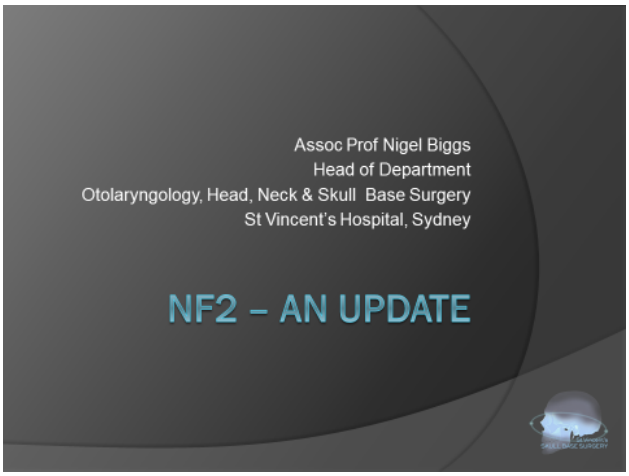
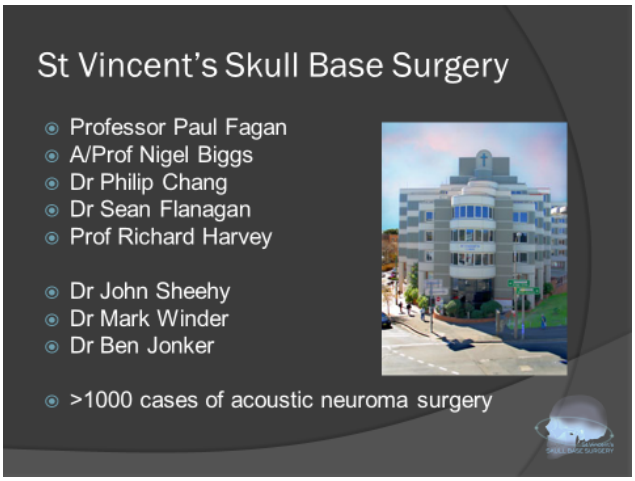
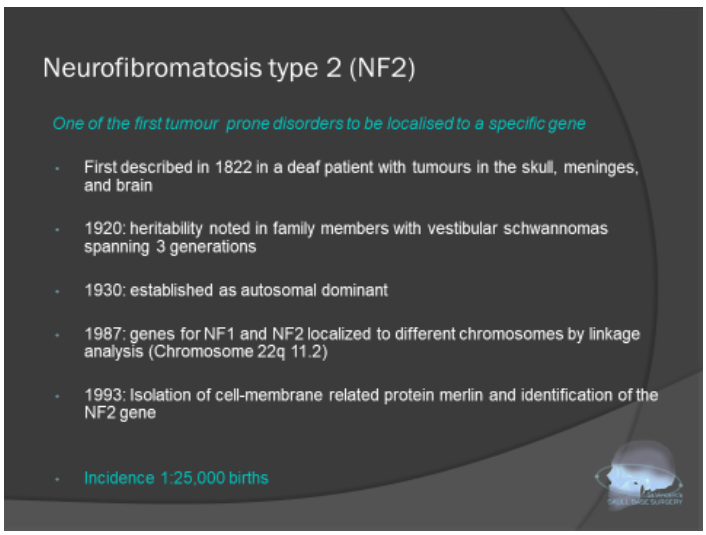
CTF Host: Dr Biggs is a specialist head and neck surgeon with extensive training and experience both here in Australia and in the UK and CTF is very pleased that Dr Biggs has taken a special interest in helping people with NF2 especially when they need his specialist surgical skills. So if everyone can remember to have their microphones muted during the presentation, we hope that the captioner will keep us informed of what Dr Biggs is saying with his slides. It is being recorded at the same time and we hope to have it up online in the next week or so. If we have time for a couple of questions, please type them in to the chat box and hopefully we can get to one or two of them at the end.

Dr Biggs: Thank you for asking me to speak. I hope I have pitched this at the right level. As you know NF2 is a complex condition so hopefully we will cover some of the many different aspects. Before I go too far, I want to acknowledge our team here at St Vincents.



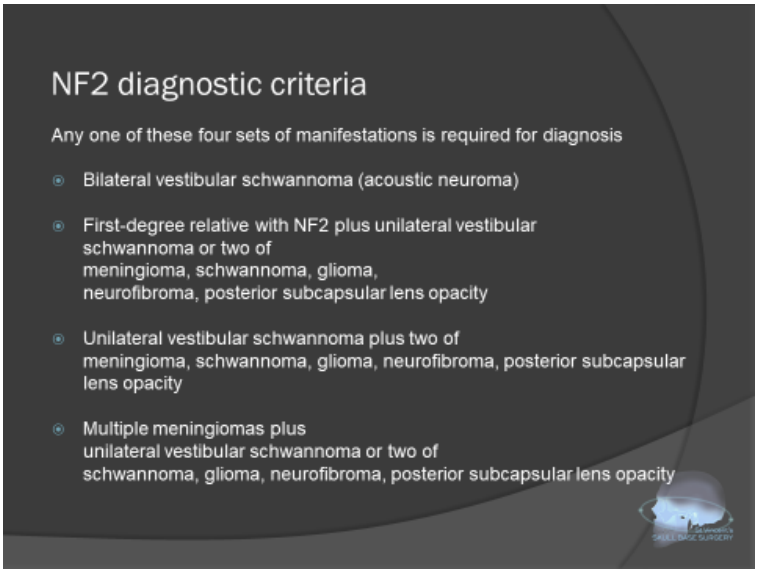


As Mona said, I'm trained as an ENT (Ear Nose and Throat) Surgeon and I have a specialist interest in otology , essentially ear based and skull based surgery. We undertake a lot of surgery of tumours of the skull base which includes acoustic neuromas and particularly NF2 which has bilateral acoustic neuromas as part of it. We have quite a team here, we've got Professor Fagan who has now retired, I've got Phil Chang and Sean Flanagan who work as otologists, Richard Harvey helps us with skull based surgery, not so much in NF2 and we have excellent neurosurgery colleagues as well. So we've certainly got some experience in working with these sorts of tumours. I had the privilege of working in Manchester which has an excellent NF2 unit led by Gareth Evans and Richard Ranson who are well known in the fields of NF2 so I was fortunate to gain a lot of experience there.

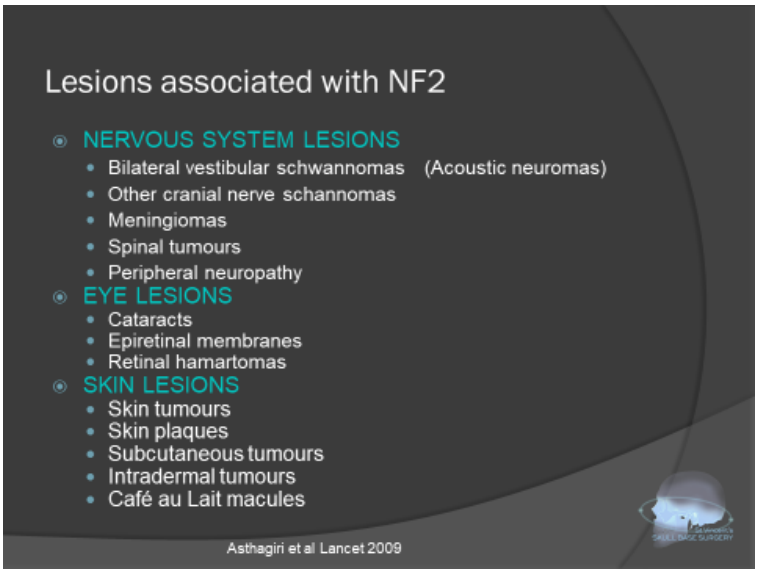


Just a little background, I don't want to tell people too much of what they already know but for some of you who may not know, NF2, the diagnosis, it's been around for a while and if you look at the history of this condition it was certainly first described in 1822. They didn't know what it was and it was really not until 1987

that we realised that neurofibromatosis type 1 and type 2 were separate conditions. There there's been advances in that time. We've localised the gene to chromosome 22, it was one of the first tumour prone disorders to be localised to a specific gene. It remains a very uncommon condition. Approximately 1 in 25,000 births, if you compare that to neurofibromatosis type 1, that's about 10 times less common than neurofibromatosis type 1.

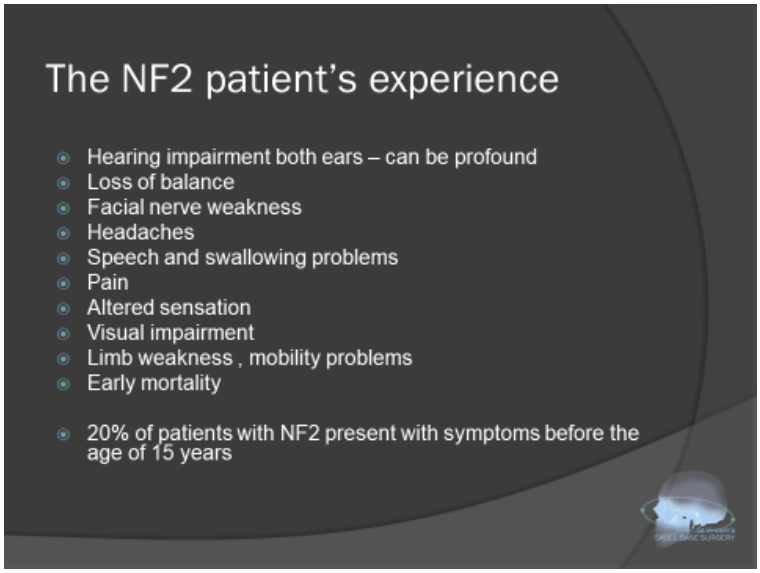


Again, I don't want to get too complex but it is a condition of multiple lesions and requires certain criteria to meet this diagnosis and the classic situation is somebody who has two or - on both sides - vestibular Schwannomas, that's the correct term we use acoustic neuromas. There can be some people who only have one but who have a family history or one vestibular schwannoma but a number of other tumours that lead to this diagnosis. It is a condition associated with quite a number of intracranial tumours, different types of intracranial tumour, the most common situation would be one where people have two or one on each side, vestibular schwannomas.



As mentioned, there are a number of tumours and if we look at another way of looking at all these tumours that occur in the neurofibromatosis type 2 we get tumours of the hearing and balance, bilateral vestibular schwannomas. We can get similar types of tumours that should say schwannomas of other nerves within our skull, cranial nerve tumours, quite commonly we see a tumour of the lining of the brain called a meningioma and also many people with NF2 can get tumours along their spine. Similar types of tumours to the acoustic neuromas but they occur in the spine. We also know people with neurofibromatosis type 2 can have problems

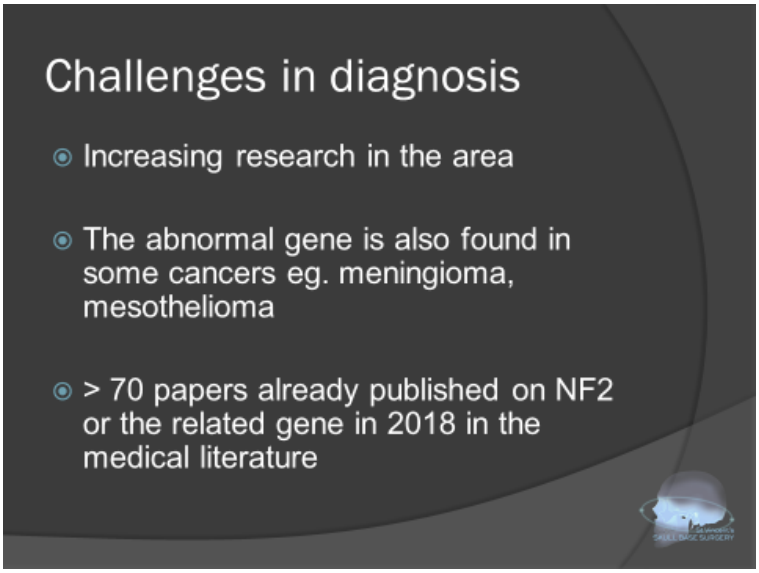
with their eyes, they can get cataracts, they can also get a number of skin lesions but normally they don't get much in the way of skin lesions like you may see in neurofibromatosis type 1, which is a separate disorder.



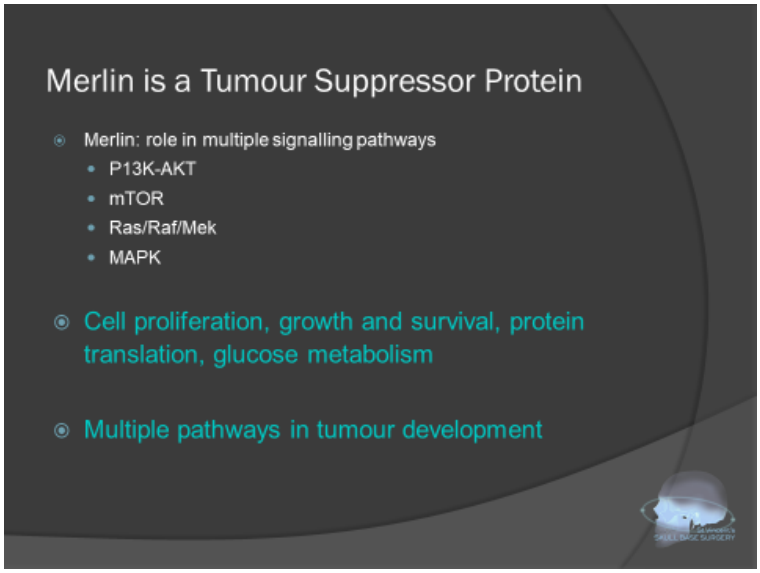
Unfortunately, all of these tumours do lead to a multitude of problems and the patient's experience can be very variable and that is largely due to the variability of this disease. Some people with neurofibromatosis type 2 have a fairly mild end of the spectrum and they will have a number of tumours but not extensive and there will be some people who are very unlucky and who will have quite a lot of tumours and it can lead to a lot of problems. So, of course if you've got bilateral acoustic neuromas it will affect your hearing, it can affect your balance, potentially - and not always - it can affect facial nerves and cause facial nerve weakness. Again, there's a risk of speech or swallowing problems, it can affect people's sensation, their mobility and it can shorten some people's lives which is a great concern to us. The other challenge of course in this condition is that we have a lot of patients who present who are very young with this and unfortunately this is a condition that can present at a very young age.

The biggest issue with NF2 or the hardest part is the challenge that this condition provides for everybody concerned. It's a challenge for the patient, it's a challenge for the physicians caring for the patient, it's a challenge for the family and it's certainly challenging in diagnosis, providing management and optimum care to our patients, particularly hearing which I'm interested in of course as an ENT surgeon, there's a real challenge.

Therefore, whenever we manage these - whenever we try and manage such a complex condition we need to manage it in a team approach. So when we have patients with NF2, there are a number of individuals who may be involved in their care, it play be a neuro-otologist, which is what I do, a neurosurgeon, often a geneticist will see the patients, they'll have an ophthalmologist, audiologist and of course counselling and support groups are incredibly important in this condition.

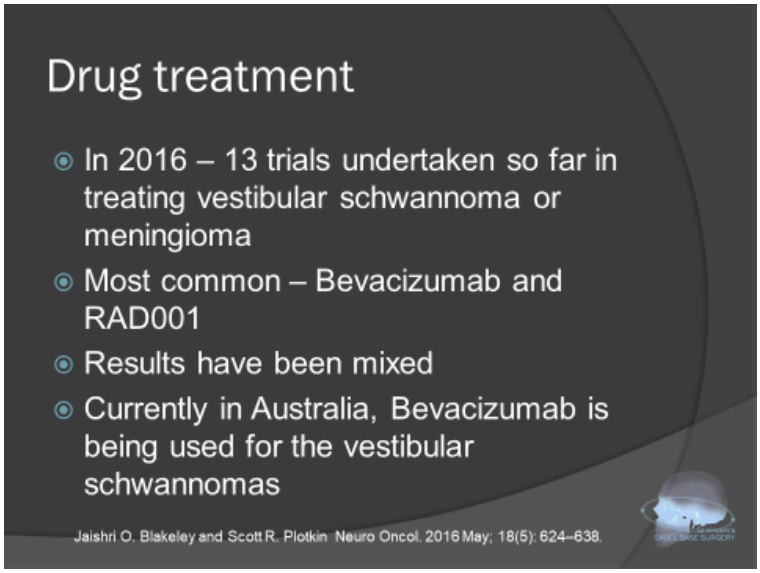


The diagnosis is a challenged by virtue of understanding the mechanism of this condition and how the gene defect causes the condition. There's a lot of research going into this area, perhaps not as much as some other conditions, but there is increasing amount of research and particularly because we now know that the gene mutation we see in NF2 is also found in some cancers and this cross fertilisation of information has helped and there's already - for example, this year alone there's been over 70 papers published on NF2 or the related gene in the context of causing cancer. A lot of research is going into this area which is encouraging.

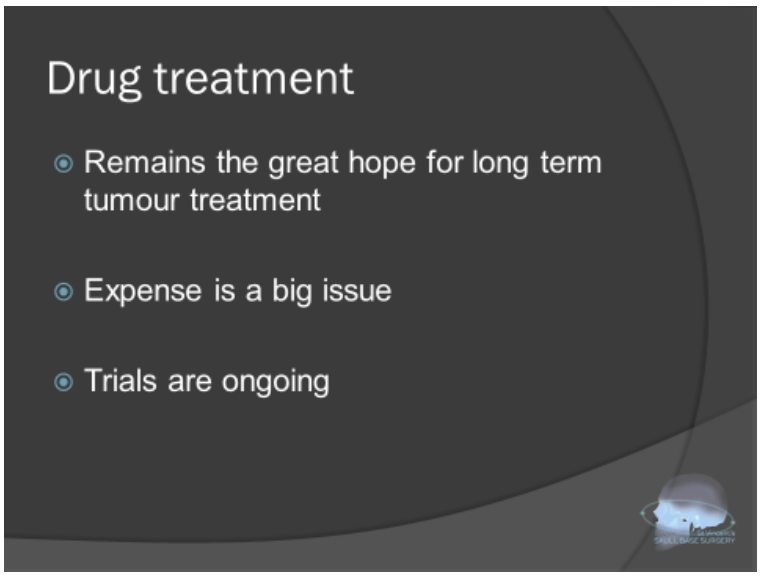


We understand the product of the gene is a protein called *Merlin* and this is what we call a "tumour suppresser gene". If you have both copies of the gene in a normal individual, you produce this protein and it supresses the development of tumours and if you have NF2, you're missing a copy of the gene so therefore you're unable to suppress tumour development. If you read about NF2, there are quite a number of pathways within cells that are involved in transmitting signals and I've just put up a list of the various signalling pathways that people may have read about and I won't - it's a very complex system, I won't pretend to understand it as a surgeon but essentially loss of this ability to suppress self-proliferation, growth and survival, glucose metabolism can lead to tumour development but potentially tumour development in a number of different pathways.

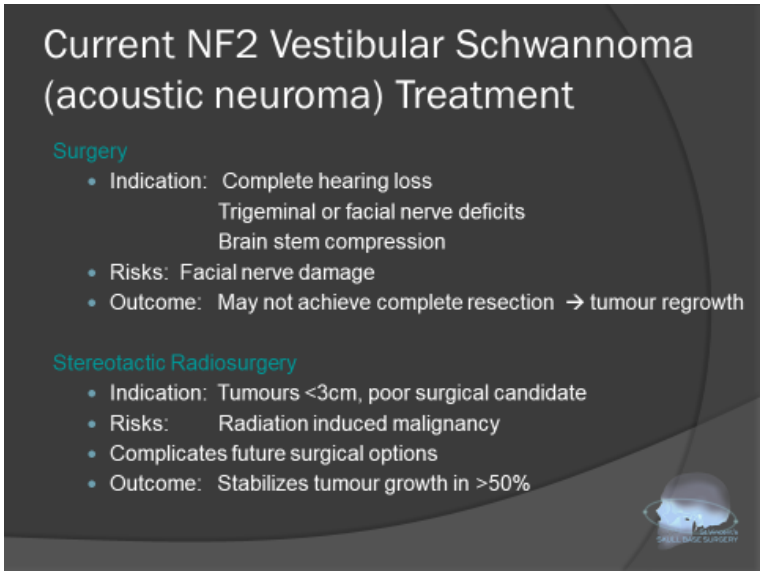
We were talking about understanding the biology of why NF2 causes these tumours and this leads us on to medical treatment or what - we use the term medical treatment, what essentially means drug treatment for neurofibromatosis, NF2, neurofibromatosis type 2. Of course the goal of any treatment is to preserve function. We want to preserve quality of life and increase life span so in NF2, since the major problem has been for both the vestibular schwannomas and meningiomas for patients, most of the drugs have been aimed at treating these two types of tumours. Our better understanding of the biology or the molecular biology of these tumours has allowed better understanding of which drugs may or may not work.



There was an excellent paper from the Hopkins group in 2016 discussing the different trials that have been undertaken so far in treating these tumours and at that stage there was 13 major trials going on. The most common trial has been with Bevacizumab which is the drug also known as Avastin and there was another drug called Rad001 and the results of these trials have been quite mixed. Currently in Australia, Bevacizumab is being used for vestibular schwannomas. There was a trial of this medication undertaken under Katherine North when she was at Westmead Children's Hospital. It's now being used in a more *ad hoc* basis but there's certainly - I know there are a number of specialists in Australia keen to perhaps undertake more trials where possible of these drugs but there's a cost and a component to these which presents a challenge.



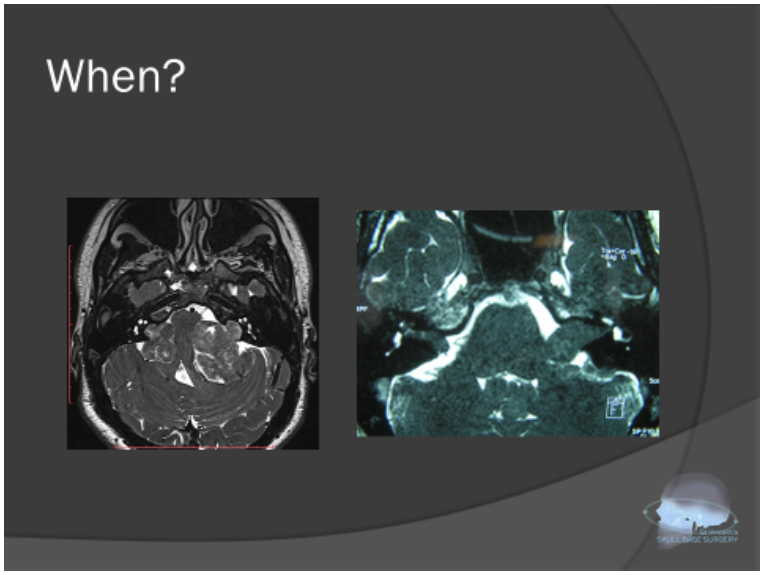
Certainly, medications remain our great hope for long-term tumour treatment. As a surgeon, I like doing surgery but I can absolutely assure you I would love to see the medication that comes out that treats these tumours, it would improve the quality of life for patients with NF2 enormously if they could avoid surgery. So we would be very, very enthusiastic about any treatment. As I mentioned, expense is currently the big issue. Avastin, which as I mentioned is the most commonly used medication, is very expensive. It's in the order of a few thousand dollars just for a couple of weeks' worth of treatment so access to the medication is very hard but we know that trials are going on around the world and we look forward to seeing more results over time.



Currently, with patients with NF2, if we're not able to provide them with Avastin or Bevacizumab then really we're left with our standard sort of treatments and the two main forms of treatment for vestibular schwannomas, which are the biggest problem in NF2, is either surgery or what they call stereotactic radio surgery or a form of radiotherapy. They both have a role. One has not replaced the other and there are many situations where one option is better than the other. There are a number of situations where we may have a choice in which may be the best option for the patient but for surgery, particularly undertaken when there's a lot of compression of the brain by these tumours, and that's probably the biggest or single-most important reason we might consider surgery, to actually take the tumour off the base of the brain and take the pressure off there. The problem with surgery is it's a very big deal, it risks damage to the facial nerve and we want to try and get all the tumour out which is not always possible.

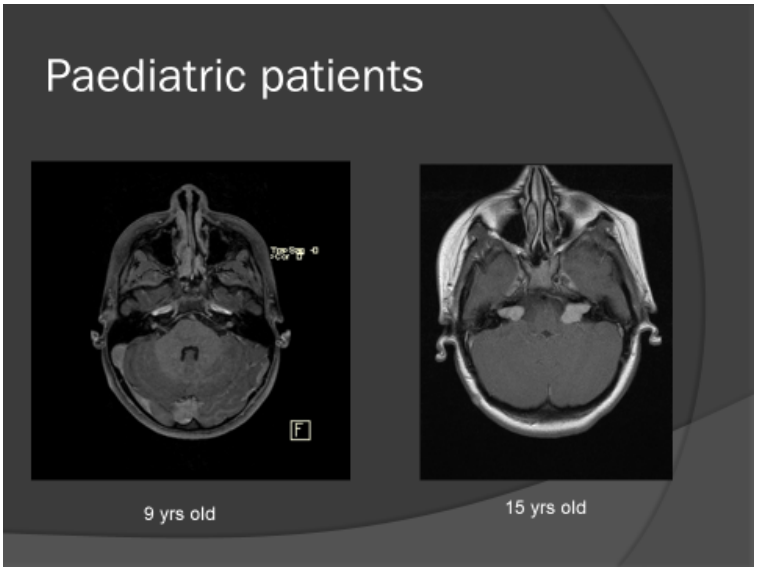
Radio surgery or radiotherapy is good for smaller tumours (I'll talk about both of these aspects a little bit further) can stabilise tumour growth. It doesn't make the tumour go away but can have its own issues.

So if we look at surgery first, there's lot of challenges in NF2. We have to think about when is a good time. We're dealing with lot of young patients. If they've got a tumour that's growing, when is the ideal time to intervene? We don't want to intervene too early. We don't want to cause any deficits or problems from surgery but, equally, we don't want to intervene too late if we allow tumours to get too large where the risks of treatment get too high. We've got to think about how we're going to surgically approach these tumours, what are we trying to achieve and we have to look very closely at our outcomes and importantly for patients with bilateral vestibular schwannomas, how we're going to manage their hearing loss.

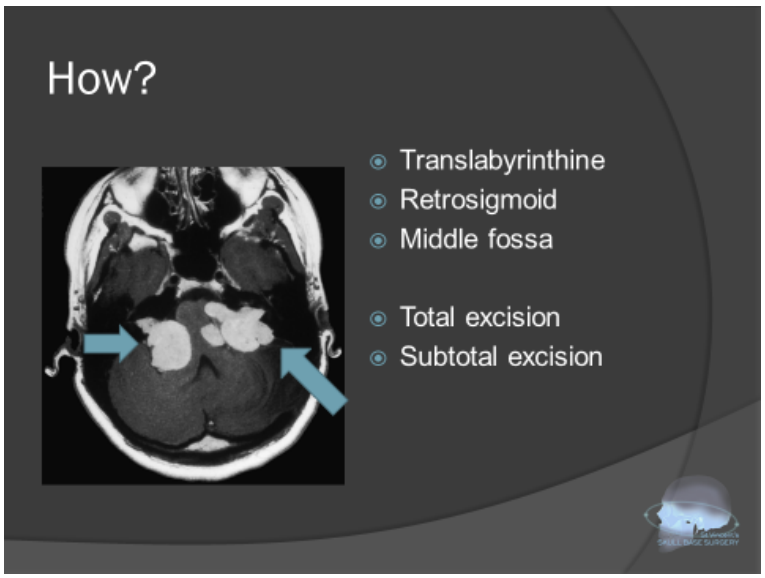


So I've put a couple of scans in that are trying to illustrate my point. The scan on the left demonstrates somebody who's got very large tumours and they've got a very squashed base of their brain there and in that sort of person, unfortunately surgery is the only option and that's critical because that person might become quite sick with that amount of brain compression. The scan on the right demonstrates only quite small tumours so somebody with small tumours like that we would not be in any hurry to consider surgery.

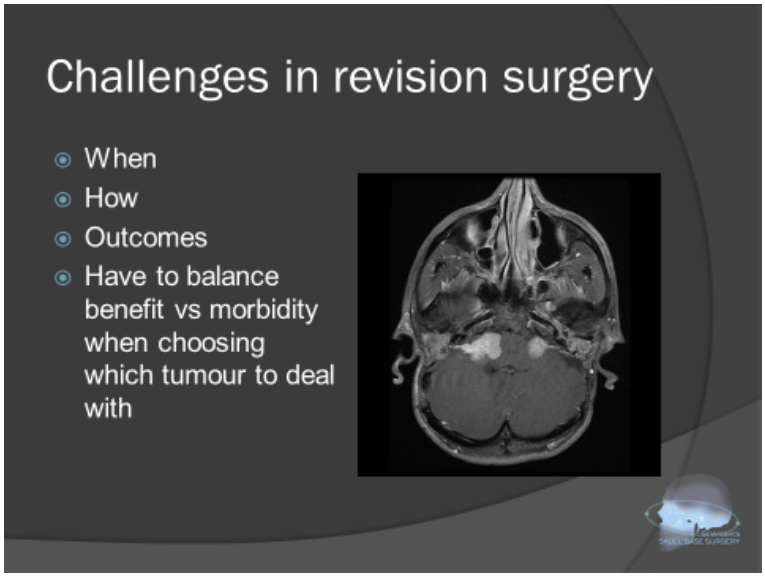
So as mentioned, we think about reasons why we would operate and mainly brain stem compression, if it's going to affect the facial nerve, if the tumour's growing fast or there's a lot of active tumours. We always consider the patient's desires when it comes to treatment and we have to take in some other factors when it comes to NF2. We have to think about what's going on in the other ear, what's the status of the hearing, what's the status of the patient's mobility and balance – what's their quality of life and their vision. Also paediatric cases or children are very challenging in this management decision.



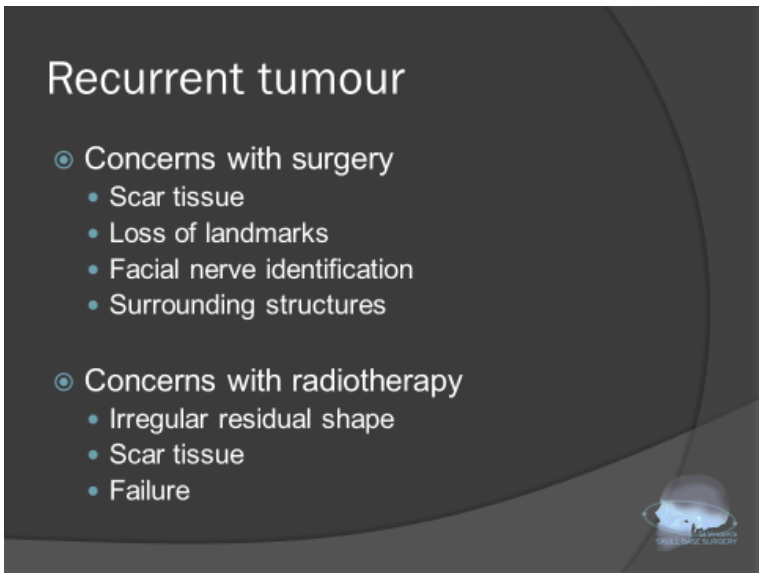
The issue we have with young children being diagnosed with these tumours is we recognise they've got tumours, we don't want to put them through a major operation too early but unfortunately adolescents with growth spurts can often cause tumours to grow significantly and that can present a real challenge for us as to when is the best time to intervene. Again, I've got these two scans here. Somebody who's 9 years old with very small tumours and then 6 years later - if you can appreciate on the scan on the right you've got two white spots which are much larger and that shows the growth of these tumours over a period of time.



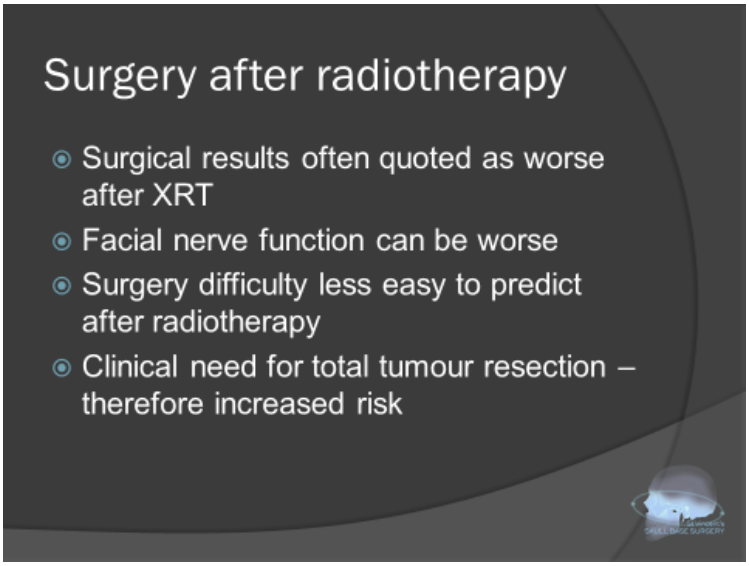
When it comes to surgery, we've got few different surgical approaches that we have to think about. We also have to think about do we want to try and remove the whole tumour or do we not want to try and remove the whole tumour? Sometimes it can be a bit difficult to understand why you would not want to remove a whole tumour but the rationale behind that can sometimes be related to how much the brain is squashed by the tumour and sometimes if you try and remove all the tumour in one go, you run the risk of causing a lot of damage to the brain or surrounding structures. So sometimes we're forced into a situation where we can only remove part of the tumour in an effort to get the patient out of trouble without causing too great damage.



Sometimes, because we're unable to remove tumours entirely, we are left with a situation where patients have residual or recurrent tumour that may grow back and then we have to balance up the timing of when are we going to treat this? We have to think about, again, all the factors that are associated in neurofibromatosis type 2 to do with hearing and balance and the general well-being of the patient. These sorts of decisions can be extremely challenging and as mentioned earlier, often comes down to a team decision in this situation.

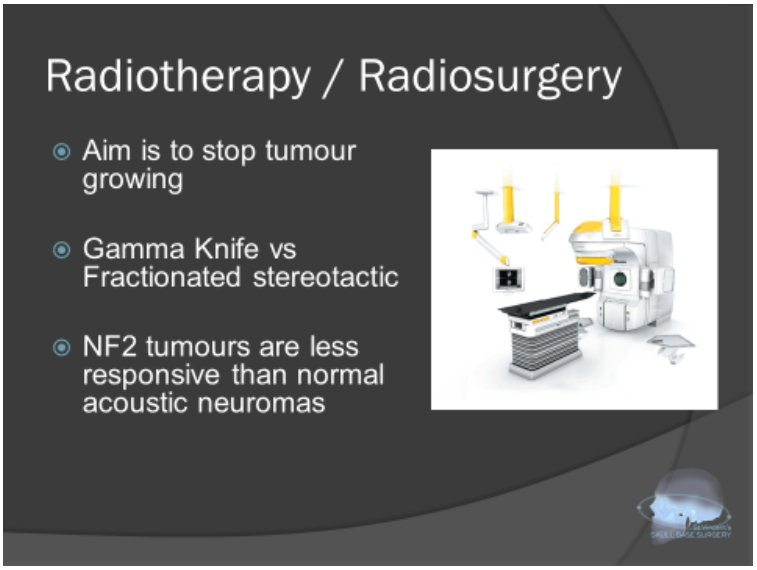


Recurrent tumours, if we have to operate, particularly if a patient's had previous surgery, can cause a lot of difficulty. Revision surgery is certainly very challenging. Sometimes we operate after radiation treatment or radiosurgery. Sometimes, if we're unable to completely remove a tumour, we might consider radiation treatment after surgery but, again, any second-line treatment has some issues if there's been some distortion of the anatomy beforehand.



Surgery after radiation treatment we definitely do. There's always a bit of a concern that the facial nerve - the risk of facial-nerve paralysis is a bit higher after radiation but sometimes it's difficult to predict. Sometimes if a patient has been unlucky and the radiation has failed to control the growth of the tumour - and surgery is our only option, we have to treat things fairly aggressively so we need to be mindful of that.

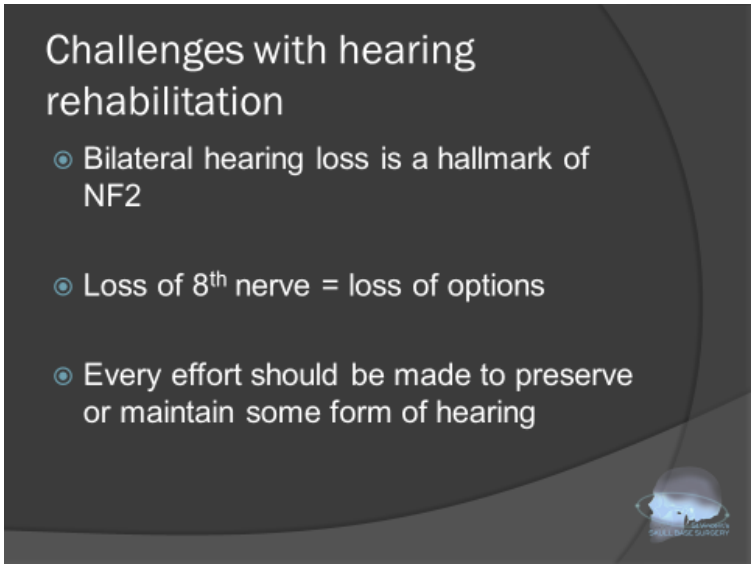
We can certainly operate after Avastin and that's been done. It hasn't been done extensively in Australia because there are not that many patients whose have taken Bevacizumab but we've operated on a patient within 8 weeks of ceasing the medication so it's certainly quite possible and there used to be a concern about taking Bevacizumab preventing further surgery but that does not seem to be the case.



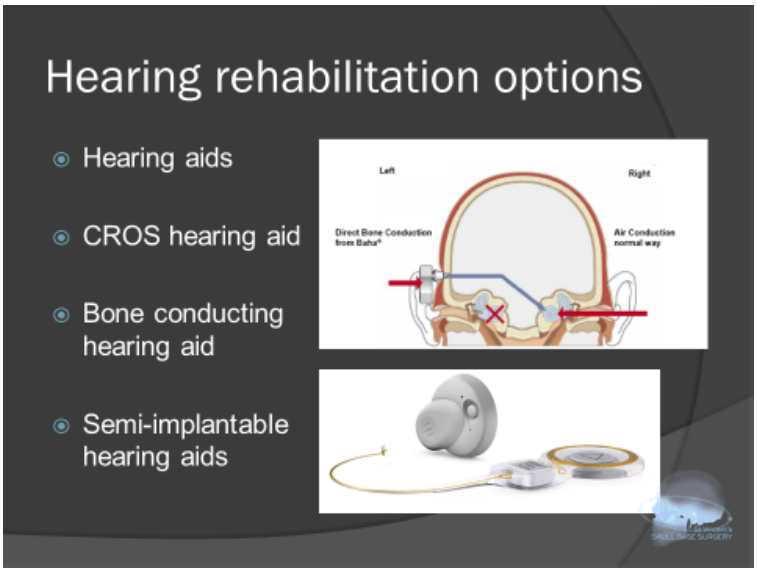
As I mentioned earlier, radiotherapy or radiosurgery is certainly performed. The aim is to stop the tumour growing. There's a number of different systems that provide radiosurgery or radiotherapy and people might have heard of a system called the gamma knife, that's actually just one type of system. There's another system called a Novalis, something called a cyber knife, so there's a number of different ways of delivering radiotherapy but the main division is whether or not it's given in a single day, single dose or whether or not the dose is broken up over a number of days and that's a decision that the radiation oncologist who delivered the radiotherapy decides.

The problem with neurofibromatosis type 2 is unfortunately the tumours in these situations are a little bit less responsive to radiation than normal acoustic neuromas are. Surgery is a bit more difficult in NF2 or radiation is a bit less successful so it certainly presents challenges for us.

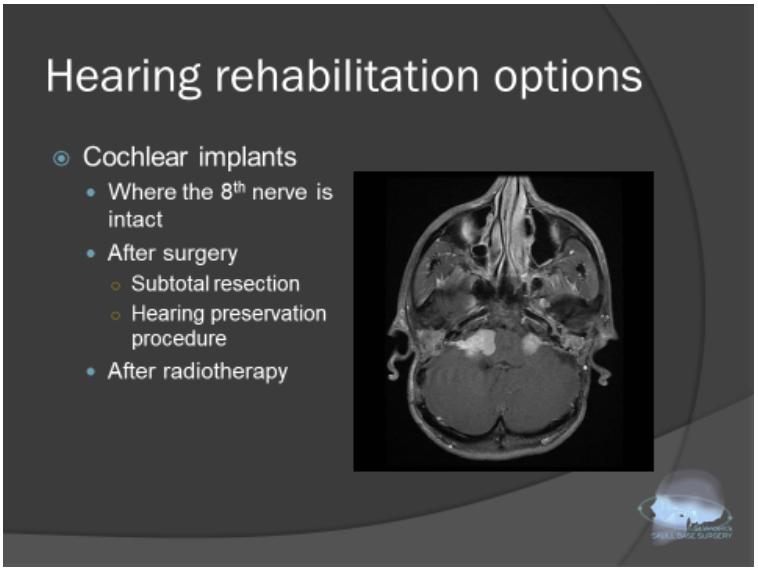
There is a bit of a size limit with tumours and radiation treatment. Once a tumour gets over a certain size, radiation is far less effective. Sometimes with radiation it can be effective in preserving hearing but not always and as mentioned earlier, unfortunately if it fails to control the tumour then we have to look at surgery. The only other point with radiation treatment is it never makes a tumour go away. So the tumour is always there and you've got to keep an eye on it longer term.



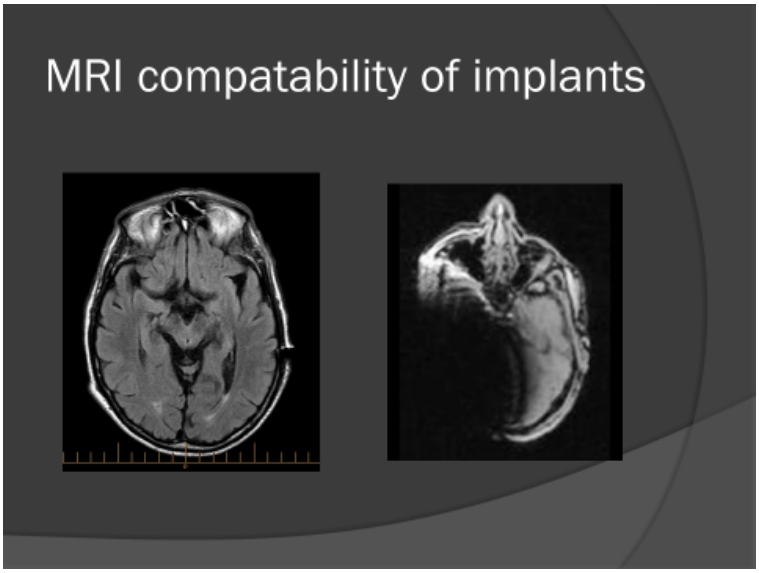
The other important issue in NF2 is hearing rehabilitation and unfortunately, hearing loss is pretty much the hallmark of NF2. Because the acoustic neuromas or vestibular schwannomas occur on the hearing and balance nerve when you go to treat that nerve, particularly with surgery, you often have to divide that nerve and that minimises some of our options in hearing rehabilitation. So we really try and undertake every effort to preserve and maintain some form of hearing.



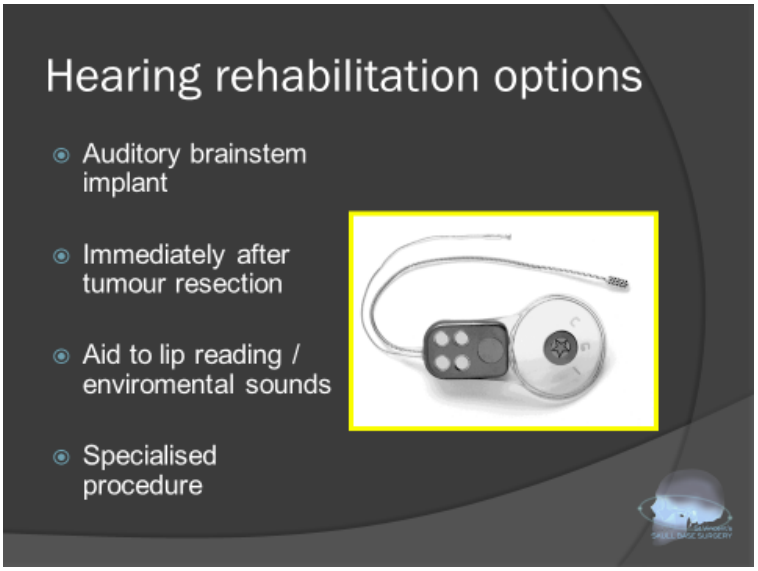
For those patients with NF2 who have very mild hearing loss they might look at hearing aids. There are a couple of types of hearing aids including things called CROS aids. CROS aids are used if somebody's got no hearing on one side and partial hearing on the other. A CROS hearing aid essentially takes a signal from the Deaf side and sends it to the other side. Sometimes we use bone conducting hearing aids and there are semi implantable hearing aids although they're not particularly used in Australia. Bone conducting hearing aids are though.



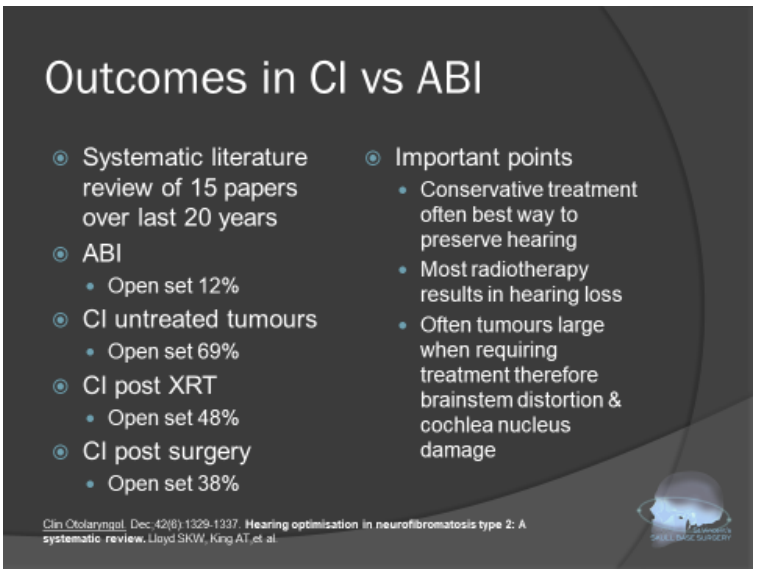
Cochlear implants are sometimes used in NF2 but essentially this requires us to keep the hearing and balance nerve in contact. So if a patient has had radiation and the nerve is in tact we can consider a Cochlear implant. If the patient's had surgery and we've not removed the whole tumour, we're able to keep the hearing nerve in tact, then we could also consider a Cochlear implant.



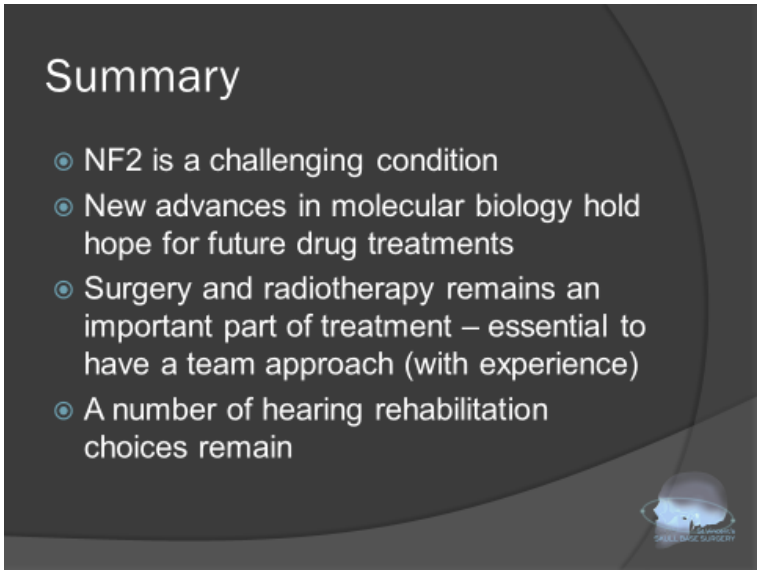
Any implant has a magnet in it and longer term a magnet can actually cause some difficulty following up a patient with MRI scans. Anybody with NF2 has a number of MRI scans and essentially the magnets throw quite a big shadow. I've put in a couple of pictures there. The picture on the left is a normal scan, the picture on the left is a big dark area and that's the magnet from a cochlear implant and it's shadowing the brain so you can't actually see on an MRI scan the brain very well.



The other option we have if the Cochlear implant's not possible is an auditory brainstem implant which is something we occasionally here at St Vincent's. They're very uncommonly done around Australia. There's only ourselves and the Eye and Ear in Melbourne that essentially undertake it. It has been - actually I should mention it has been done in Perth as well. It's a difficult and challenging procedure because we essentially put in a brainstem implant at the time of removing an acoustic neuroma. The problem we've got with these devices is, - they're like a cochlear implant but we're putting the electrodes directly on the brain and the hearing results are not that great with them.



If we actually look at the difference between a cochlear implant and a brain-stem implant or ABI, the cochlear implants seem to do better where possible so we certainly lean these days, wherever possible too, try and put in a cochlear implant. But that's not always the case. We certainly have brain-stem implants up our sleeve if we're unable to look at any other form of hearing rehabilitation. So, these results are not universal and these are - I've got a few terms there. Open set on this slide refers to the ability to understand words. So cochlear implants certainly can have a role to play. The only trouble is sometimes over time the cochlear implant function deteriorates.



In summary, NF2 is certainly a challenging condition. There's new advances in molecular biology and this certainly holds hope for future drug treatments and that's, I think, where we're heading in the long-term. Surgery and radiation treatment certainly remain an important part of managing NF2 patients and a team approach is very, very important and we do have hearing rehabilitation options for the patients but everybody's an individual and we have to assess everybody on an individual basis but hopefully that's given us - giving you a bit of an overview of where we are in NF2 and the different treatments available.

So, Mona, I think that ends my presentation. Before I forget, I would just like to acknowledge a number of my colleagues around Sydney who have a particular interest and those of you have an interest in NF2 will be aware of people such as Katherine North, Simone Ardern-Holmes, Katrina Morris who are absolutely essential to the management of NF2 patients.

CTF Host: Thank you so much, Dr Biggs. That was a fantastic overview and update from my perspective and hopefully from everyone else who's attending. We do have one question if it's OK. If anyone else has any others, feel free to pop them into the chat window and we'll try and get to them. The first question we've got is from Michelle who's a mum with a son who was diagnosed with a unilateral acoustic neuroma when he was 5. He's seen a number of doctors and she's wondering what's the youngest patient you've seen and her son doesn't have a formal diagnosis of NF2 as yet because genetic testing was negative but they've recently sent a sample to Manchester to check for mosaic so her son's now 9 and she wants to know what do you think is the options for him later on, especially since he hasn't got a formal diagnosis yet. Do you have any thoughts?

Dr Biggs: My youngest patient was 5 at diagnosis but unfortunately had a family history so we sort of knew that that was a real possibility. In that situation where the diagnosis is not clear, NF2 is certainly a risk and it's probably something that's going to be - it's difficult to reconcile if a person's not sure which way things are going to go. Hopefully, the tumour's small and not doing terribly much. I think in that situation I would be treating the patient as if there's a very real possibility of NF2, so what that means is I would not be too aggressive in treating the acoustic neuroma, I wouldn't rush into treatment too quickly because there's always a possibility something else could pop up later. Hopefully, the diagnosis isn't NF2 and it's just a very, very rare situation but certainly I'd be concerned that there was a bit of a risk of NF2 becoming evident over time.

CTF Host: OK. Michelle's also then just followed up asking whether you feel there are more advances or treatments available overseas or are we getting the best of the best here, which I tend to think we are.

Dr Biggs: I think we are. I think the only difference I would say overseas is the availability of drug company funding for research or trials is greater and that's probably the biggest difference, and of course in some centres where there are larger numbers of patients they can undertake a trial more readily but as far as our surgical techniques, our radiation techniques, as good as if not better than anywhere I've seen overseas. I think we've got - we certainly have available everything that is overseas.

CTF Host: That's great. Michelle says thank you, as do we. Just another quick one which I think is important especially because you mentioned that support groups are a very beneficial part of treatment. With NF2 being so rare, there is a very small NF2 Australia Facebook group. Do you know how we can increase awareness of the support group or of the fact that there are contacts out there for NF2?

Dr Biggs: I think that probably comes down to education of - probably education in some respects of the specialists who might come across NF2 because hopefully people in my situation who look after patients with NF2 are aware of that but it can vary. Depends on who the patient presents to. The neurosurgeons - there are some neurosurgeons who specialise in dealing with acoustic neuromas and NF2 and some who don't and if the patient was under the care of one who wasn't particularly aware of it - I don't want to be disparaging of my neurosurgical colleagues, they're excellent, but not all of them specialise in acoustic neuromas. In ENT, your general ENT surgeon would not undertake the care of a patient with NF2. They would normally refer them to a specialist centre such as St Vincent's or elsewhere. In neurosurgery it's not quite as clear cut as that and that would be the - but I think amongst neurosurgeons and ENT surgeons who specialise in the area that would be worthwhile knowing about.

CTF Host: Great, that's something CTF can take on board to continue getting the messages out there. The questions have slowed down and we've taken up your time. Thank you so much again for an informative presentation. We really do - an informative presentation. We really do appreciate it, particularly in NF awareness month of May. We hope you enjoy the rest of your day.

Dr Biggs: Thank you very much, Mona.

CTF Host: It was great.

Dr Biggs: Thank you.