayed loss in serviceable hearing although it was not possible to be precise about the exact timing of this (41). The duration of follow up varied between 12 to 74 months.

The authors of the retrosigmoid series had clearly attempted to preserve hearing in all patients no matter what the tumour size and this was a very different approach to the middle fossa series which contained only smaller tumours. A like for like comparison of hearing preservation outcomes is therefore difficult. A comparable group of small tumours from the retrosigmoid series would have had maintenance of serviceable hearing in somewhere between 22 and 57% of cases.

There was one middle fossa series (37) and one retrosigmoid series that included a significant number of patients managed with planned subtotal removal (36). The hearing preservation rates in these series were 95% and 72% respectively but in both these series at least 10-15% required further surgery for growing tumours. Based on this, it would appear that there is a greater chance of preserving hearing if there is a subtotal removal but this...
approach increases the risk of further growth of residual tumour and therefore the risk to hearing loss if further treatment is required.

Disease severity may have a negative correlation with hearing outcome. Conversely, smaller size, younger age at surgery and family history of NF2 may be associated with better hearing outcomes (40).

There was a further paper describing outcomes of middle fossa decompression of the internal auditory meatus as a technique for hearing preservation, published by the House group (42). This included 45 NF2 patients with a mean follow up of 48.7 months. The mean tumour size was 19mm with 56% of tumours growing at the time of surgery. At 3 months post-operatively, there was no significant change in hearing with 91% of patients preserving their AAO hearing class. At 1 year 66% of patients had preserved their AAO hearing class. Twenty two patients had had 4 years of follow up and 41% had retained the same AAO class. The mean duration of AAO hearing class maintenance was 2.2 years.

Outcomes of Auditory Brainstem Implantation

Forty papers relevant to ABI in NF2 were identified. Fifteen presented audiological data that was not repeated in other publications although it is likely that there was still some duplicate reporting (43-57). There was considerable variability in the type of implant used. This was because of local preferences and changes in the type of device available over time. Devices used included Cochlear Nucleus 22 ABI, Cochlear Nucleus 24 ABI, Cochlear Nucleus CI8+1M, Cochlear Nucleus 541, MEDEL Combi 40+ ABI, MEDEL Concerto Mi1000 and Digisonic. Table 3 summarises the auditory outcomes of auditory brainstem implantation in NF2.

The mean word scores with ABI and lip reading and with ABI alone were 72.9% and 35.3% respectively. The mean sentence scores with ABI and lip reading and with ABI alone are 57.7% and 12.3% respectively. The proportion of patients with open set speech discrimination was 11.6%. The non-user rate was 13.2%. It is important to note that the auditory benefit from ABI continues to improve over several years and in this way differs.

This article is protected by copyright. All rights reserved.
from CI where most of the improvement is seen in the first year (46, 52, 57). Therefore, ABI only infrequently allows open set speech discrimination and for the majority of patients provides assistance in lip reading.

There were 3 papers that report subjective benefits of ABI(47, 58, 59). The mean duration of daily use in these series ranged from 8.5 to 13 hours with a range of 4 to 16 hours a day. 95 to 100% of patients were able to differentiate between speech and environmental sounds. 18 to 20% switched their device off in noisy environments and around 40% switch off their device when tired. The ABI was reported as most useful in conversation in a quiet place with a familiar voice with a median usefulness score of approximately 4/6 without lip reading. With a familiar speaker in a loud environment the median score was around 2.5/6 without lip reading. With an unfamiliar speaker in a quiet place the median score is around 1.5/6 and with an unfamiliar speaker in a loud place the median score is around 1/6. Lip reading improved usefulness scores by at least one point in every type of environment.

There are a number of factors that may influence auditory outcomes in patients with ABI. The number of active electrodes may be important although the evidence is contradictory. Ramsden et al found a positive correlation(57) although Behr et al did not(60). Non-auditory stimulation was seen in almost all patients and necessitated deactivation of a variable number of electrodes. There were also often electrodes that produced no auditory stimulation. The number of electrodes providing auditory stimulation was therefore very variable from one patient to another. Device choice may also influence outcome although the evidence is again somewhat contradictory (52, 61). It is unclear whether any difference is due to the processing strategy employed (CIS for MEDEL vs SPEAK and ACE for Cochlear), to design differences (smaller electrode paddle with fewer electrodes in the MEDEL device) or to the availability of a probe electrode with the MEDEL device to test auditory stimulation prior to final implantation. Surgical position may also influence outcome with some authors suggesting that the semi-sitting position provides better outcomes (60, 61). Other possible factors important for optimizing outcome include duration of deafness prior to implantation, quality of the intra-operative and post-operative EABR and ABI stimulation rate although the evidence is again contradictory(57, 60). Tumour size and age at surgery do not appear to influence outcome(57).

This article is protected by copyright. All rights reserved.
There are a number of papers discussing novel approaches to central auditory implantation. An ABI with a penetrating electrode (PABI) has been developed but the results to date have been disappointing with only 25% of penetrating electrodes showing any auditory stimulation compared to 60% of surface electrodes (62). Lenarz et al have also developed a midbrain auditory implant that is designed to penetrate the inferior colliculus. Early results have also been disappointing (63).

Outcomes of Cochlear Implantation

There are 28 papers including 59 ears in the literature related to the use of cochlear implantation in the rehabilitation of hearing in NF2. Speech discrimination scores in quiet without lip reading were most consistently reported and this was the main outcome measure used to perform the meta-analysis. It was not possible to take account of other confounding factors in terms of outcome because of the very small number of patients in each group. The evidence base for hearing outcomes in patients receiving cochlear implants is shown in Table 4.

Cochlear Implantation in Untreated Tumours

There were three papers and a total of 5 patients in this group in the literature (64-66). All patients had significant benefit from their device with a mean sentence score in quiet without lip reading of 69.3%.

Cochlear Implantation in Ears With Tumours Treated with Radiotherapy

There were 6 papers and 17 patients in this group (64-69).

Most patients were treated with stereotactic radiosurgery although several papers did not report the type of radiotherapy used. The outcomes appear to be less predictable following radiotherapy than in untreated tumours not withstanding other confounding factors that might also influence outcome. The mean sentence score in quiet without lip reading was 48.6%.

This article is protected by copyright. All rights reserved.
This technique is limited to tumours of less than 15mm in the cerebellopontine angle, unless there is a subtotal resection. There were 7 papers that included patients in this group and a total of 16 ears of which useful data was available in 13\cite{50, 65, 67, 68, 70-72}.

One patient had subtotal removal of their tumour and had a 92% speech discrimination score afterwards. The others had total tumour removal (where data was available). One author\cite{67} showed very poor outcomes with this technique. The other papers showed more encouraging outcomes. The mean sentence score in quiet without lip reading was 38.2%.

Failed Hearing Preservation Surgery and Cochlear Implant Outcomes

Again, this technique is limited to tumours of less than 15mm in the cerebellopontine angle, unless there is a subtotal resection. There were 13 papers in total in this group with 16 ears who had retrosigmoid surgery and 5 ears in the group that had had middle fossa surgery\cite{50, 64, 65, 68, 72-76}. Useful data was available in all but one case.

Data regarding completeness of tumour removal was very inconsistent but most patients, in whom data was available, had complete tumour removal. All but one patient (where data was available) were using their device and the mean sentence score in quiet without lip reading was 45.2% for the retrosigmoid approach and 30% for the middle fossa approach. There was no information about how many patients did not proceed to cochlear implantation because of failed cochlear nerve preservation in these groups.

Discussion

Table 5 compares auditory outcomes for the hearing preservation treatments. There is no reliable way of preserving hearing in NF2 but conservative management offers the best chance of preservation in stable tumours. The use of bevacizumab probably improves the likelihood of hearing preservation in growing tumours at least in the short term and is probably more effective than hearing preservation surgery and radiotherapy in preserving hearing. Of the hearing preservation interventions, hearing preservation surgery probably
offers better hearing preservation rates than radiotherapy but is limited to small tumours and has a very high chance of further growth of residual tumour.

Table 6 compares the outcomes of auditory implantation in patients who had profound hearing loss. Cochlear implantation rather than auditory brainstem implantation should be used whenever possible as this offers significantly better auditory outcomes. Patients with untreated stable tumours are likely to achieve the best outcomes. Those who have had their tumours treated with surgery or radiotherapy do not gain as much benefit from cochlear implantation than those with untreated tumours but these interventions offer further useful options for hearing restoration. These findings are consistent with recommendations recently published by the UK NF2 group(77).

In sporadic vestibular schwannoma cases hearing preservation surgery is usually recommended for patients with serviceable hearing (AAO class A or B). In NF2, if hearing preservation surgery is being considered, it is likely that hearing that is class C or even good class D will be helpful if the contralateral ear is profoundly deaf and hearing preservation surgery should not necessarily be confined to those with class A or B hearing. Failure of this type of surgery may still allow cochlear implantation if cochlear nerve electrophysiological testing suggests that the nerve is still functional. The middle fossa approach may offer slightly better hearing preservation rates but completeness of tumour resection may be poorer with the middle fossa approach resulting in a much higher recurrence rate. It remains unclear how long any preserved hearing will continue for as long term follow up data is limited.

Whilst this review has concentrated on the hearing preservation or restoration outcomes of various treatment modalities, in reality, these cannot be taken in isolation. Hearing preservation must be balanced with the need for tumour control and with the potential risks of a given intervention. This is made more complicated by the fact that both ears must be taken into consideration.

The results of the analysis of this study have not taken into consideration other factors that could potentially influence hearing results. This includes tumour size, tumour behaviour,
patient age, patient co-morbidities, presence of multiple CPA tumours, tumour cysts, cochlear involvement with tumour, patient preference and local expertise.

The strength of evidence for all treatment modalities is low. There are very few prospective studies and very limited comparative studies. There is wide variation in the way results are reported and some papers lack data that would be helpful to have presented. Meta-analysis of outcomes has, however, strengthened the evidence for any given intervention although compromises had to be made to allow analysis.

Further well designed prospective and comparative studies with larger cohorts of patients would add significantly to the existing literature, particularly in auditory implantation. It is unlikely that adequately powered studies will be achievable especially in auditory implantation but recruitment from multiple centres may facilitate adequate cohort sizes.

References


This article is protected by copyright. All rights reserved.


This article is protected by copyright. All rights reserved.


This article is protected by copyright. All rights reserved.
Legends

Table 1. Summary table of hearing preservation rates following radiotherapy in NF2

Table 2. Summary table of hearing preservation rates following the use of bevacizumab in patients with NF2

Table 3. Summary table of hearing outcomes of auditory brainstem implantation in patients with NF2

Table 4. Summary table of hearing outcomes of cochlear implantation in patients with NF2

Table 5. Summary table comparing auditory outcomes of hearing preservation treatments

Table 6. Summary table comparing auditory outcomes of auditory implantation for rehabilitation of profound deafness in NF2
Table 1 Summary table of hearing preservation rates following radiotherapy in NF2

<table>
<thead>
<tr>
<th>No. of papers</th>
<th>No. of ears</th>
<th>Technique</th>
<th>Mean marginal dose (Gray)</th>
<th>Size (cm³)</th>
<th>Mean maintenance of serviceable hearing(^\wedge) (%)</th>
<th>Tumour control (%)</th>
<th>Duration of follow up (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stereotactic Radiosurgery</td>
<td>9</td>
<td>271</td>
<td>Gamma knife</td>
<td>13.2</td>
<td>4.1</td>
<td>41.1</td>
<td>81.4</td>
</tr>
<tr>
<td>Hypofractionated</td>
<td>1</td>
<td>15</td>
<td>LINAC</td>
<td>5 x 20</td>
<td>25mm</td>
<td>20</td>
<td>100</td>
</tr>
<tr>
<td>Fractionated</td>
<td>3</td>
<td>33</td>
<td>LINAC</td>
<td>25-38 fractions of 1.8-2Gray</td>
<td>No data</td>
<td>57.3</td>
<td>92.6</td>
</tr>
</tbody>
</table>

\(^\wedge\)AAO class A or B

This article is protected by copyright. All rights reserved.
Table 2 Summary table of hearing preservation rates following the use of bevacizumab in patients with NF2

<table>
<thead>
<tr>
<th>No of papers</th>
<th>No of ears with hearing</th>
<th>Dose (mg/kg)</th>
<th>Pre-treatment tumour size (ml)</th>
<th>Pre-treatment annual growth rate (%)</th>
<th>Median change in tumour size (%)</th>
<th>Proportion with reduction in size (%)</th>
<th>Proportion with hearing improvement (%)</th>
<th>Median change in WRS (%)*</th>
<th>Mean Follow up (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>7</td>
<td>60</td>
<td>2.5-10</td>
<td>12.9 (Range -19 to 282)</td>
<td>51.5 (Range -19 to 282)</td>
<td>-22.4 (n=27)</td>
<td>66.9 (n=58)</td>
<td>48.3 (n=60)</td>
<td>10 (Range -44 to 89)</td>
<td>21</td>
</tr>
</tbody>
</table>

*Data from Plotkin et al, 2012 was extrapolated from a chart and was therefore an estimate. No median figure was provided.

WRS=word recognition score

Likely to be some duplication in data as one author published 2 papers, the latter with more patients and longer follow up (Plotkin 2009, Plotkin 2012)
Table 3 Summary table of hearing outcomes of auditory brainstem implantation in patients with NF2

<table>
<thead>
<tr>
<th>No. of papers</th>
<th>No. of ears</th>
<th>% of active electrodes</th>
<th>Non-user rate (%)</th>
<th>Sentence score* (%)</th>
<th>Word score (%)</th>
<th>Proportion open set speech discrim (%)</th>
<th>FU duration (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>LR and ABI</td>
<td>ABI only</td>
<td>LR and ABI</td>
<td>ABI only</td>
</tr>
<tr>
<td>15</td>
<td>377</td>
<td>50.1</td>
<td>13.2</td>
<td>57.7</td>
<td>12.3</td>
<td>72.9</td>
<td>35.3</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Range 0-100 n=203</td>
<td>Range 0-100 n=247</td>
<td>Range 0-100 n=120</td>
<td>Range 0-100 n=177</td>
</tr>
</tbody>
</table>

* Speech discrimination scores exclude non-users

LR Lip reading
Table 4 Summary table of hearing outcomes of cochlear implantation in patients with NF2

<table>
<thead>
<tr>
<th>No of papers</th>
<th>No of ears</th>
<th>Mean tumour size (mm)</th>
<th>Technique</th>
<th>Marginal dose (Gray)</th>
<th>Total removal (%)</th>
<th>Cochlear nerve testing used (%)</th>
<th>Mean sentence score* (%)</th>
<th>Proportion of users (%)</th>
<th>FU (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Untreated tumours</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>5</td>
<td>7.7</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>69.3</td>
<td>-</td>
<td>100</td>
</tr>
<tr>
<td><strong>Radiotherapy</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>17</td>
<td>15.9</td>
<td>SRS 66.7</td>
<td>SRT 33.3</td>
<td>14.7</td>
<td>-</td>
<td>48.6</td>
<td>-</td>
<td>94.5</td>
</tr>
<tr>
<td><strong>Failed hearing preservation surgery</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>16</td>
<td>13.5</td>
<td>Retrosig</td>
<td>-</td>
<td>83</td>
<td>75</td>
<td>45.2</td>
<td>-</td>
<td>81.8</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>n=13</td>
<td>n=6</td>
<td>n=16</td>
<td>Range 0-100</td>
<td>n=11</td>
<td>n=16</td>
</tr>
<tr>
<td>4</td>
<td>5</td>
<td>11</td>
<td>Middle fossa</td>
<td>-</td>
<td>100</td>
<td>100</td>
<td>30</td>
<td>-</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>n=5</td>
<td>n=2</td>
<td>n=5</td>
<td>Range 0-80</td>
<td>n=3</td>
<td>n=3</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>16</td>
<td>16</td>
<td>CNPTL</td>
<td>-</td>
<td>90.9</td>
<td>60</td>
<td>38.2^</td>
<td>-</td>
<td>68.8</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>n=9</td>
<td>n=11</td>
<td>n=10</td>
<td>Range 0-96</td>
<td>n=13</td>
<td>n=11</td>
<td></td>
</tr>
</tbody>
</table>

*In quiet, without lip reading

^The actual mean speech score is probably slightly higher than this. Two patients were reported as having excellent or open set speech discrimination but no percentage score was reported
SRS=Stereotactic radiosurgery
SRT=Fractionated stereotactic radiotherapy
CNPTL=Cochlear nerve preserving translabyrinthine surgery
Table 5 Summary table comparing auditory outcomes of hearing preservation treatments

<table>
<thead>
<tr>
<th></th>
<th>Conservative</th>
<th>Radiotherapy (SRS only)</th>
<th>Bevacizumab</th>
<th>Middle fossa hearing preservation</th>
<th>Retrosigmoidal hearing preservation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of ears</td>
<td>393</td>
<td>271</td>
<td>60</td>
<td>121^</td>
<td>175^</td>
</tr>
<tr>
<td>Rate of serviceable hearing preservation (%)</td>
<td>64</td>
<td>41.1</td>
<td>86.6*</td>
<td>65.1</td>
<td>59.5</td>
</tr>
<tr>
<td>Follow up (months)</td>
<td>56</td>
<td>58</td>
<td>21</td>
<td>12-72</td>
<td>No data</td>
</tr>
</tbody>
</table>

*Includes all patients, not just those with pre-treatment serviceable hearing.

^Significant duplication of patients.

Table 6 Summary table comparing auditory outcomes of auditory implantation for rehabilitation of profound deafness in NF2.

<table>
<thead>
<tr>
<th></th>
<th>Cochlear implant alone</th>
<th>Cochlear implant after radiotherapy</th>
<th>Cochlear implant after failed hearing preservation surgery</th>
<th>Cochlear implant after CNPTL surgery^</th>
<th>Auditory brainstem implant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of ears</td>
<td>5</td>
<td>13</td>
<td>21</td>
<td>16</td>
<td>247</td>
</tr>
<tr>
<td>Speech discrimination score (%)*</td>
<td>69.3</td>
<td>48.6</td>
<td>42.2</td>
<td>38.2</td>
<td>12.3</td>
</tr>
<tr>
<td>Follow up (months)</td>
<td>60.5</td>
<td>18</td>
<td>41.4</td>
<td>33.1</td>
<td>23.8</td>
</tr>
</tbody>
</table>

*In quiet without lip reading

^CNPTL=Cochlear nerve preserving translabyrinthine surgery