Management Strategy in Patients with Bilateral Acoustic Schwannoma in NF 2

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Neurofibromatosis type 2 (NF2)

- An autosomal dominant genetic disorder
- Birth incidence of approximately 1/33,000.
- Caused by inactivation of the NF2 gene located on chromosome 22q, which codes for the NF2 gene product, Merlin.
- Merlin acts both at the cell cortex and the nucleus, directly affecting multiple signaling pathways related to contact inhibition and tumor suppression.
Merlin

- Merlin has substantial sequence homology to members of the Ezrin/Radixin/Moesin (ERM) family of proteins, which link a variety of cell-adhesion receptors to the cortical actin cytoskeleton.
- It is a major effector of cell contact inhibition.
- In addition, Merlin can affect a variety of mitogenic signaling pathways, including Rac–PAK, mTOR, EGFR–Ras–ERK and PI3K–Akt, and contribute to the activation of the Hippo tumor-suppressor pathway.
Merlin has been recognised to pleiotropically affect cell signaling by migrating into the nucleus and inducing a growth-suppressive program of gene expression through direct inhibition of the CRL4DCAF1 E3 ubiquitin ligase - derepressed CRL4DCAF1 promotes activation of the Hippo pathway component YAP by inhibiting Lats1 and 2 in the nucleus.

Hippo signaling is an evolutionarily conserved pathway that controls organ size by regulating cell proliferation, apoptosis, and stem cell self-renewal. In addition, dysregulation of the Hippo pathway contributes to cancer development.
NF2 and Tumours

- NF2 patients develop multiple tumors affecting the central and peripheral nervous system tumors, i.e. schwannomas, meningiomas and ependymomas.
- The majority of NF2 patients develop progressive hearing loss in young adulthood due to bilateral vestibular schwannomas.
• Schwannomas frequently also involve other cranial nerves, impacting on neurologic function such as swallowing, vision and facial function.

• Meningiomas and less commonly, ependymomas, involve the brain and spine, leading to mass effect and/or neurological dysfunction, based on size and location.
NF2 Tumor Growth Pattern

- NF2 tumors have 4 different potential growth patterns:
  - **Sporadic**: Irregular, erratic, random pattern, growth might be in leaps rather than by gradual transitions
  - **Linear**: consistent growth
  - **Exponential**: steady doubling increase of growth
  - **Dormant**: not dead, but no growth after initial development
Hearing decline and Tumour Growth in NF2

• The natural history of VS growth and hearing decline in newly diagnosed, untreated NF2 patients:
  – rate of hearing decline: 5%, 13% and 16% at 1, 2 and 3 years, respectively;
  – rate of tumour progression: 31%, 64% and 79% at 1, 2 and 3 years, respectively.
  – median time to tumour progression: 14 months and
  – median time to hearing decline: 62 months.

Hearing Loss in NF2

• Hence hearing loss is almost inevitable in NF2 and is one of the main factors influencing quality of life.
• 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.
Traditional Treatment Paradigm

• The traditional treatment paradigm for NF2 patients consisted of clinical observation and surveillance imaging observation, with judicious use of surgical intervention for symptomatic tumours, and sometimes radiotherapy.

• The main reason for the traditional approach is to preserve hearing.

• However, 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.
Developing a Management Strategy

• Preserving hearing for as long as possible
• Learning to lip read while still able to hear
• Good quality of life
• Staying alive
Evidence

• Hearing Change in Conservatively Managed Patients
• The Effect of Radiotherapy on Hearing
• The Effect of Chemotherapy on Hearing
• Outcomes of Hearing Preservation Surgery
• Outcomes of Auditory Brainstem Implantation
• Outcomes of Cochlear Implantation
Hearing Change in Conservatively Managed Patients

• 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.

• In one systemic review - 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%

• These patients had relatively small tumours, and 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.
• Hence 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.

• In 2 studies, there was no correlation between change in hearing threshold and tumour growth.

• In contrast, another study found that there was a correlation between greater tumour size at presentation and poorer hearing threshold.

• Hearing loss in one ear does not appear to be correlated with hearing loss in the second ear.

Kontorinis et al. Eur Arch Otorhinolaryngol. 2014.
The Effect of Radiotherapy on Hearing

- Radiotherapy modalities in NF2 include:
  - stereotactic radiosurgery (SRS)/Gamma Knife
  - hypofractionated radiotherapy
  - fractionated radiotherapy
### Table 1 Summary table of hearing preservation rates following radiotherapy in NF2

<table>
<thead>
<tr>
<th>Technique</th>
<th>No. of papers</th>
<th>No. of ears</th>
<th>Mean marginal dose (Gray)</th>
<th>Size (cm3)</th>
<th>Mean maintenance of serviceable hearing(^\dagger) (%)</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>13.2 Range 12-15</td>
<td>4.1 Range 1.6-5.6</td>
<td>41.1 Range 27-75 n=174</td>
<td>81.4 Range 50-98</td>
<td>58</td>
</tr>
<tr>
<td>Hypofractionated</td>
<td>1</td>
<td>15</td>
<td>5 x 20</td>
<td>25mm</td>
<td>20 n=15</td>
<td>100</td>
<td>49</td>
</tr>
<tr>
<td>Fractionated</td>
<td>3</td>
<td>33</td>
<td>25-38 fractions of 1.8-2Gray</td>
<td>No data</td>
<td>57.3 Range 33-75 n=33</td>
<td>92.6 Range 91-94</td>
<td>78</td>
</tr>
</tbody>
</table>

\(^\dagger\)AAO class A or B
• 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 - dosage was reduced over time due to awareness of the relatively poor hearing outcomes from higher doses.
• In some series a significant proportion of patients had had previous surgery on the tumour being treated.
• The SRS results appear to be poorer than those achieved with fractionated radiotherapy (57.3% serviceable hearing preservation) but note 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.
Chemotherapy in NF2

• Angiogenesis occurs in VS, and VEGF receptors are expressed in these tumors.
• Bevacizumab, an anti-VEGF monoclonal antibody, has recently emerged as a medical treatment option for NF2 patients with progressive VS.
• The initial reports, based on case series and off-label use of bevacizumab, suggested that treatment was effective in the majority patients, including not only imaging responses, but also hearing improvement, which in some patients was dramatic.
• However the responses can only be sustained with continued treatment, which poses a challenge due to dose-limiting long-term toxicities (hypertension and proteinuria).
Table 2

Novel therapies for NF2 associated tumors – recently completed or published studies and ongoing clinical trials

<table>
<thead>
<tr>
<th>Drug (ClinicalTrials.gov identifier)</th>
<th>Mode of action</th>
<th>Trial design</th>
<th>Age [years]</th>
<th>n</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Prospective therapeutic studies for NF2 patients with progressive VS</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lapatinib [53]*</td>
<td>Dual EGFR/ErBB2 inhibitor</td>
<td>Phase 2 (two-stage) Single arm Open label</td>
<td>&gt;3</td>
<td>17</td>
<td>Volumetric response 24%, hearing response 31%</td>
</tr>
<tr>
<td>Everolimus [56]*</td>
<td>mTORC1 inhibitor</td>
<td>Phase 2 (two-stage) Single arm Open label</td>
<td>&gt;3</td>
<td>9</td>
<td>No objective hearing or volumetric responses</td>
</tr>
<tr>
<td>Bevacizumab (NCT01207687)</td>
<td>VEGF A inhibitor</td>
<td>Phase 2 Single arm Open label</td>
<td>≥12</td>
<td>14</td>
<td>Enrollment completed, results pending</td>
</tr>
<tr>
<td>Bevacizumab (NCT01767792)</td>
<td>VEGF-A inhibitor</td>
<td>Phase 2 (two-stage) Single arm Open label</td>
<td>12–30</td>
<td>14–22</td>
<td>Study ongoing</td>
</tr>
<tr>
<td>Axitinib (NCT02129647)</td>
<td>Multi-kinase inhibitor (VEGFR2, PDGFR, c-kit)</td>
<td>Phase 2 (two-stage) Single arm Open label</td>
<td>≥18</td>
<td>9–17</td>
<td>Study ongoing</td>
</tr>
<tr>
<td><strong>Phase 0 (pharmacokinetic/pharmacodynamic, non-therapeutic) studies for NF2 VS/ meningioma</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lapatinib (NCT00863122)</td>
<td>Dual EGFR/ErBB2 inhibitor</td>
<td>Phase 0</td>
<td>≥18</td>
<td>Enrollment completed, results pending</td>
<td></td>
</tr>
<tr>
<td>Everolimus (NCT01880749)</td>
<td>mTORC1 inhibitor</td>
<td>Phase 0</td>
<td>≥18</td>
<td>Study ongoing</td>
<td></td>
</tr>
</tbody>
</table>

EGFR = endothelial growth factor receptor; mTORC1 = mammalian target of rapamycin complex; PDGFR = platelet derived growth factor; c-kit = cellular homolog of feline sarcoma viral oncogene v-kit; VEGF = vascular endothelial growth factor; HDAC = histone deacetylase
Review of Bevacizumab on Hearing in NF2

- Lloyd et al reviewed the 7 papers in the literature related to use of bevacizumab (Avastin) that include hearing outcomes.
- 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%.
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>Pretreatment 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</td>
<td>51.5 (Range -19 to 262)</td>
<td>-22.4</td>
<td>66.9</td>
<td>48.3</td>
<td>10 (Range -44 to 89)</td>
<td>21</td>
</tr>
</tbody>
</table>

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)

*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
Targeted therapy

- Based on recent insights into the biology of Merlin-deficient tumors, a number of molecular targeted agents have been repurposed for testing in preclinical models of NF2, including genetically engineered mouse models for schwannomas and meningiomas.
- Major molecular targets validated in NF2 preclinical models that have been recently translated into clinical trials include EGFR/ErbB2 (lapatinib), mTOR (rapamycin/everolimus) and VEGFR/PDGFR/c-kit (sorafenib, axitinib)
• In a phase 2 clinical trial for adult and pediatric NF2 patients with progressive VS, lapatinib showed modest activity with objective volumetric and hearing response rates of 24% and 31%, respectively. The hearing responses, however, were predominantly minor and not sustained.
• In contrast, a similarly designed phase 2 study with everolimus failed to yield any objective volumetric or hearing responses.


Phase II study of everolimus in children and adults with neurofibromatosis type 2 and progressive vestibular schwannomas.


• Another phase 2 study also do not show VS shrinkage with everolimus


Phase II study of mTORC1 inhibition by everolimus in neurofibromatosis type 2 patients with growing vestibular schwannomas.

Goutagny S, Raymond E, Esposito-Farese M, Trunet S, Mawrin C, Bernardeschi D, Larroque B, Sterkers O, Giovannini M, Kalamardes M.
Outcomes of Hearing Preservation Surgery

• Retro-sigmoid approach (Samii et al) – usually larger tumours
  – 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.
• Middle fossa approach (House group) – only for smaller tumours
  – 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
Surgery

• 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.
Outcomes of Auditory Brainstem Implants and Cochlear Implants
Cochlear and Auditory Brainstem Implants

• The Cochlear Implant was designed to direct sound to the Cochlea when bones in the ear or other internal parts of the middle ear are damage.

• But if damage occurs to the Vestibulocochlear Nerve, an ABI (Auditory Brainstem Implant) is the only option to regain hearing.

• ABIs direct sound straight to the brainstem, bypassing the ear components completely.

• The brain requires time to adjust and adapt or relearn the new form of hearing and improves over the course of the first year.
• The ABI's quality of sound is different than natural hearing.
• But with an ABI speech reading (lip-reading) is often easier.
• Effectiveness of use of an ABI and lip-reading may vary from person to person and can become easier to use to understand speech better over time.
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</td>
<td>Range 0-100</td>
<td>Range 0-100</td>
<td>Range 0-100</td>
</tr>
<tr>
<td></td>
<td></td>
<td>n=304</td>
<td>n=358</td>
<td>n=203</td>
<td>n=247</td>
<td>n=120</td>
<td>n=177</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>11.6</td>
<td>23.8</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Speech discrimination scores exclude non-users

LR Lip reading
<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>Untreated tumours</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>100</td>
<td>60.5</td>
</tr>
<tr>
<td></td>
<td></td>
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<td></td>
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<td>Range 49-93 (n=5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Radiotherapy</td>
<td></td>
<td></td>
<td></td>
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<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>94.5</td>
<td>18</td>
</tr>
<tr>
<td></td>
<td></td>
<td>n=14</td>
<td>n=9</td>
<td>n=6</td>
<td></td>
<td></td>
<td>Range 13.7-97 (n=13)</td>
<td>n=17</td>
<td></td>
</tr>
<tr>
<td>Failed hearing preservation surgery</td>
<td></td>
<td></td>
<td></td>
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<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>81.8</td>
<td>40.1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>n=13</td>
<td></td>
<td>(n=6)</td>
<td>n=16</td>
<td></td>
<td>Range 0-100 (n=16)</td>
<td>n=11</td>
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<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>100</td>
<td>46.4</td>
</tr>
<tr>
<td></td>
<td></td>
<td>n=5</td>
<td></td>
<td>(n=2)</td>
<td>n=5</td>
<td></td>
<td>Range 0-80 (n=4)</td>
<td>n=3</td>
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</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>68.8</td>
<td>33.1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>n=9</td>
<td></td>
<td>(n=11)</td>
<td>n=10</td>
<td></td>
<td>Range 0-96 (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.
Cochlear Implant in NF2

• Continued growth of a tumor on any of these nerves, can result in not just damage to the nerve for the connection of the implant

• Because of this, the CI might only work for a short time if tumors are present.

• However, chemotherapy like use of Avastin have started to allow for an increased period of effectiveness with CI.
Summary

• 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.
• 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.
• 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.
• 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.
• Other factors that could potentially influence hearing results 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.
THANK YOU!