

The English national neurofibromatosis (NF1) networks

Sue Huson, Consultant clinical geneticist,
Manchester NF service, Manchester centre for
genomic medicine on behalf of the complex
NF1 and NF2 networks

National specialised commissioning

- Services usually cover management of long term conditions with <500 patients (was 1000) or complex surgical procedures with <500/year
- Services provided by limited number of centres (3-4 maximum)
- Advisory Group for National Specialised Services (AGNSS) advises Health Ministers which services should be nationally commissioned
- Process led by NSCT, National Specialist Commissioning Team

National specialised commissioning 2

- ONLY covers England, Scotland buys into many services but not Wales and Ireland; EU patients eligible
- At outset we worked with a NSC Medical Advisor and Manager who monitor service outcomes, quality improvement, patient satisfaction and involvement with service development etc
- One of main roles for medical conditions is rapid consideration of new therapies e.g. Bevacizumab (Avastin) for Schwannomas in NF2

English NF2
community grateful
to Dr Edmund
Jessop, Dr Tom
Kenney, Sara
Watson and
Matthew Johnson



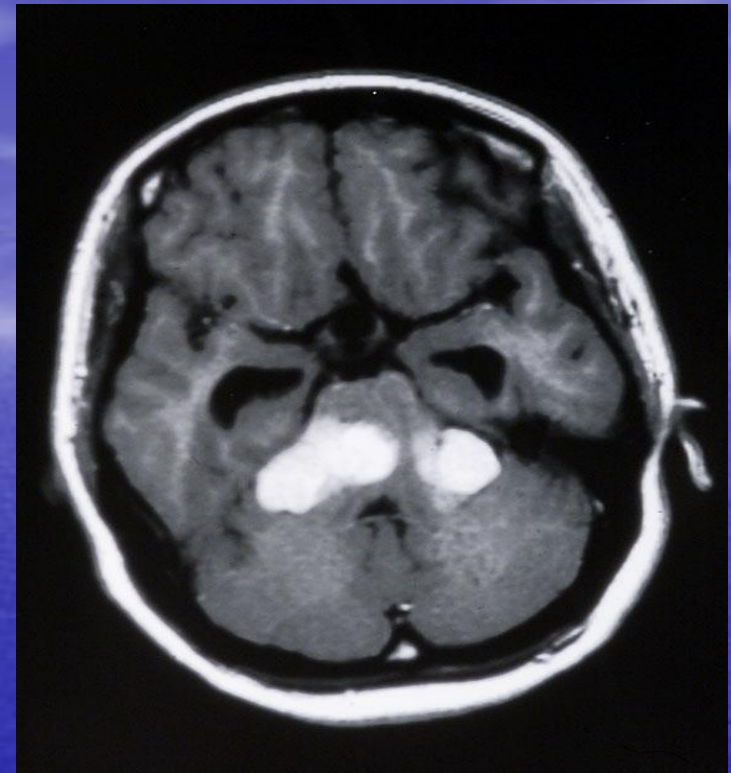
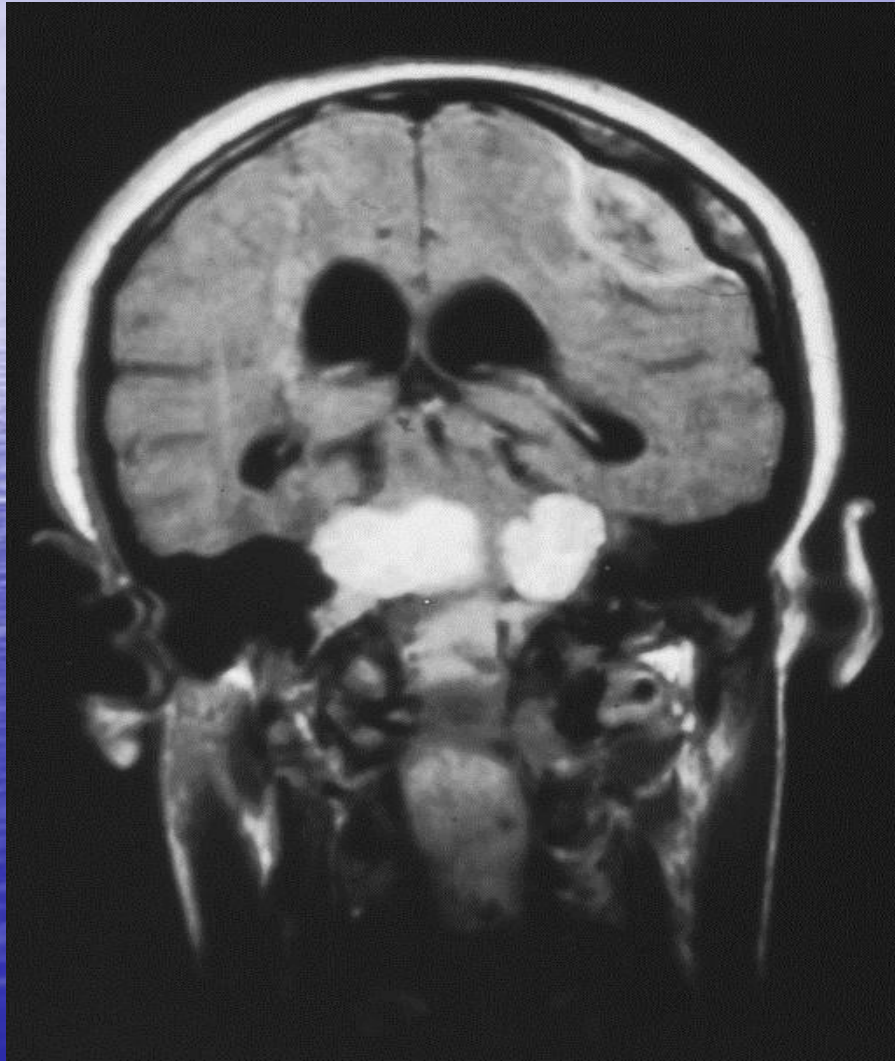
So what is neurofibromatosis?

- A group of genetic conditions characterised by a predisposition to tumours of the nervous system
- NF1 one of commonest dominant disorders with prevalence of 1/4560
- NF2 less common, 1/56161

NF2:summary

- Predisposes to benign tumours of the 'linings' of the nervous system
- Schwannomas on cranial, spinal root and peripheral nerves
- Meningiomas and ependymomas
- Most frequent tumours are bilateral vestibular schwannomas (acoustic neuromas)

NF2: Imaging



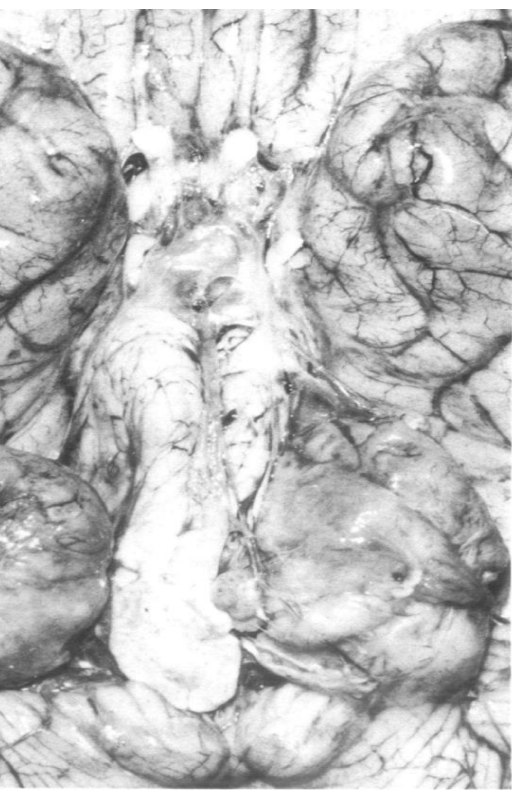
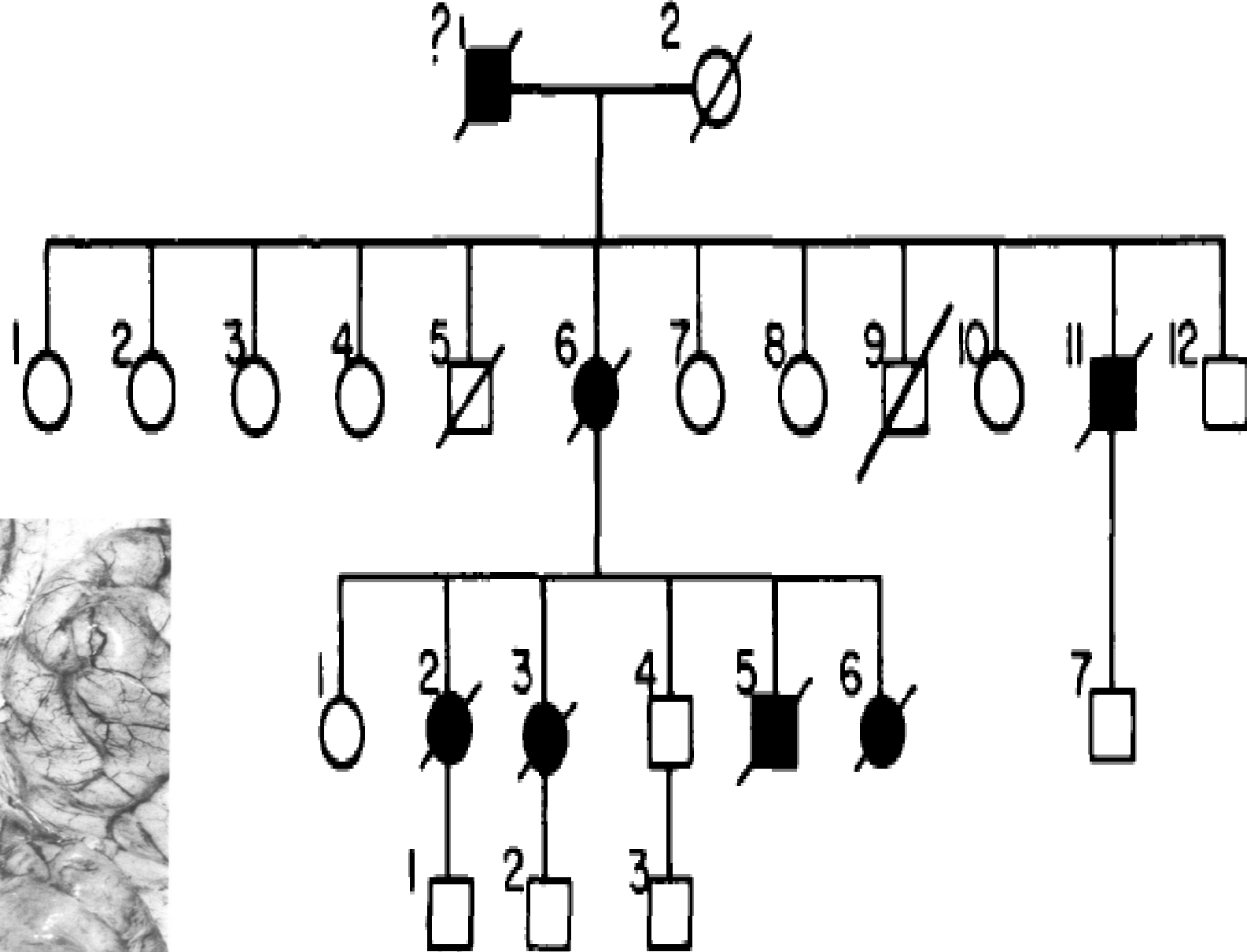


FIG. 1. Pedigree of family in study.

Young et al, JAMA 1970, 214: 347-53

- 1150 family members over 8 generations
- 97 members with definite (57) or possible (40) bilateral vestibular Schwannomas
- Mean onset of symptoms 20 years (9-34 years)
- Mean survival WITHOUT surgery 18.5 years (4-44 years)
- Mean survival WITH surgery 9.2 (3-19 years)

NF2 In Oxford - Background

- Pre-1994 patients seen by a variety of Neurosurgeons
- As skull base service developed (from December 1993) majority of newly diagnosed cases under Richard Kerr (Neurosurgeon) and Chris Milford (ENT)
- Frequent cross referrals to Neurofibromatosis Clinic (SMH) ... occasional disagreement re: management

Oxford NF2 Clinic: Physician coordinated care

- Coordinated by SMH with support of Clinical Assistant and Genetic Counsellor
- MORNING Assessments – Clinical Review (SMH and Clinical Assistant), audiology (Richard Gledhill), ophthalmology (John Elston)
- Support from Neurofibromatosis Association (NFA) specialist advisors (Jo Castle/Sarah Lawrey) and hearing therapy (Helen Tinley)

Oxford Nf2 Clinic: Organisation 2

- Initially patients scanned in am, then lunchtime MDT and in afternoon saw Messrs Kerr/Milford with SMH
- BUT very stressful on radiology staff/patients alike; Radiologist 'missed' things on brief scan review
- Moved to scans on separate day prior to clinic
- Lunchtime MDT and surgical review afternoon

NF2

Specialist care

- 109 treated at 3 centres: 259 at other UK centres
- RR of mortality 0.3 (95% CI 0.12-0.98)
- Facial nerve damage much less in specialist centres
- Results of meningioma surgery better
- Watch and wait often correct for spinal tumours and meningiomas

Baser et al A J Hum Genet 2000

NF2: what the families experienced

- UK NFA established a network of specialist advisors 1991 onwards with specialist NF2 advisor 1998 onwards
- Increasing awareness of lack of coordinated care
- NFologists often asked to see families to provide overview
- Main issue lack of understanding in non-expert centres of difference between isolated VS and NF2 VS; over reaction to scans!
- Different approaches to treatment – surgery vs. radiosurgery for vestibular schwannomas

NF2: family feedback 2

- Lack of continuity of care from at risk to affected to terminal stages
- Management of 'at risk' more complex than in other AD tumour predisposition syndromes
- Sporadic severe NF2 presenting in children particularly complex
- Very little attention to hearing rehabilitation/facial nerve reconstruction

Management of NF2 (Evans et al 2005)

- Neuro foundation sponsored consensus meeting 2002
- Team approach involving neurosurgeons, otolaryngologists, geneticists/neurologists, clinic coordinator, auditory rehabilitation
- Full discussion re treatment options vis. watch and wait/operate/stereotactic radiosurgery
- Full access to auditory rehabilitation- aids/lip reading/implants

NF2 NCG service

- Four designated centres: Manchester (**Evans**/Huson), GSTT (Ferner), Cambridge (*Axon*), Oxford (Parry/Halliday)
- NF2 nurse specialists to coordinate seamless care
- VS treatments and implants only in specialist centres
- All patients discussed in regional MDT at least once per year
- Funding for specialist auditory rehabilitation/facial nerve assessment

But the surgeons didn't agree!!!

- Initial application with drawn at 11th hour...
- 'This would be professional suicide'
- National commissioning team worked with Prof Evans and NFA to develop service specification
- Finally commissioned April 2010

NF2 in England (population 50.6 million)

- At any time 860 affected people
- 38 new diagnoses per year
- Mainstay of management monitoring
- ONLY 70 NF2 VS surgeries per year
- 15 ABI insertions
- 15 radiosurgeries
- MDT clinics in Birmingham, Cambridge, GSTT, Leeds, Manchester, Newcastle, Oxford, Plymouth and Sheffield

NF2 NCG service aims

- Improve quality of life by coordination of care, improved information and improved rehabilitation [short term]
- Hearing preservation [medium term]
- Decrease disease related morbidity and mortality [long term]
- Unique patient cohort for natural history studies and treatment trials

Centres
and units

Manchester
Hospitals

Liverpool

Birmingham

Oxford

Bristol

Plymouth

Southampton

Newcastle

Leeds

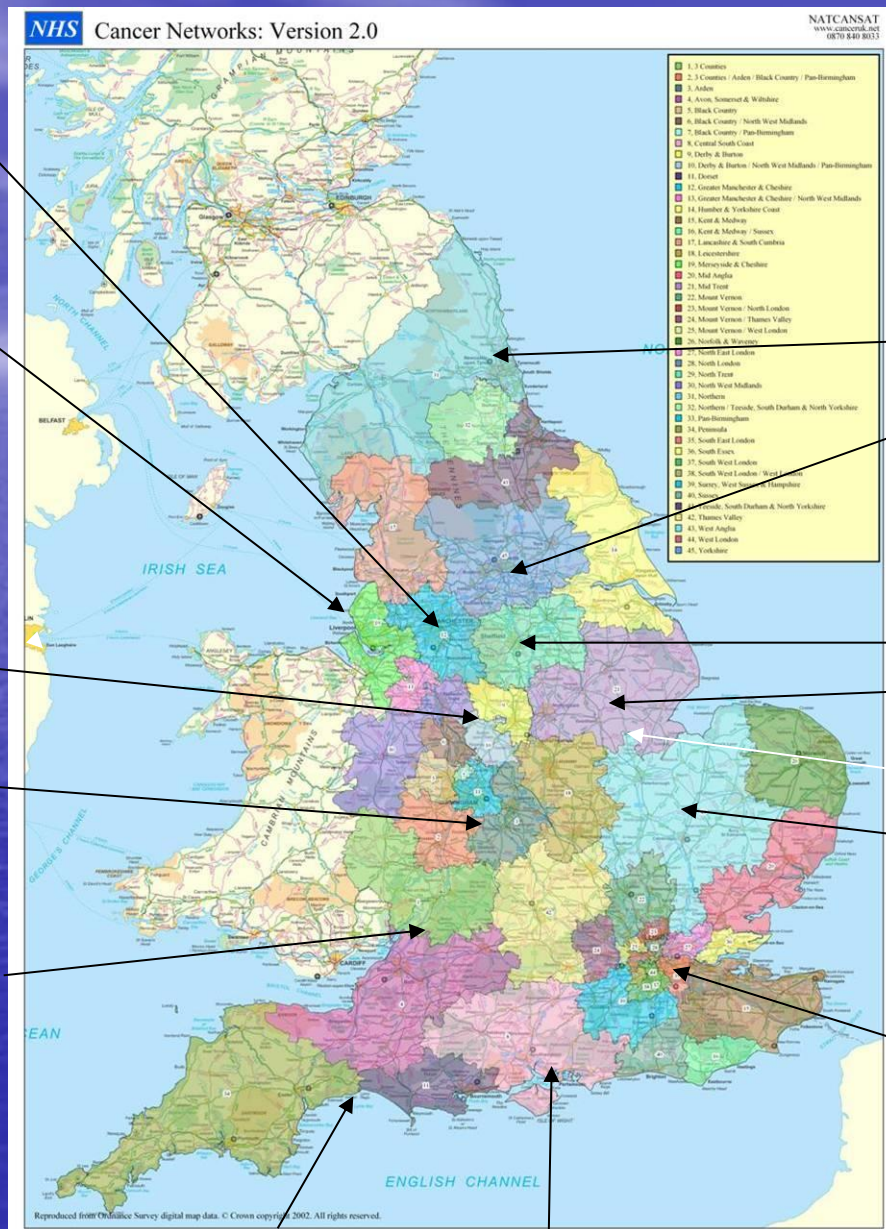
Sheffield

Nottingham

Leicester

Cambridge

GSTT
London.



Hearing concern LINK

- Charity for adults with hearing loss
- Run 5 day courses covering communication/resources/home adaptations etc
- Run NF2 specific courses for approx 10 years working with Neuro Foundation specialist advisors
- Increasingly difficult to get NHS funding...now 20 places/year guaranteed and cheaper!

- **NF2 imaging protocol and standardised reporting of VS.**
- **Imaging Protocol (MRI)**
- BRAIN
- Axial T2 whole head
- Axial T1 post contrast 3mm through whole head
- Coronal T1 post contrast through whole head
- SPINE
- Sagittal and Coronal T1 post contrast sequences through whole spine as 2 field of view (Cervical and upper Thoracic & lower Thoracic and Lumbar)
- **Manchester Standardised reporting protocol**
- This heading based format is used by all the Neuroradiologists reporting the NF2 patient scans.
- BRAIN
- Schwannomas
- Right 7th and 8th Nerves (measurements for VS should include maximum overall length including IAM component, maximum cisternal depth, cisternal oblique width and cranio-caudal height)
- Left 7th and 8th Nerves
- Other schwannomas (under headings as appropriate eg. Left 9-11th nerve complex or right 5th nerve)
- Meningiomas
- Infratentorial lesions
- Supratentorial lesions
- Other brain lesions
- SPINE
- Intramedullary lesions (e.g. ependymomas)
- Intradural Extramedullary lesions (e.g spinal schwannomas)
- Extrapinal lesions (e.g brachial/lumbar plexus schwannomas)
- **The following measurements for VS to be included on all reports have been agreed with the other 3 NF2 centres:**
- Maximum overall length (including IAM and cisternal components, parallel to IAM)
- Maximum Cisternal depth (perpendicular to petrous ridge)
- Maximum Cisternal width (parallel to petrous ridge)
- Maximum height
- The cisternal measurements may be taken from different slices to ensure that the maximum measurement is made.

The NEW ENGLAND JOURNAL *of* MEDICINE

ORIGINAL ARTICLE

Hearing Improvement after Bevacizumab in Patients with Neurofibromatosis Type 2

Scott R. Plotkin, M.D., Ph.D., Anat O. Stemmer-Rachamimov, M.D.,
Fred G. Barker II, M.D., Chris Halpin, Ph.D., Timothy P. Padera, Ph.D.,
Alex Tyrrell, Ph.D., A. Gregory Sorensen, M.D., Rakesh K. Jain, Ph.D.,
and Emmanuelle di Tomaso, Ph.D.

Plotkin et al NEJM 2009;361:358-67.

- VEGF was expressed in 100% of vestibular schwannomas on IHC
- 10 NF2 patients treated
- Median pre treatment annual volumetric growth rate was 62%
- After bevacizumab treatment VS shrank in 9 patients
- 6 patients had an imaging response, which was maintained in 4 patients during 11 to 16 months of follow-up
- Of the 7 people with hearing, it improved in 4

Avastin- English approach

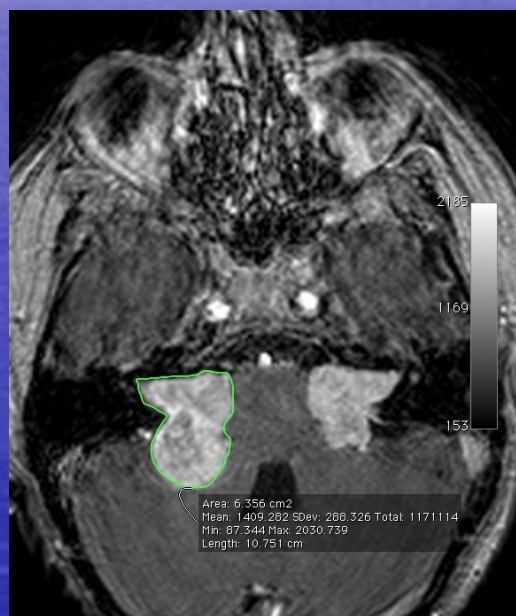
- Drug company had no interest in trial
- Commissioners and service agreed a national protocol with strict treatment criteria and standardised follow-up
- Patients treated 2011 onwards

Imaging Right Ear

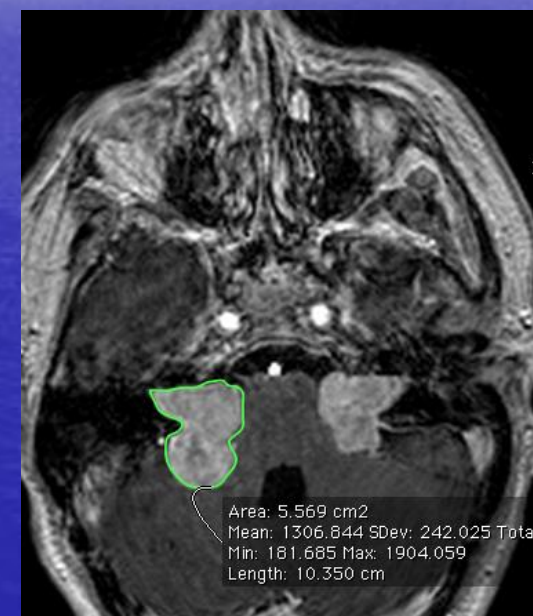
Pre Avastin



3 Days Post Avastin

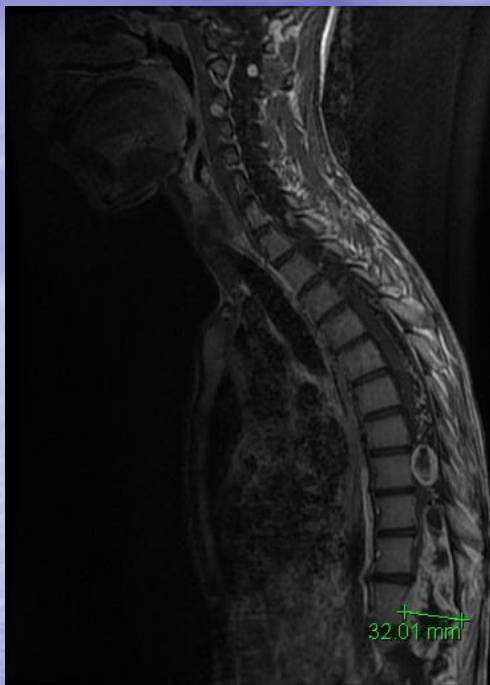


3 Months Post Avastin

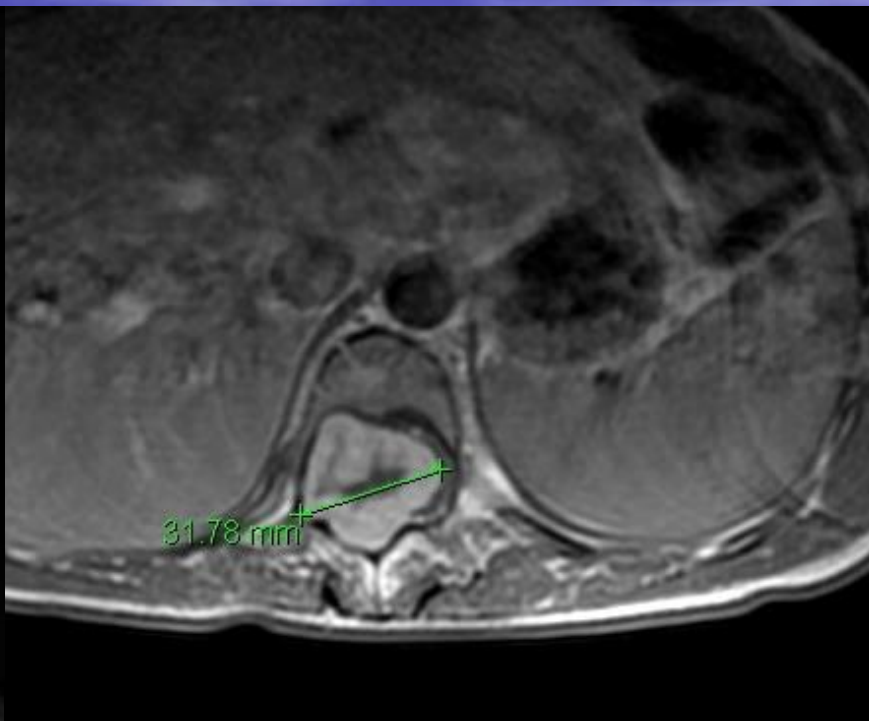


	Pre Avastin	3 Days Post Avastin	3 Months Post Avastin
Volume (cm ³)	6.5	6.4	5.6

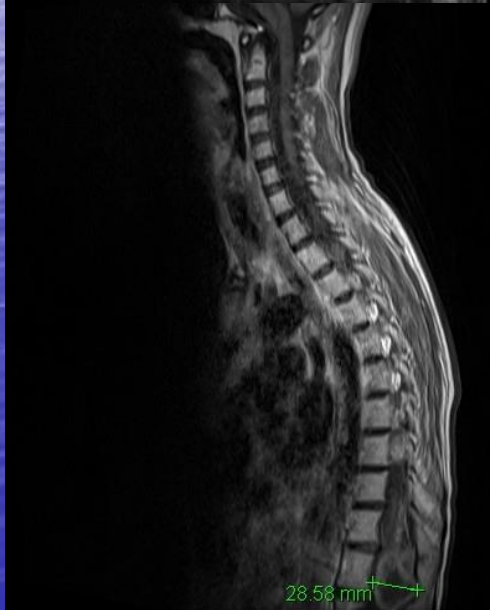
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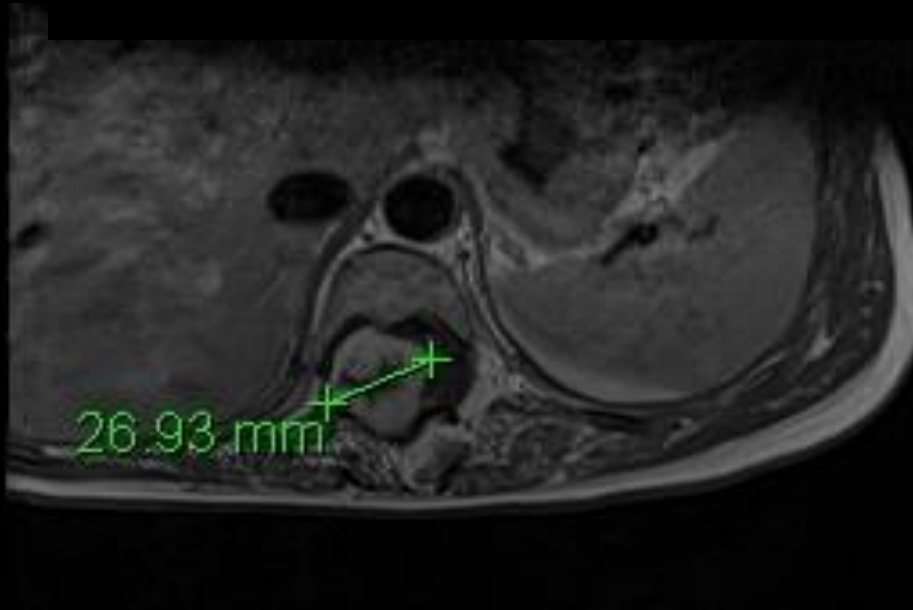
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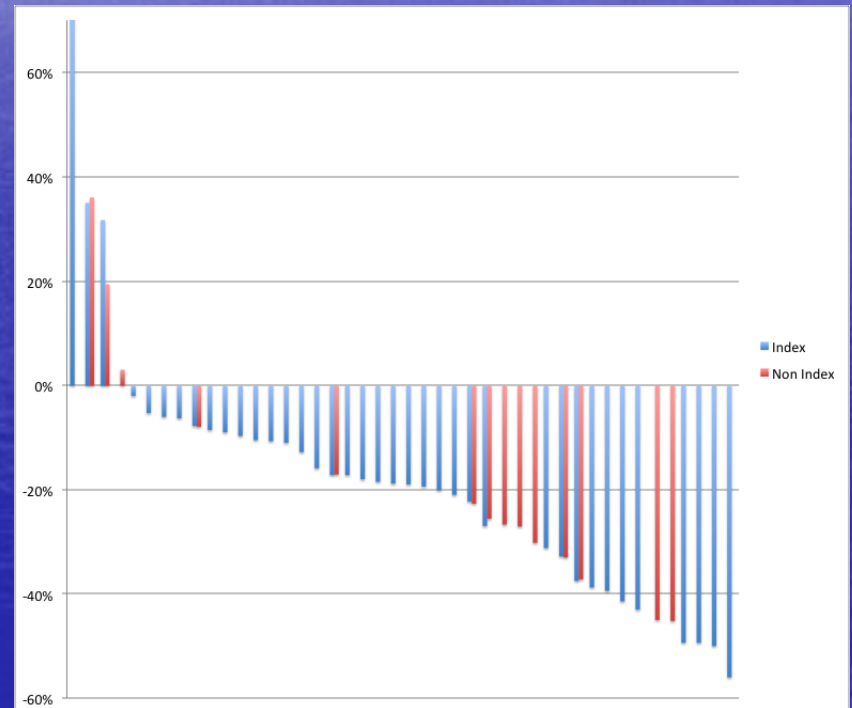


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Avastin summary 2015

- 61 patients
- 90% had growth stabilisation, 39% volume response
- Hearing was maintained or improved in 86% of patients with some hearing at the start of treatment
- BUT tumours regrow when stopped
- Improved patient reported QOL



NF2 and implants

- Until 1990s most people became deaf
- Use auditory brain stem implants if hearing nerve cut
- Cochlear implants if hearing nerve intact



Implants: value of NF2 network

- Rapid dissemination of new ideas/techniques
- E.g. 'Head wrap' scans enabling MRI scans with implant in situ
- Cochlear implants for people with stable tumours but decreased hearing

Complex NF1 service

- For patients with the rare major physical problems where seeing an NF ologist makes a difference
- Unusual phenotypes
- Who need complex genetic analysis for genetic counselling



Segmental NF1

- Midfacial CALpigmentaion from early childhood
- Both plexiform/dermal NFs from early teens
- Sure do not want to take risk... felt some health professionals did not understand this
- Analysis of 3 separate areas of neurofibroma showed intragenic deletion and whole gene deletion





INTERNATIONAL

EUROPEAN

NATIONAL

REGIONAL

Learning and behaviour/routine checks

With many thanks to...

- Prof Gareth Evans (national NF2 lead)
- Prof Ros Ferner (national complex NF1 lead)
- NF2 centre leads- Allyson Parry, Dorothy Halliday, Patrick Axon, Shazia Affridi
- NF2 and complex NF1 teams in Manchester