Paediatric CNS Tumours

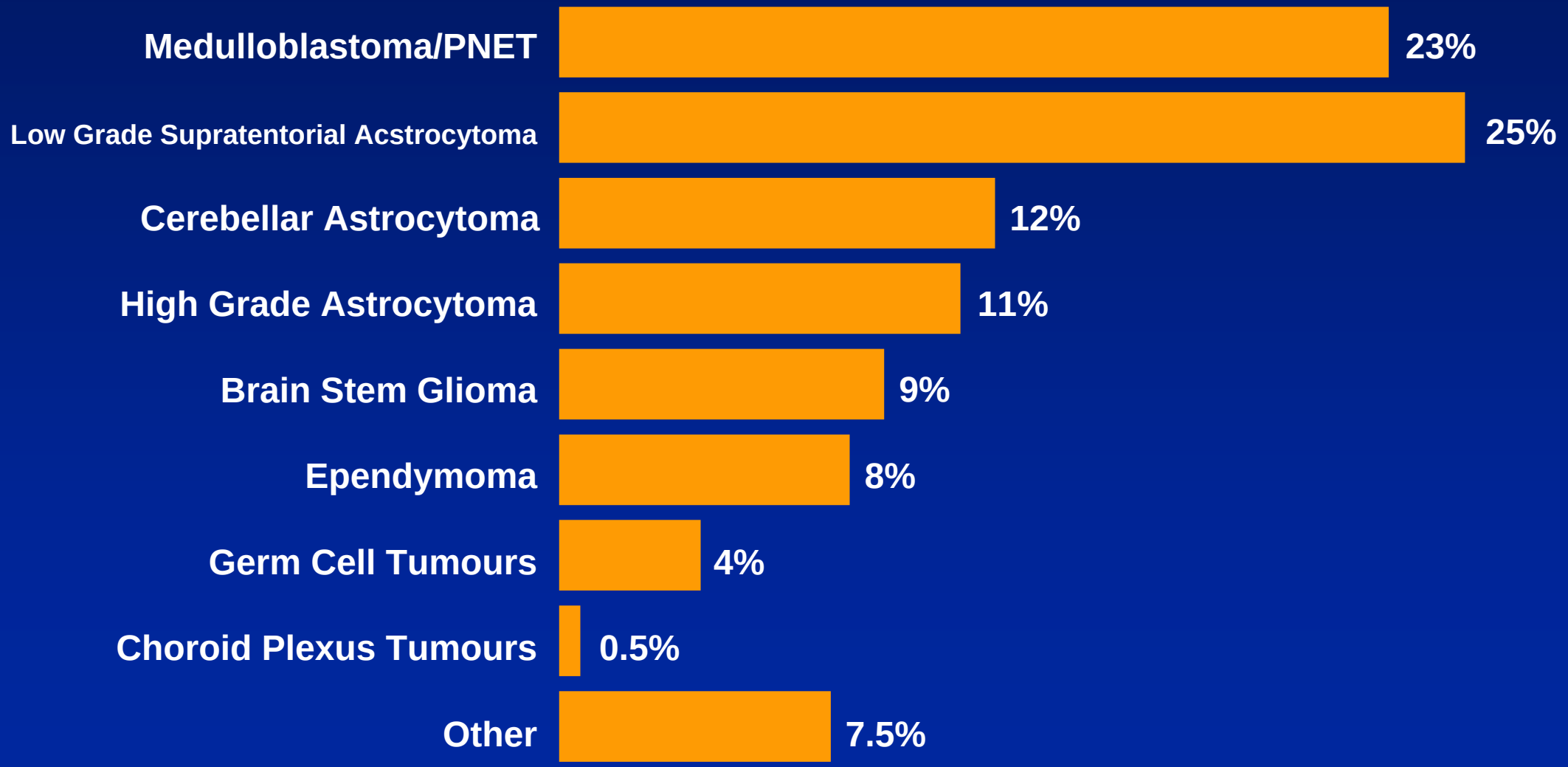
Challenges and research
NBCNS meeting Sweden 2009

Dr Antony Michalski
Great Ormond Street Hospital, London

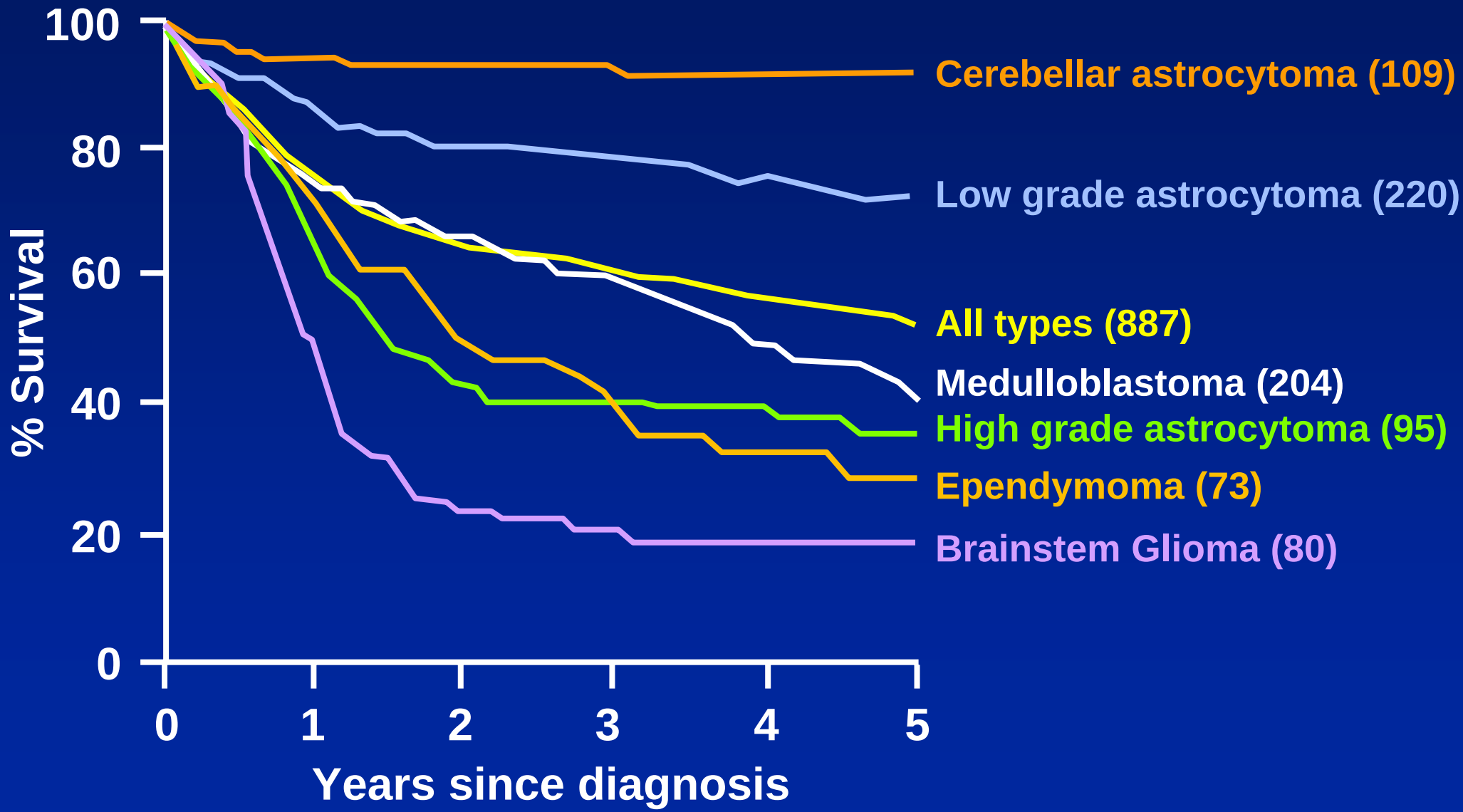
Structure of Presentation

- The scale of the problem of CNS tumours
- History of evolution of studies
- How improved tools facilitate research
- New solutions lead to new problems
- Potential strategies for the future
- Discussion – lots of discussion!

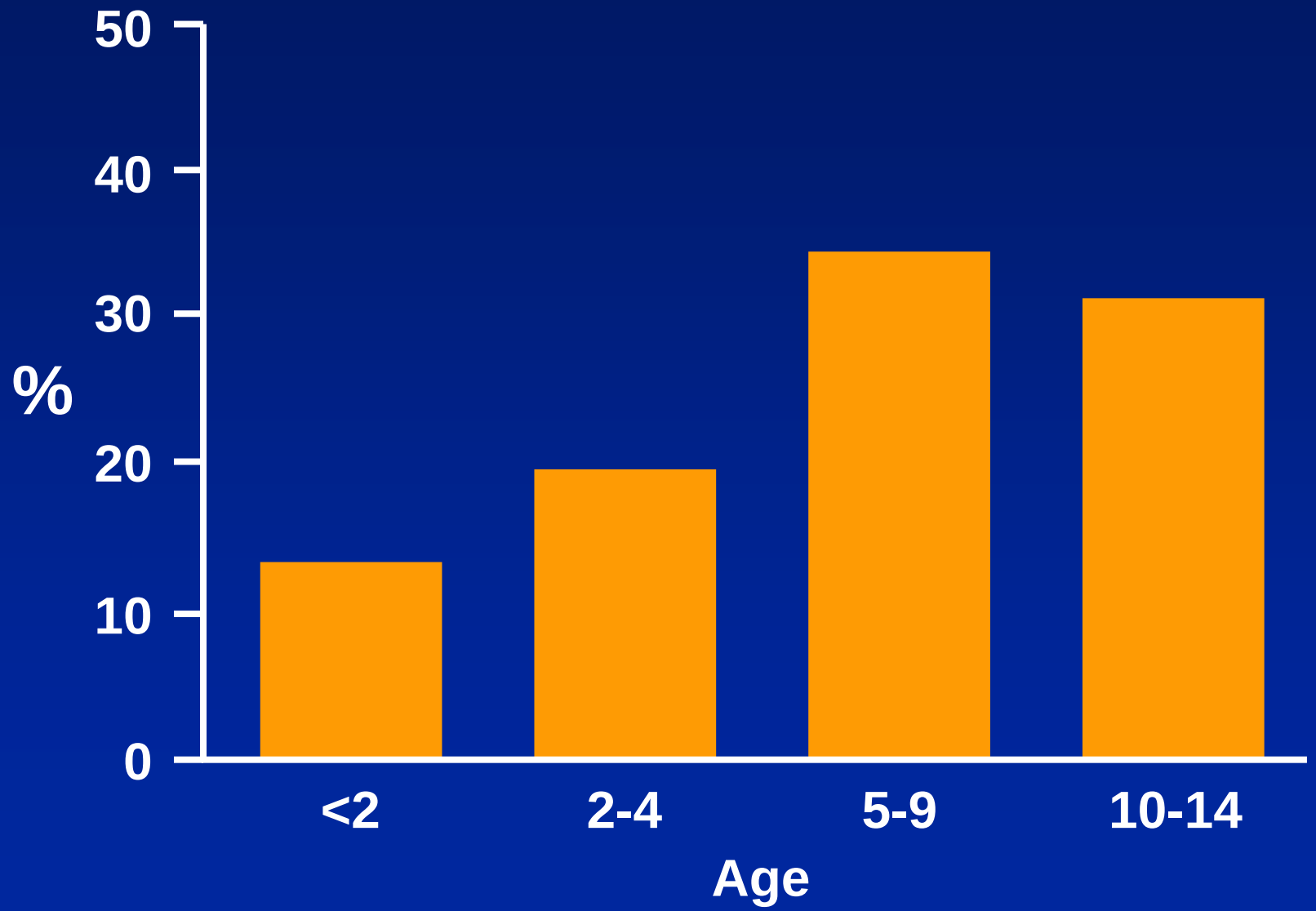
Malignant Brain Tumours in Children <15 years: Distributed by tumour type



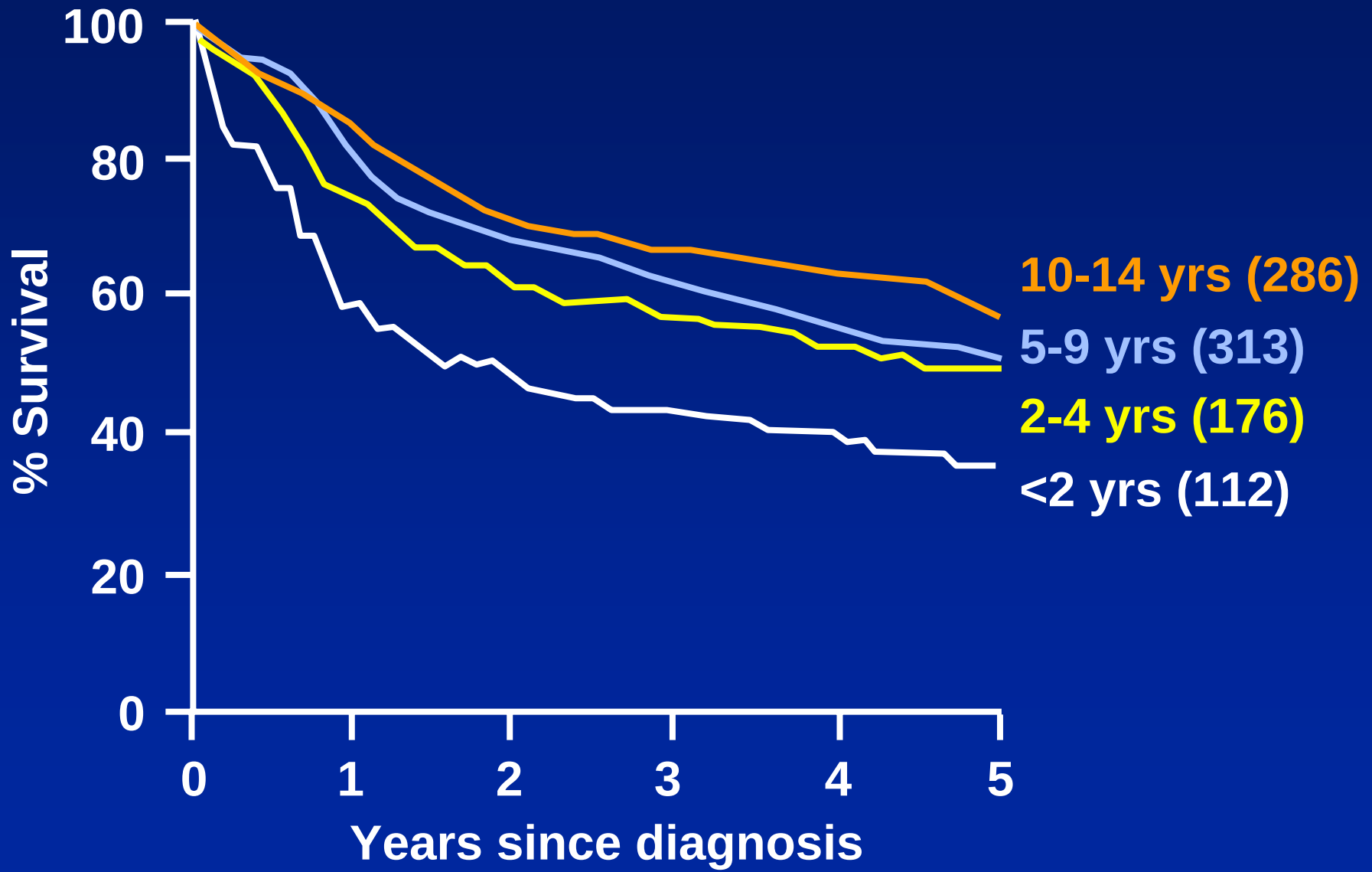
Survival According to Tumour Type



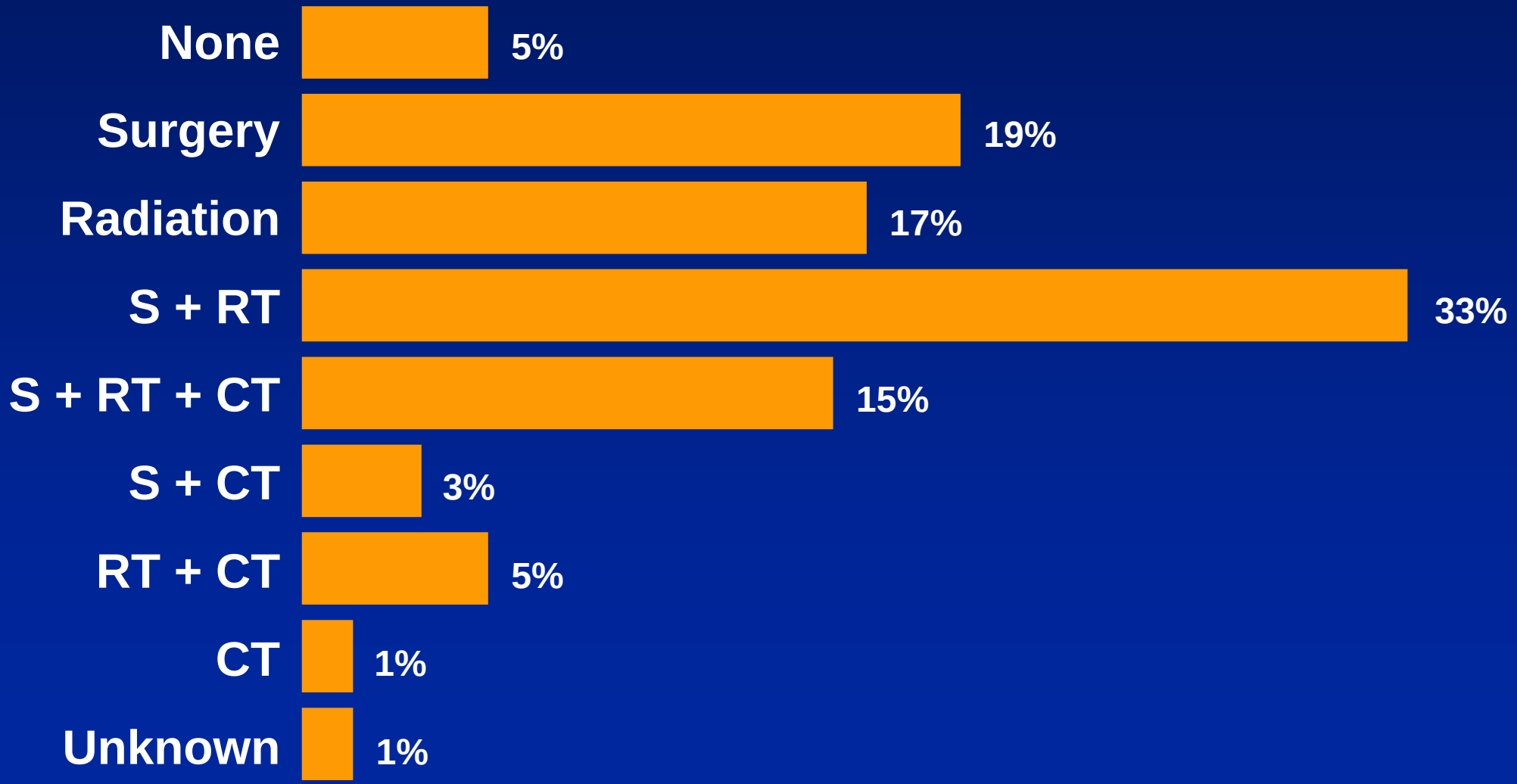
Percent by Age *(distribution of all types)*



Survival According to Age at Diagnosis



Brain Tumours <15 years: Treatment Approaches



Why was neuro-oncology the Cinderella of cancer therapy?

- Fragmentation of service delivery
- Difficulties in tissue collection
- Problems with histological classification
- Inability to judge response of therapy accurately and non-invasively

Neuro-oncology research c1970s

- **Intracranial tumours: response and resistance to therapeutic endeavors, 1970-1980.**

  Bloom et al, IJROBP 1982 1083-1113

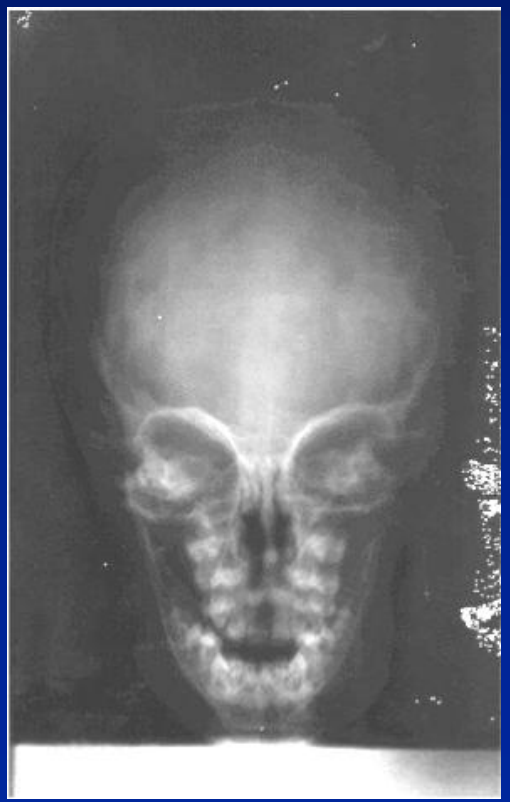
>2 decades of improved ability to perform clinical trials

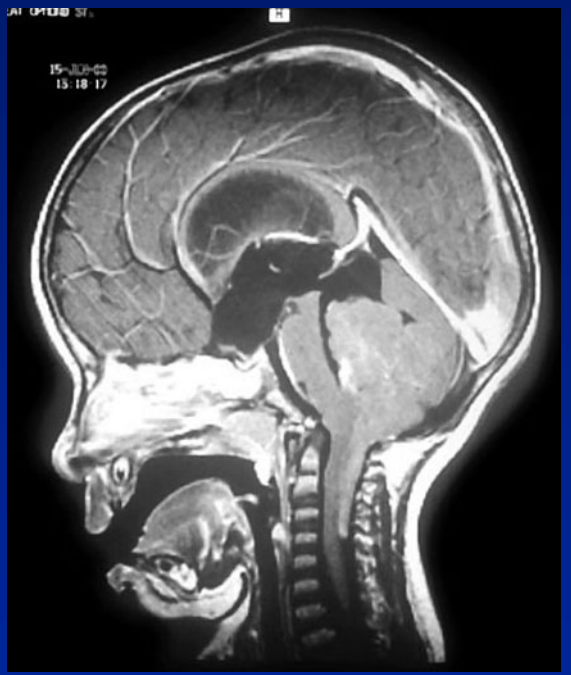
- Improved surgical and anaesthetic technique allowed tissue to be obtained – operating microscope and beyond
- Agreed histopathological classification (we all agreed what we were treating ….well almost all of us did)
- Improved neuroimaging allowed us to stage disease and measure response to therapy other than clinical response and survival
- More collaboration (we all agreed what the problems were)
- Increased recognition and improved measurement of late effects of therapy

How does neuroradiology help an oncologist?

- Helps make a diagnosis
- Stages disease – neuraxis spread
- Allows assessment of response to treatment – internationally agreed response criteria
- Helps diagnose a recurrence

Astonishing progress…..





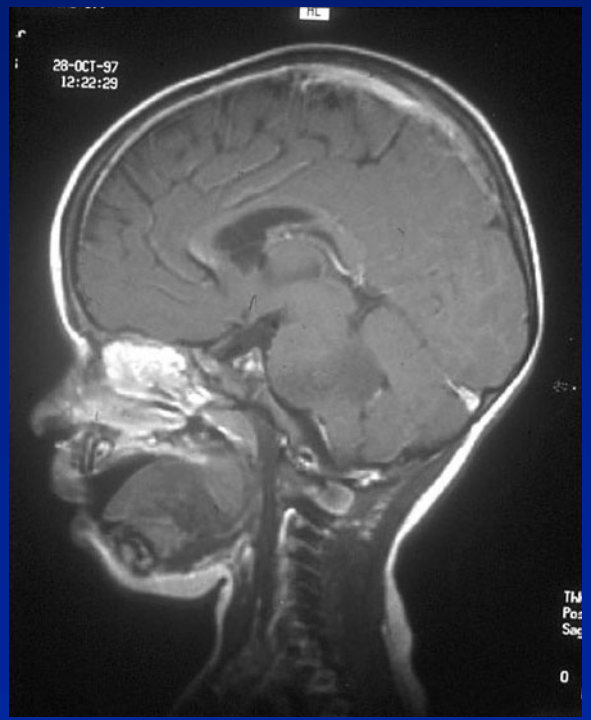
CT scan

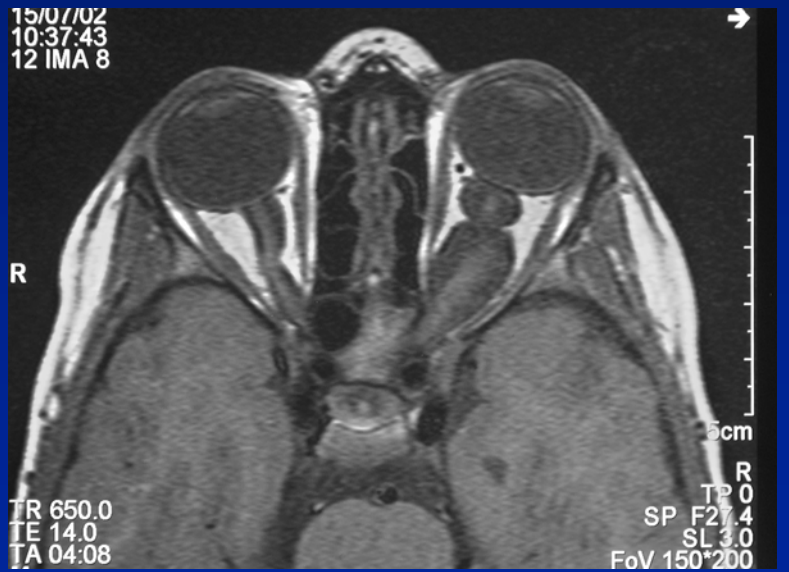
MRI scan

PET scanner

Angiography suite

Making a diagnosis – sometimes without histological confirmation

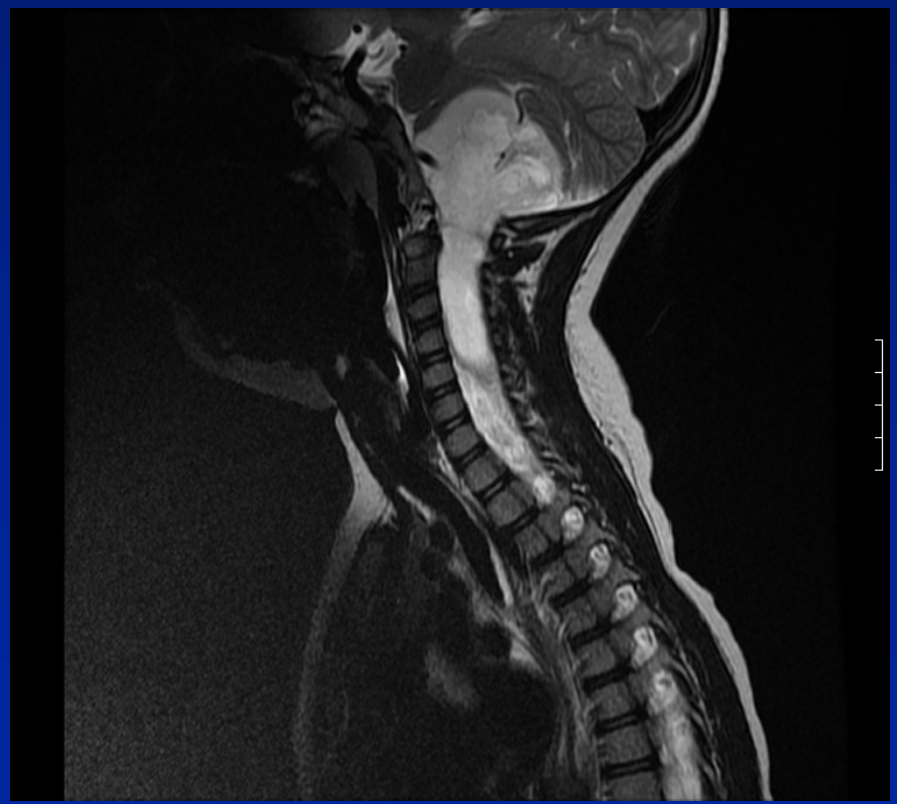


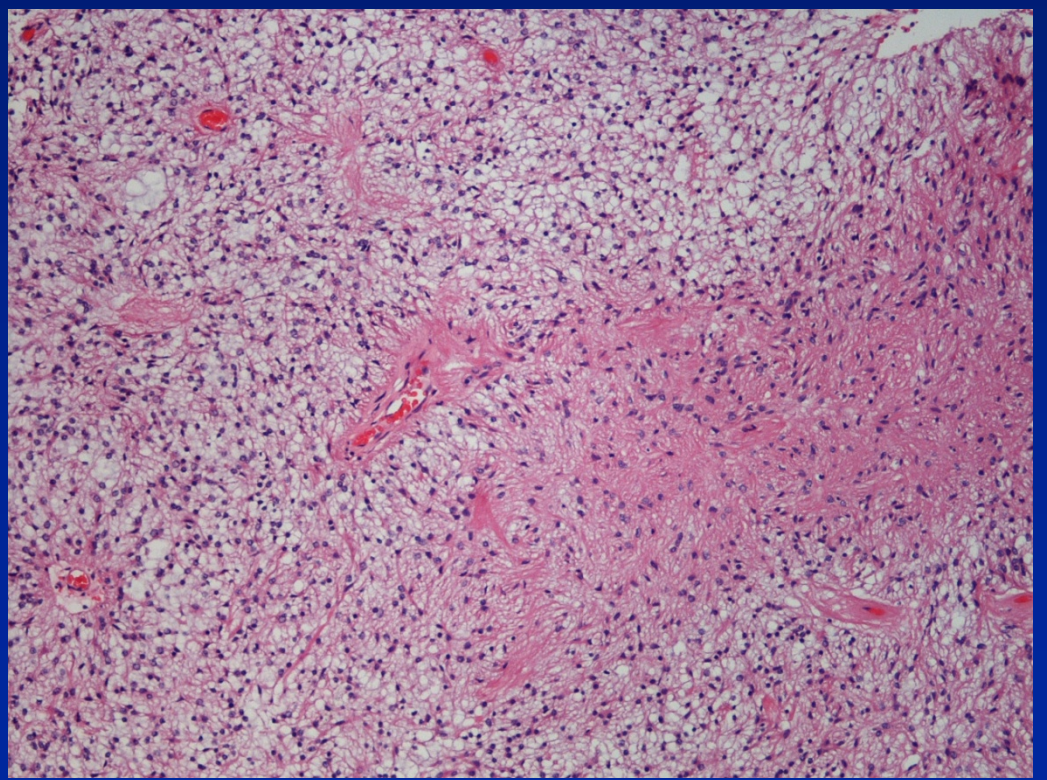


Collaboration- how data set was obtained is important - don't do your best!

- Care delivered on risk-adapted protocols
- The radiological diagnosis changes the treatment group
- Treatment groups need to be homogeneous
- Therefore, techniques should be reproducible and consistent between participating hospitals
- Risk of 'stage migration'
- Role of central radiological review

More usually a diagnosis is made using radiology and pathology





Agreed and updated classification

The WHO Classification of Tumors of the Nervous System

Kleihues P, Louis D, Scheithauer B et al

Journal of Neuropathology & Experimental Neurology: 2002 - Volume 61 - Issue 3 - p 215-225

Names are important

What is a diagnosis?

- Not just a label
- The data set necessary to do a job:
  - planning therapy
  - giving a prognosis
  - entry on to a scientific or clinical research protocol
- The data varies with the job to be done

Diagnostic labels – not static

- **New histopathological entities identified**
  - ATRT from what was called PNET
- **Subclassification within entities**
  - Desmoplasia in PNET
- **Massive impact of molecular biology**
  - What defines a tumour?
  - Need for collaboration between biologists and neuropathologists

So, problem solved ?

- All the major tools in place
- Just use the same tools in different disease types
- Just continue to develop the technology

Really good trials

- **HIT/SIOP PNET 4**
  - Randomised comparison of two different radiation techniques in standard risk medulloblastoma
  - Tightly defined population, central review of key data, multinational , biological and late effects questions
  - Run from Sweden

Technological development

- Further development of current tools
- Interaction with technological developers
- It is all very exciting but how does it help us?

Technological development in neurosurgical issues

- **Knowing where you are in the brain**

  Open surgery direct vision

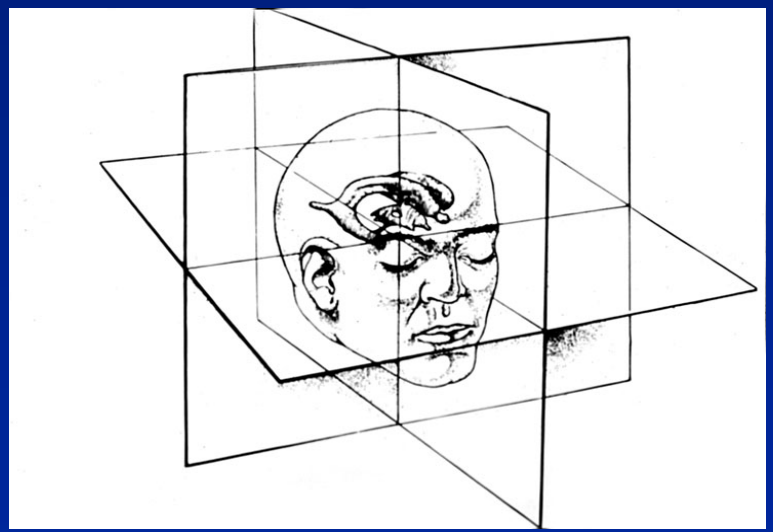
  Operating microscope

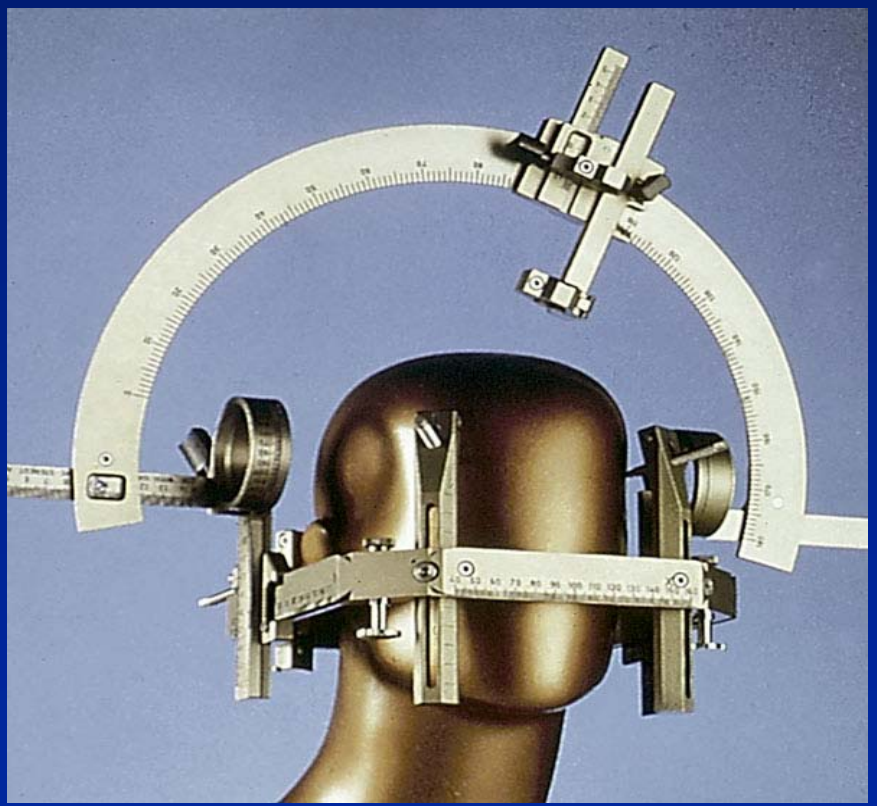
  Stereotaxy and neuronavigation

Finding you way in neurosurgery - traditional

Stereotaxy



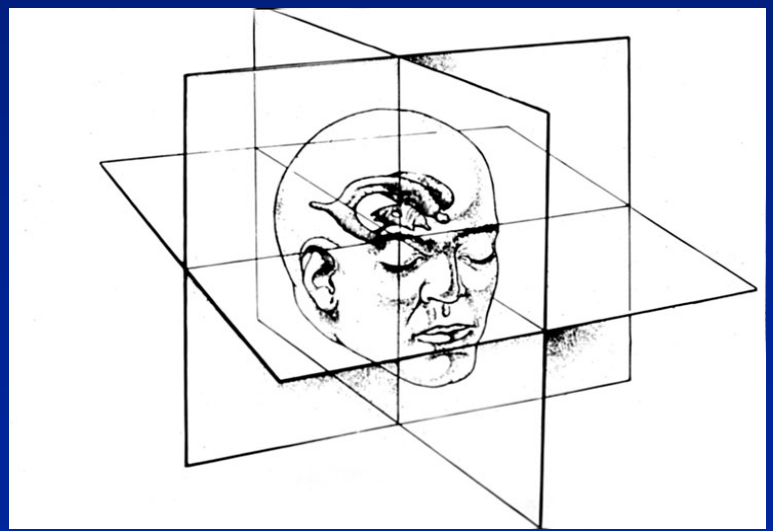
Frame based

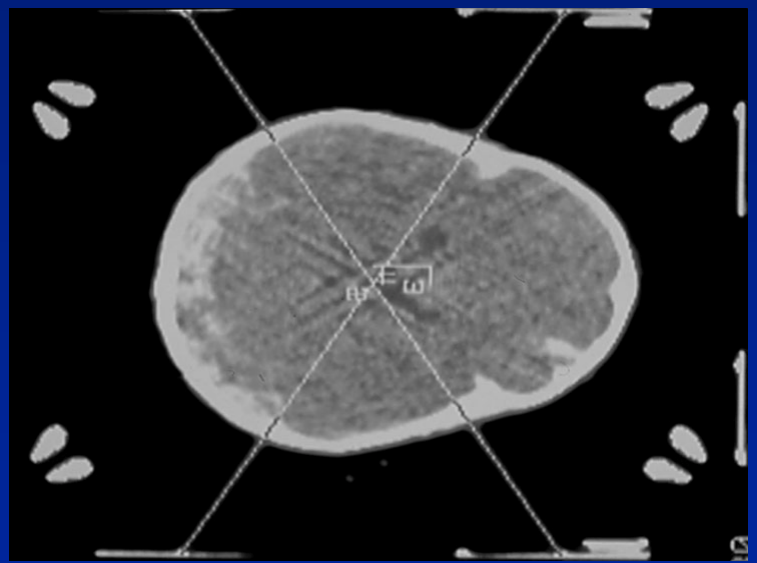


Finding you way in neurosurgery

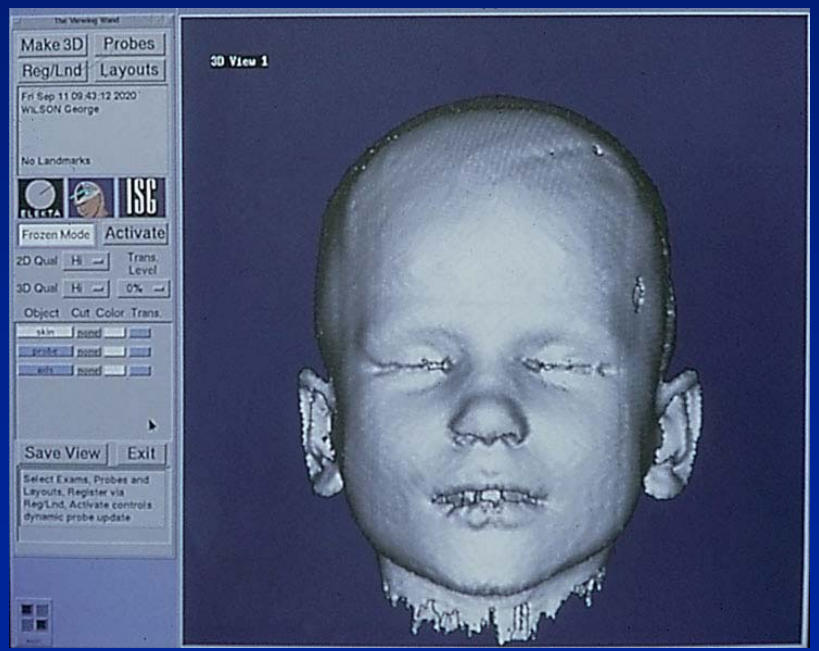
Frame based

Stereotaxy

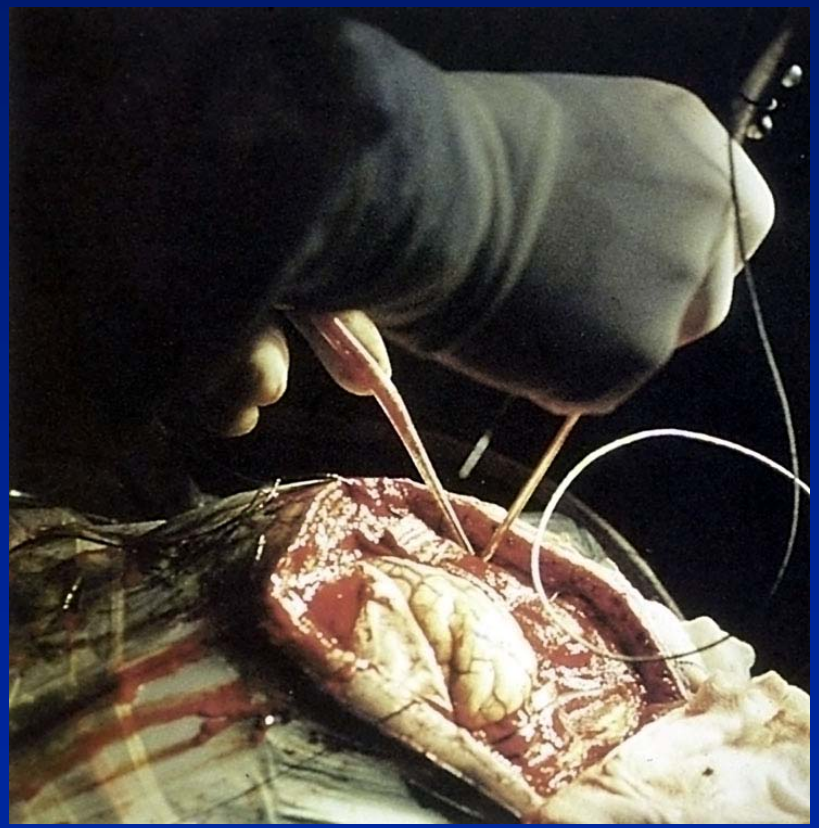




Finding you way in neurosurgery –contemporary Image guided surgery



Frameless stereotaxy



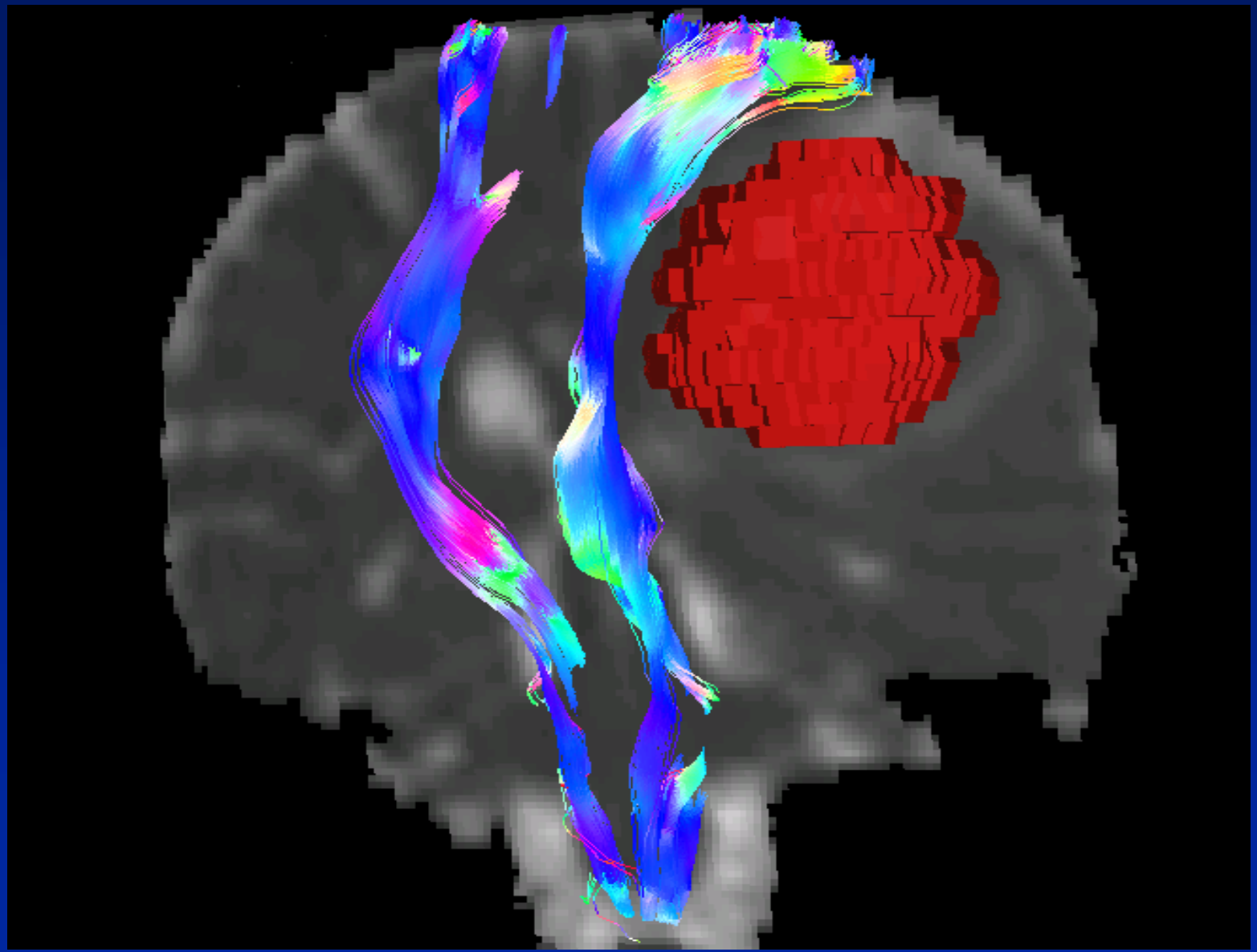
Don’t cut that; it’s important

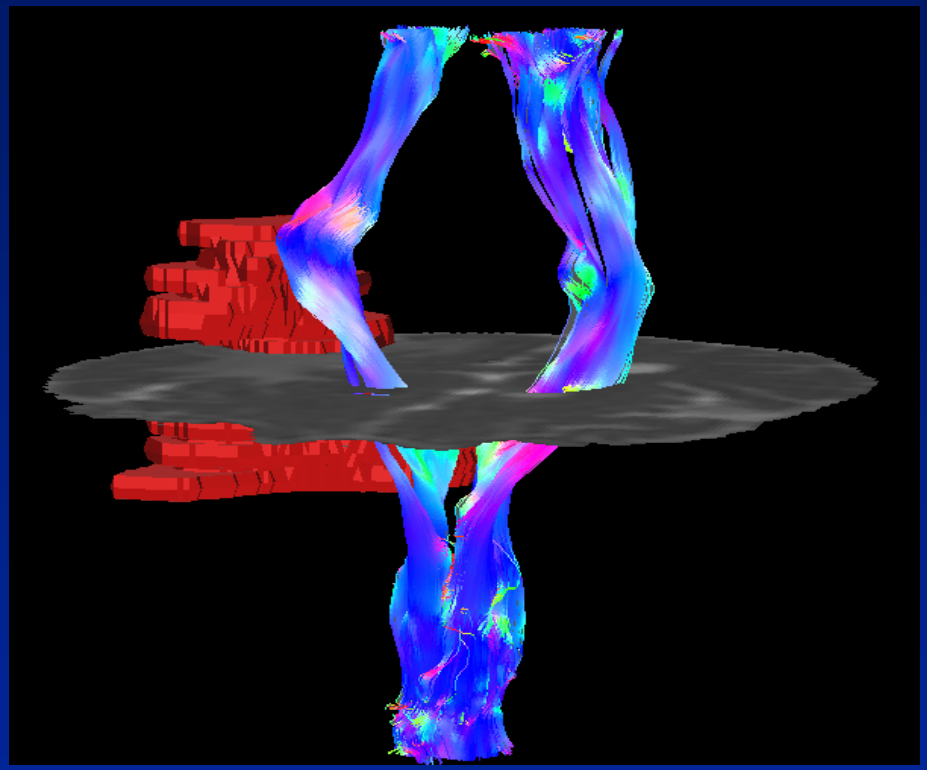
- Neuronavigation is largely based on the anatomy doing what it normally does
- Plasticity of nervous system means that other areas can take over function
- How do you resect as much as possible safely?

Functional imaging

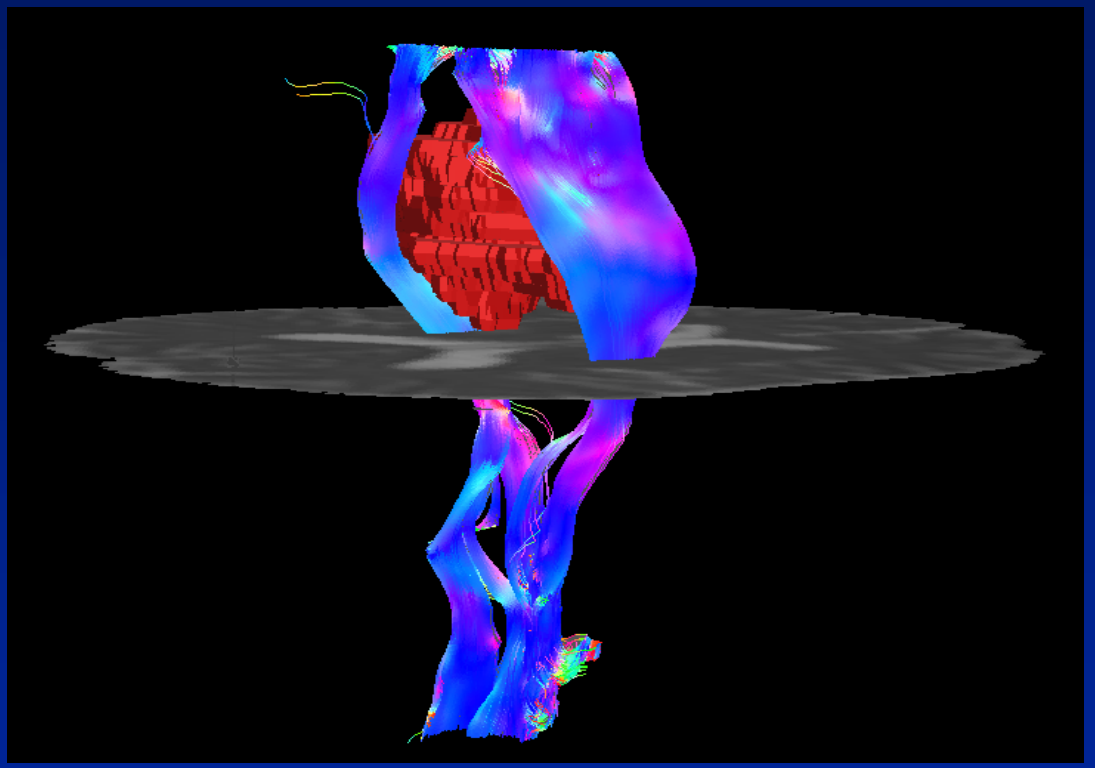
- Functional MRI
- Tractography (Dr Chris Clark, ICH, London)

Neurosurgical planning





Recurrent meningioma
No hemiparesis



Anaplastic Astrocytoma
Left Hemiparesis

Chris Clarke, ICH

Problems with studies

Better defined subsets result in small numbers of patients to study – the story of ‘Baby brains’

‘Baby-Brain’ Studies

- **Duffner: VCR, cyclo, cisplat, etoposide**

  NEJM ’93 328 1725
- **Baram: MOPP**

  Cancer ’87 60 173
- **Geyer: 8 in 1**

  Cancer ’95 75 1045, JCO ’94 12 1607
- **Jeng: VBL, cisplat, etoposide IT triples**

  Child’s Nerv Syst ’93 9 150
- **UKCCSG: VCR, carbo, MTX, cyclo, cisplat**

Different groups – different philosophies…

- POG – delay radiotherapy for all reduce dose for those responding to chemotherapy
- UKCCSG - defer or avoid radiotherapy by using ‘intensive’ (but not dose intensive) chemotherapy
- SFOP – treat gently – no RT - salvage recurrences with myeloablative chemotherapy and focal irradiation
- HIT – defer (and eventually avoid) radiotherapy by using chemotherapy and intraventricular chemotherapy
- No agreement over age or diagnosis as entry criteria

UKCCSG trials

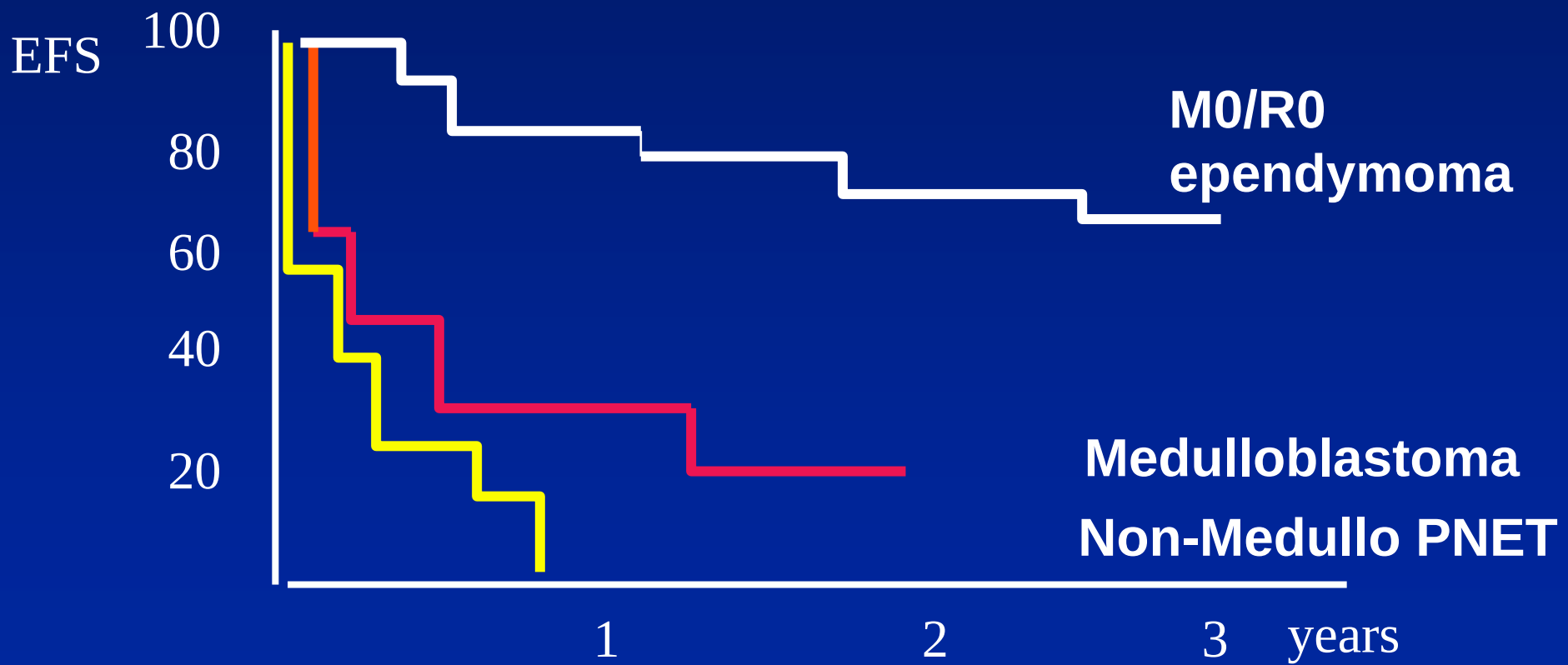
Evolution of understanding of PNET

UKCCSG Baby Brain Study

Aimed to:

- **Delay Radiation for all**
- **Withdraw radiation for patients in CR at end of chemotherapy**

UKCCSG CNS 9204 - results



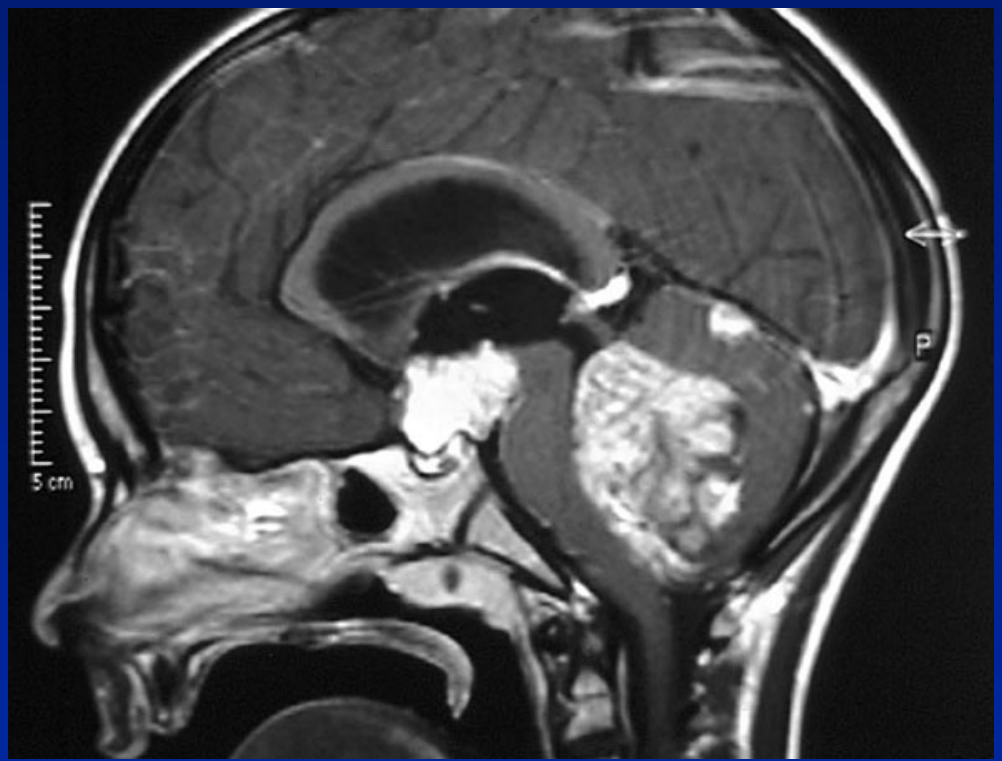
Cure-alls don’t work:
Specific therapy
for specific diseases.

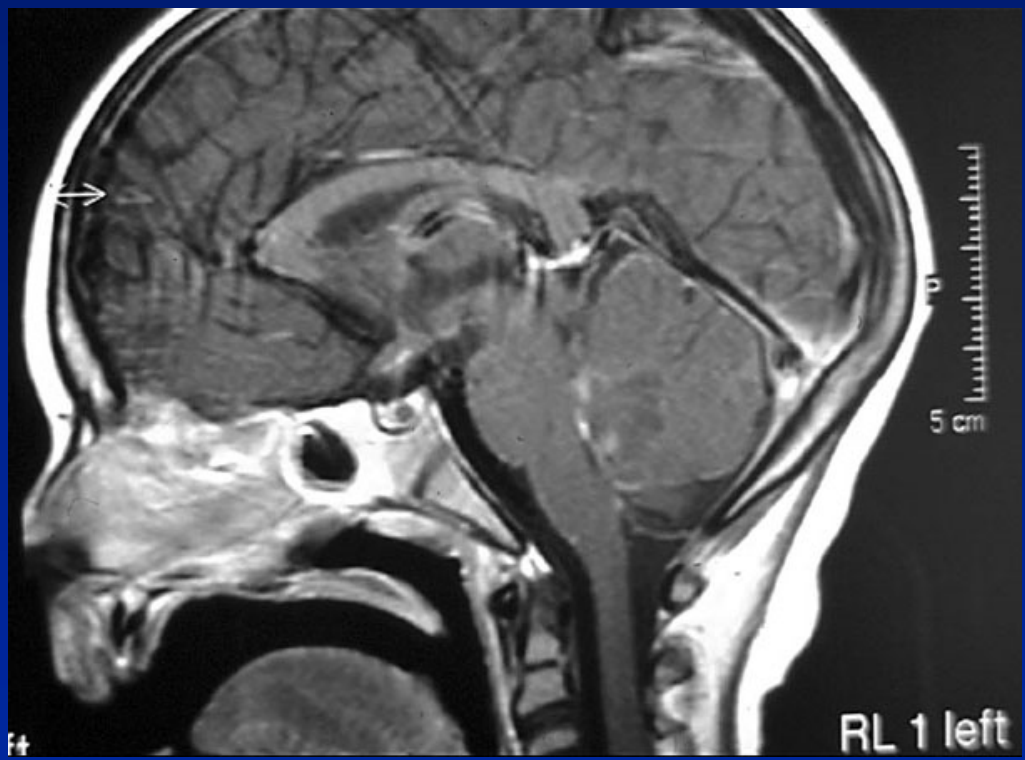
The end of the
‘baby-brain’ era.

Infant PNET study

- Aimed to investigate maximum tolerated dose of cyclophosphamide when given with G-CSF and stem cell rich blood.
- Dose intensive induction
- Focal radiotherapy for focal disease post induction
- Continuation therapy post radiotherapy

Response to chemotherapy



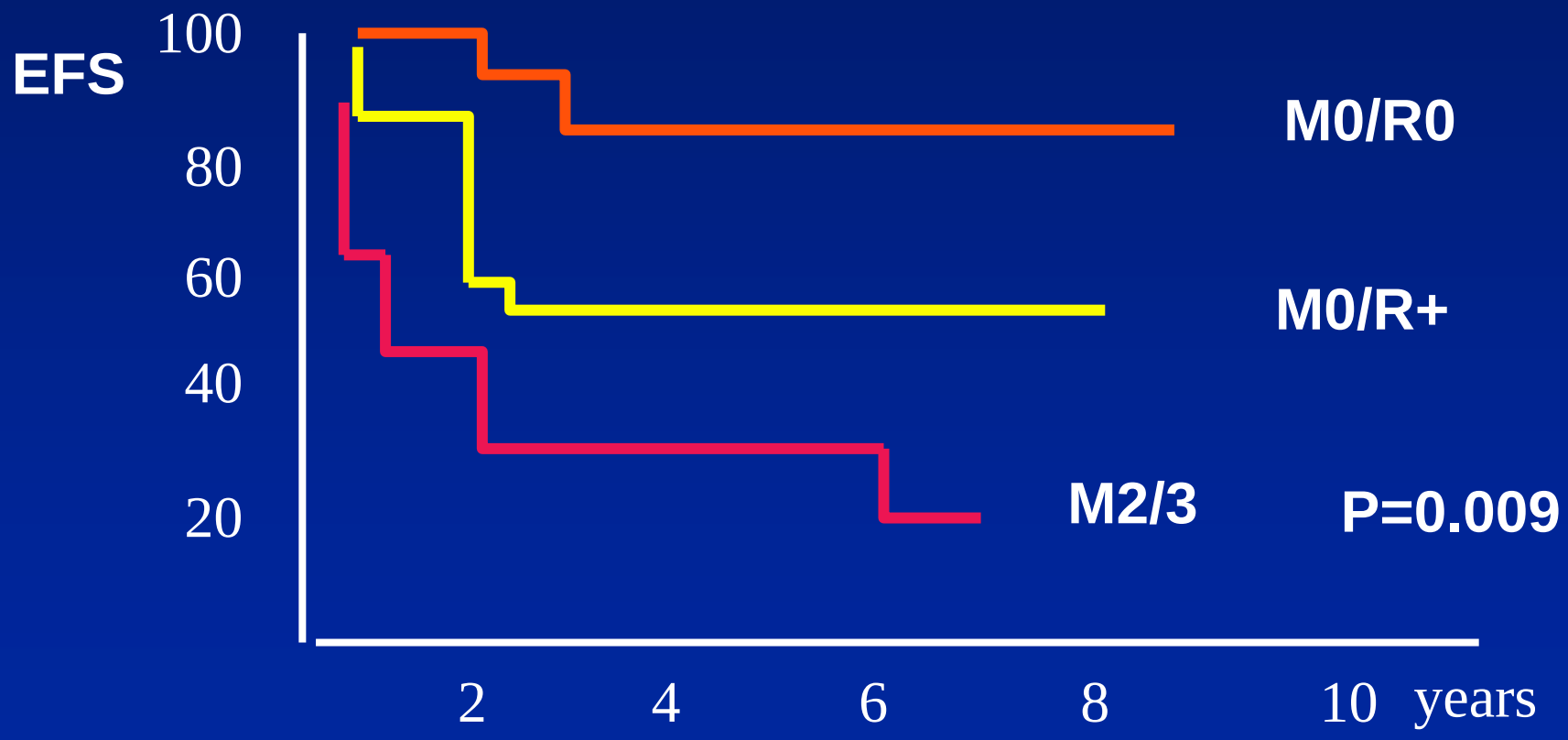


Survival by diagnosis

- Medulloblastoma 20/29 alive (70%)
- Supratentorial PNET 1/6 alive (17%)
- Pineoblastoma 1/8 alive (12.5%)
- Choroid plexus carcinoma 0/3 alive
- ATRT 0/2 alive
- Other – 2/4 alive

The end of the ‘PNET’ era?

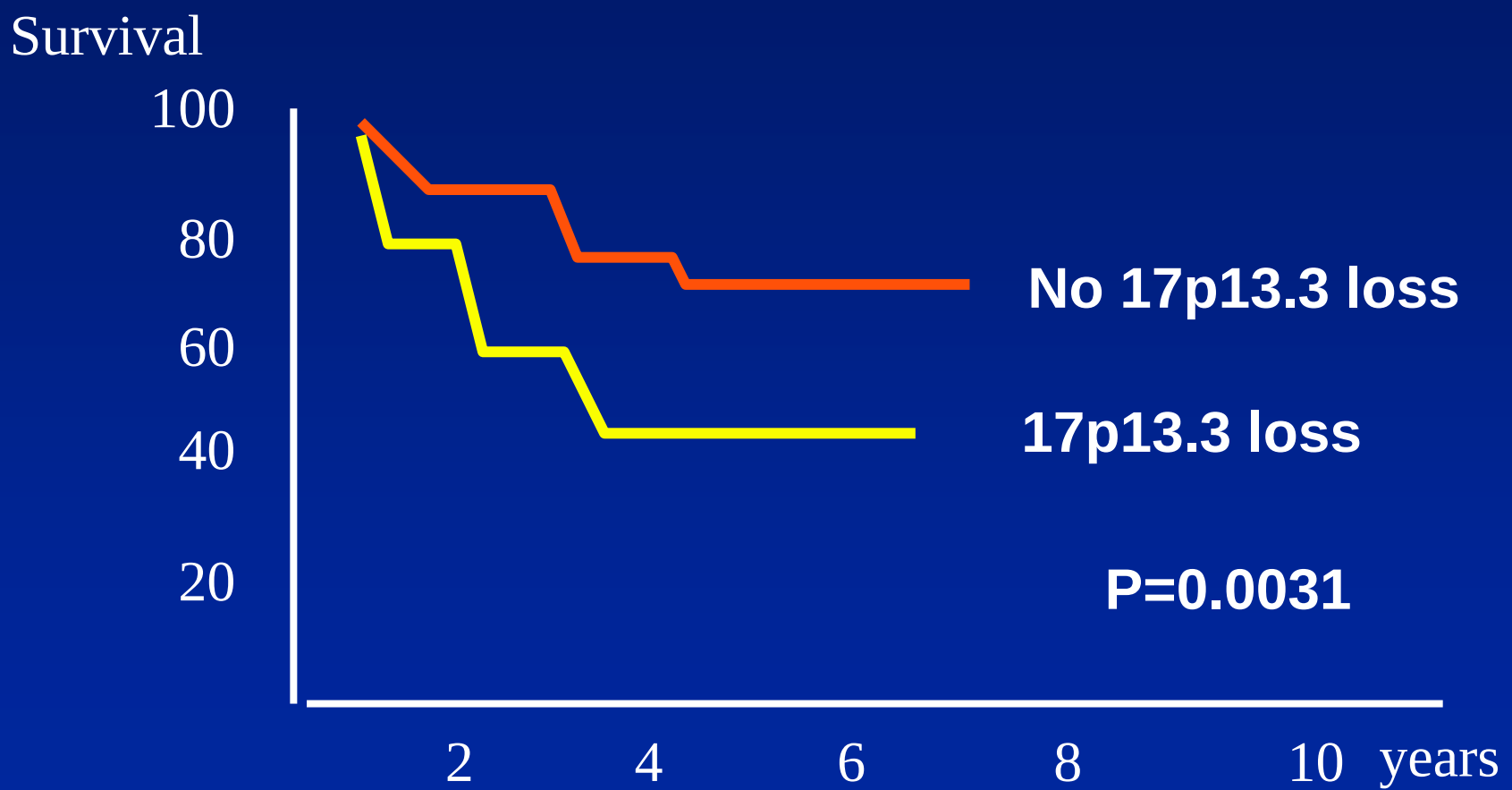
Results of HIT/SKK



NEJM 2005

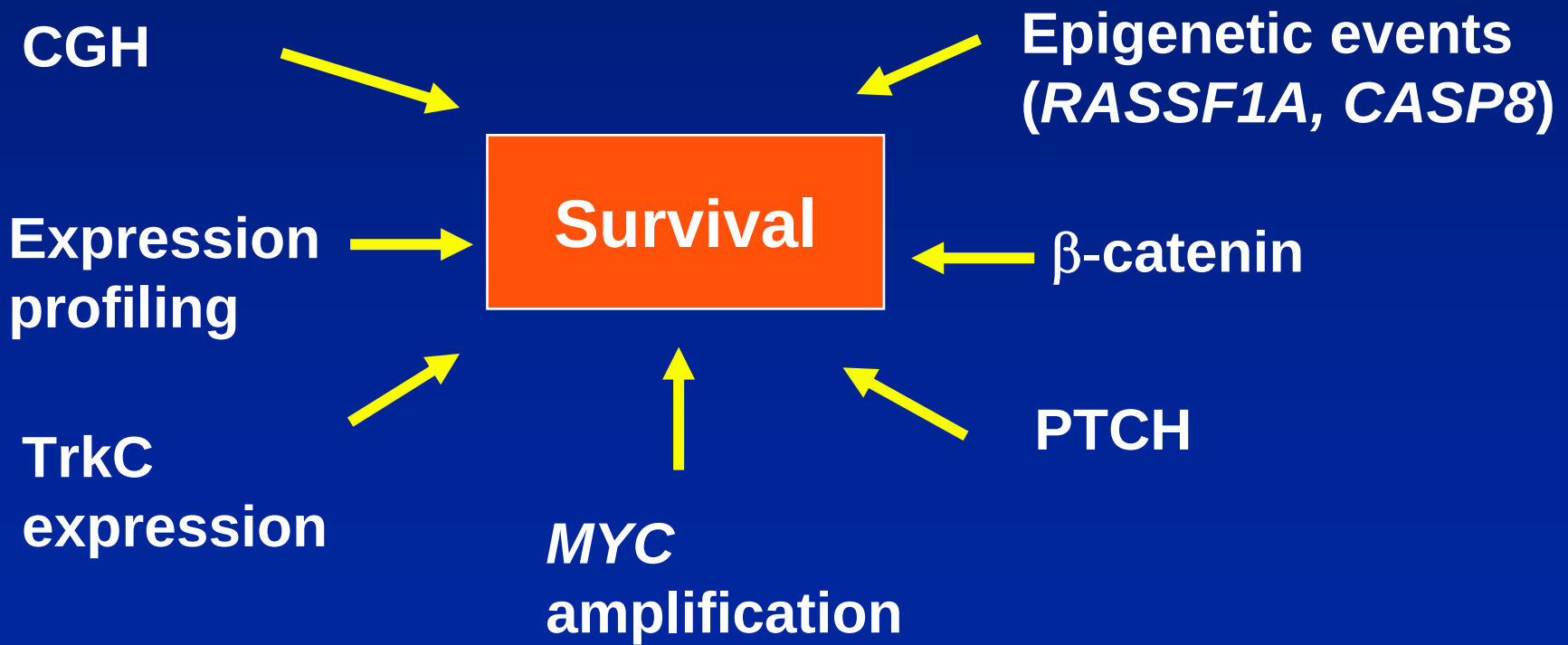
The end of the infant medulloblastoma era?

In >3y olds biology predicts ‘bad actors’



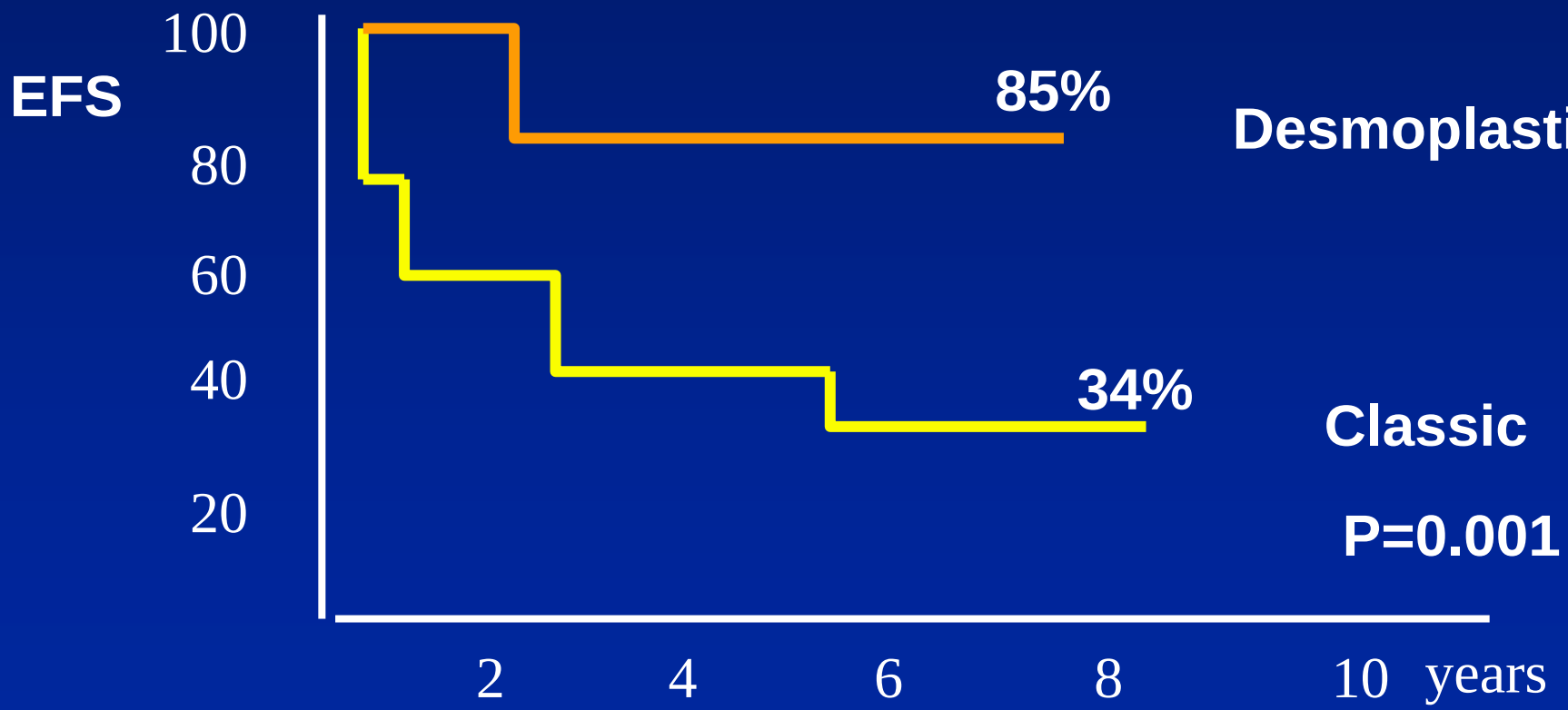
Clinical Cancer Res 2004

More biological prognosticators..



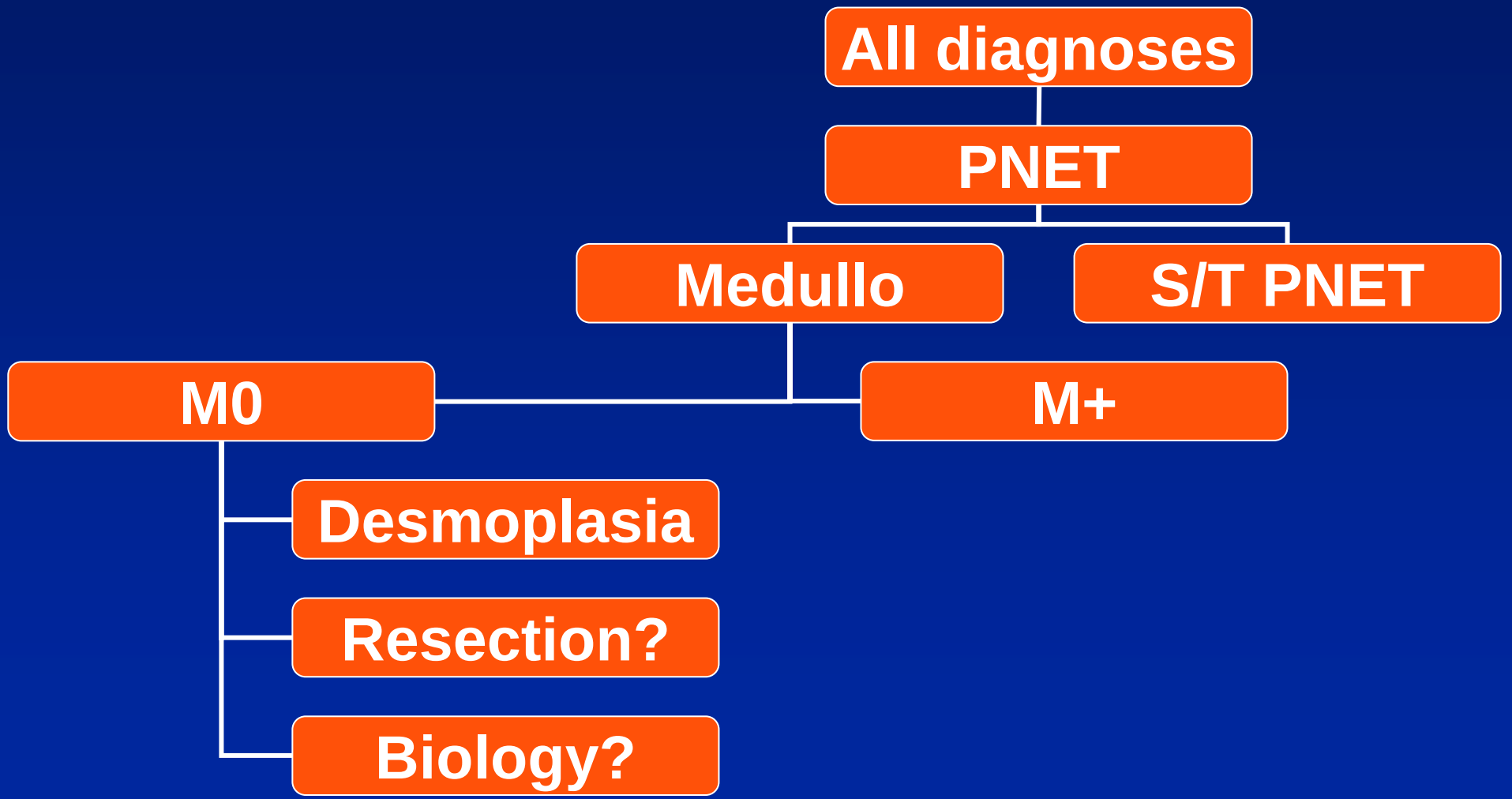
Does that mean we need to split M0 infant medulloblastoma group any more?

Role of desmoplasia in <3year olds



NEJM 2005

Evolution of ‘baby-brain’ trials



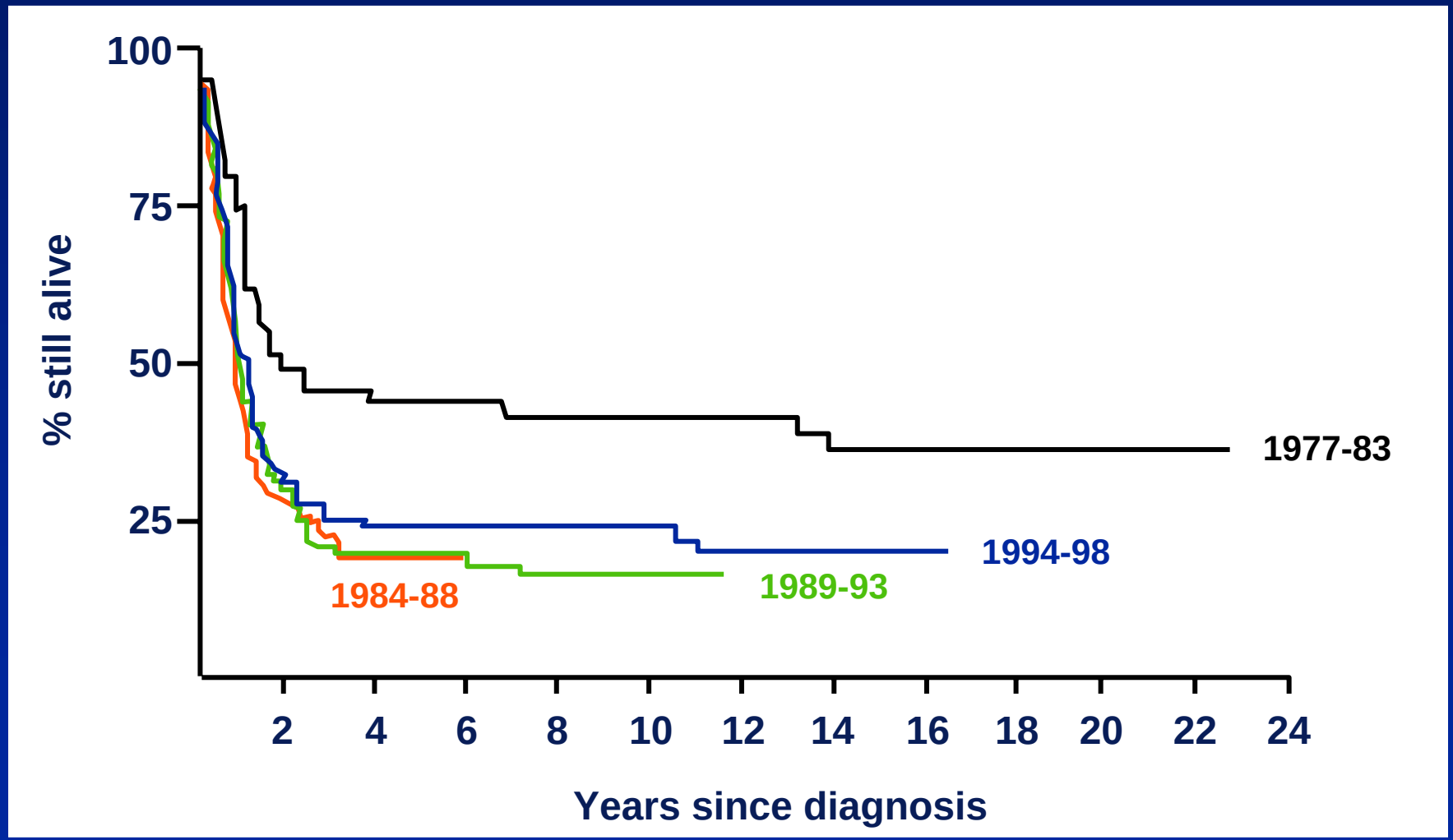
Future studies in infant medulloblastoma

- Small groups with different outcomes
- Small numbers
- No chance of running randomised studies with decent power
- How do we run small studies? First past the post, pick a winner, Baysian stats?
- Do we believe results?

Lots of problems persist

Survival of UKCCSG Patients Diagnosed 1977-98, by Calendar Period

High-Grade Astrocytoma



Novel molecular therapies in neuro-oncology

- Blocking tumour angiogenesis
- Blocking signal transduction from overactive oncogenes
- Blocking tumour invasion
- Promoting apoptosis
- Decreasing DNA transcription - histone de-acetylation
- Response my not result in immediate shrinkage in size
- Do we have the tools to measure what we are doing?

Herrington and Kieran 2009 Pediatr Blood and Cancer 53 312-7

Rational molecular therapy

- Confirm target is present in a given tumour
- Show drug gets to target
- Show drug blocks target
- Show that this has desired effect on molecular pathway (no escape)
- Investigate clinical response to blockade

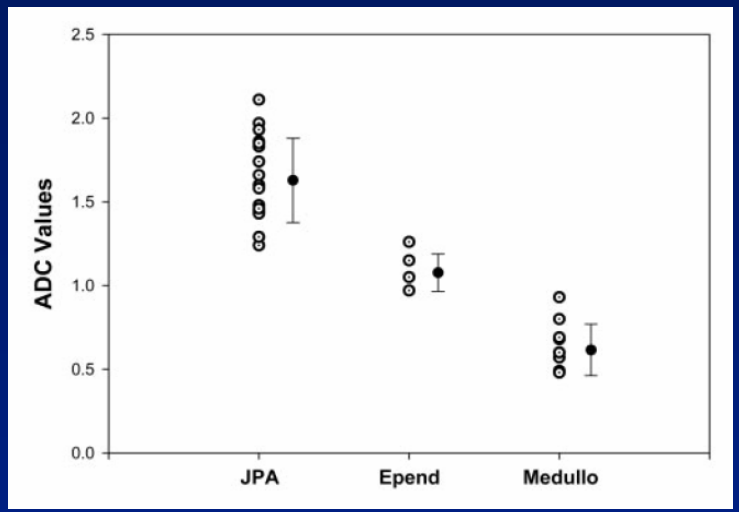
Is this practical?

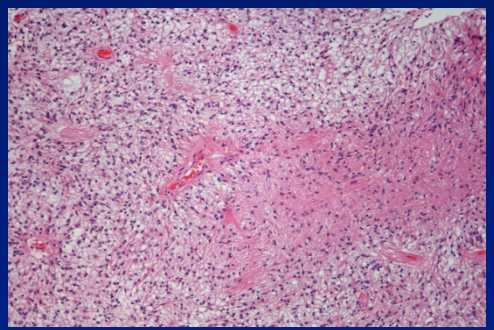
Surrogates for response

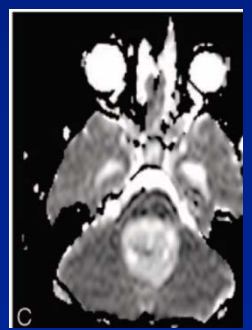
- Measuring tumour vascularity
- Measuring tumour metabolism (MRS, PET)
- Changes in tumour ‘aggressiveness’

Molecular neuro-imaging: From conventional to emerging techniques Hammoud et al 2007 Radiology 245 21-42

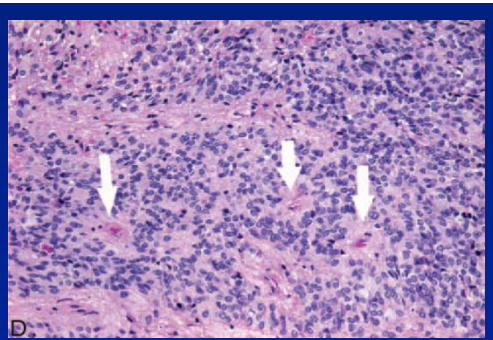
MR diffusion

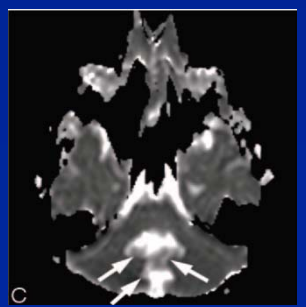






JPA





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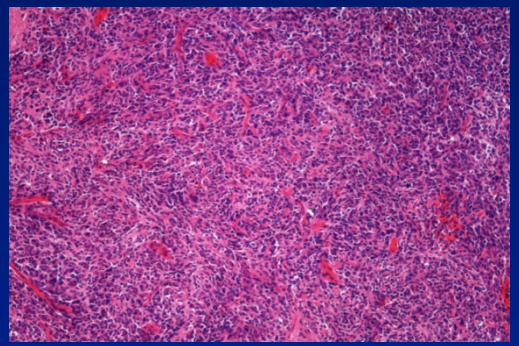
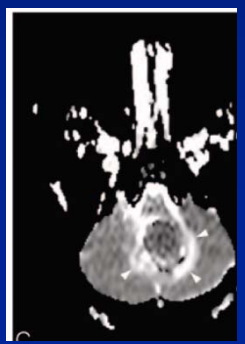
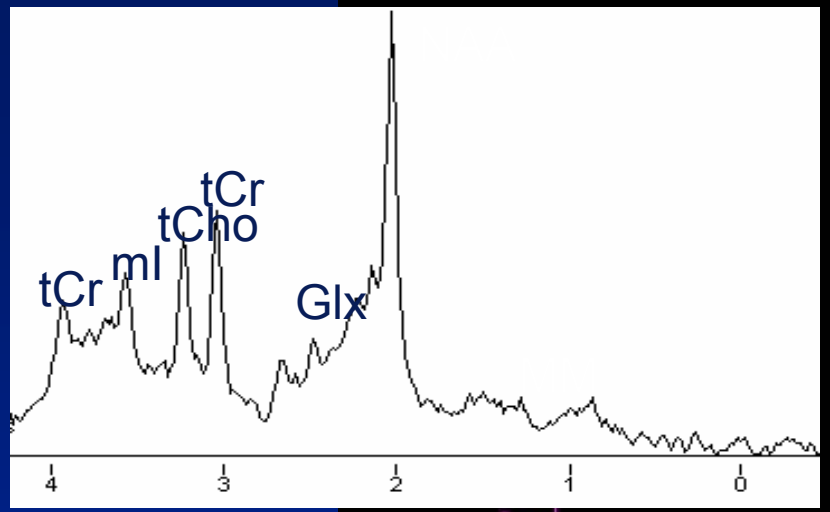




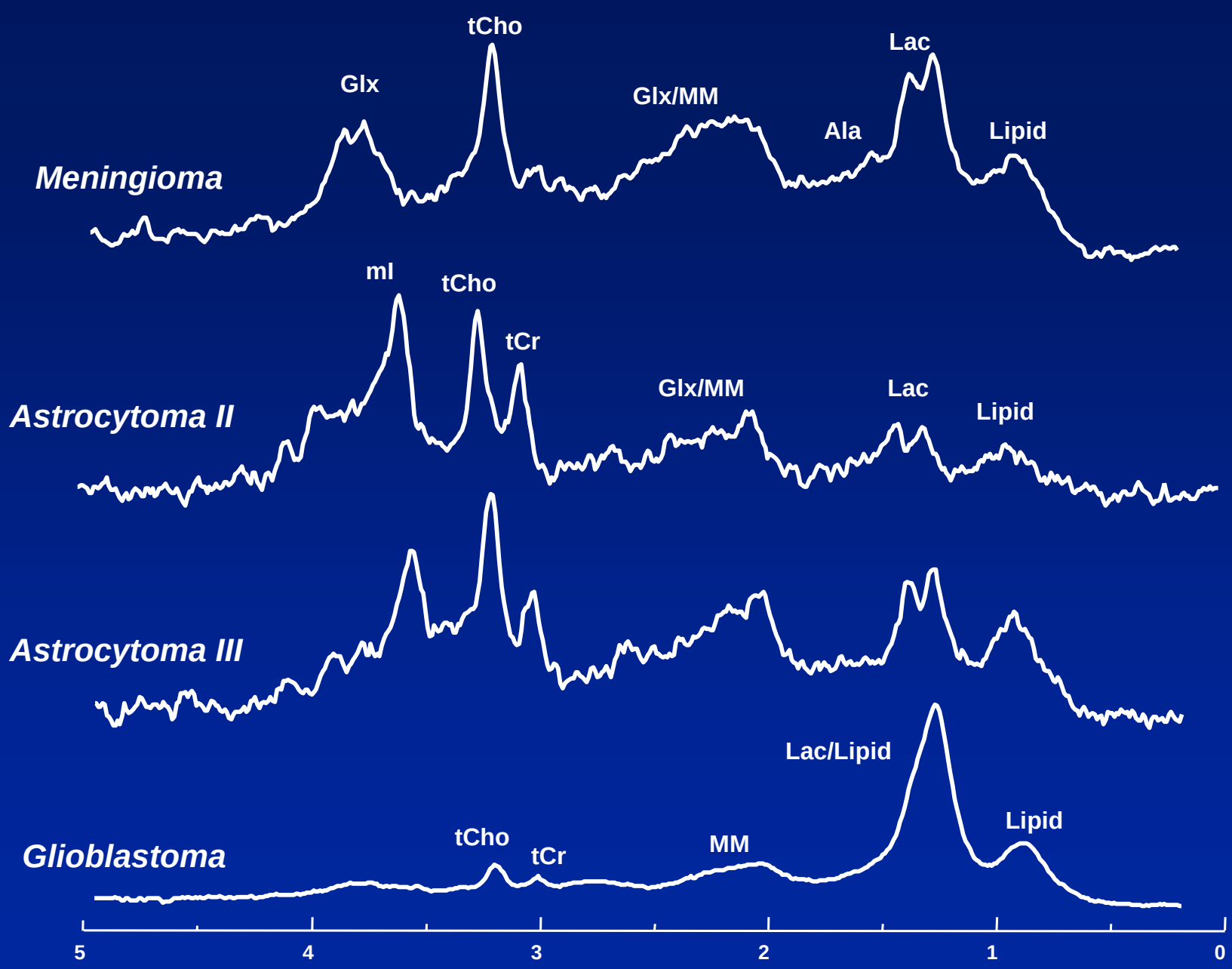
Medullo

Rumbolt et al., 2005

MR Spectroscopy



Average spectra of human brain tumours

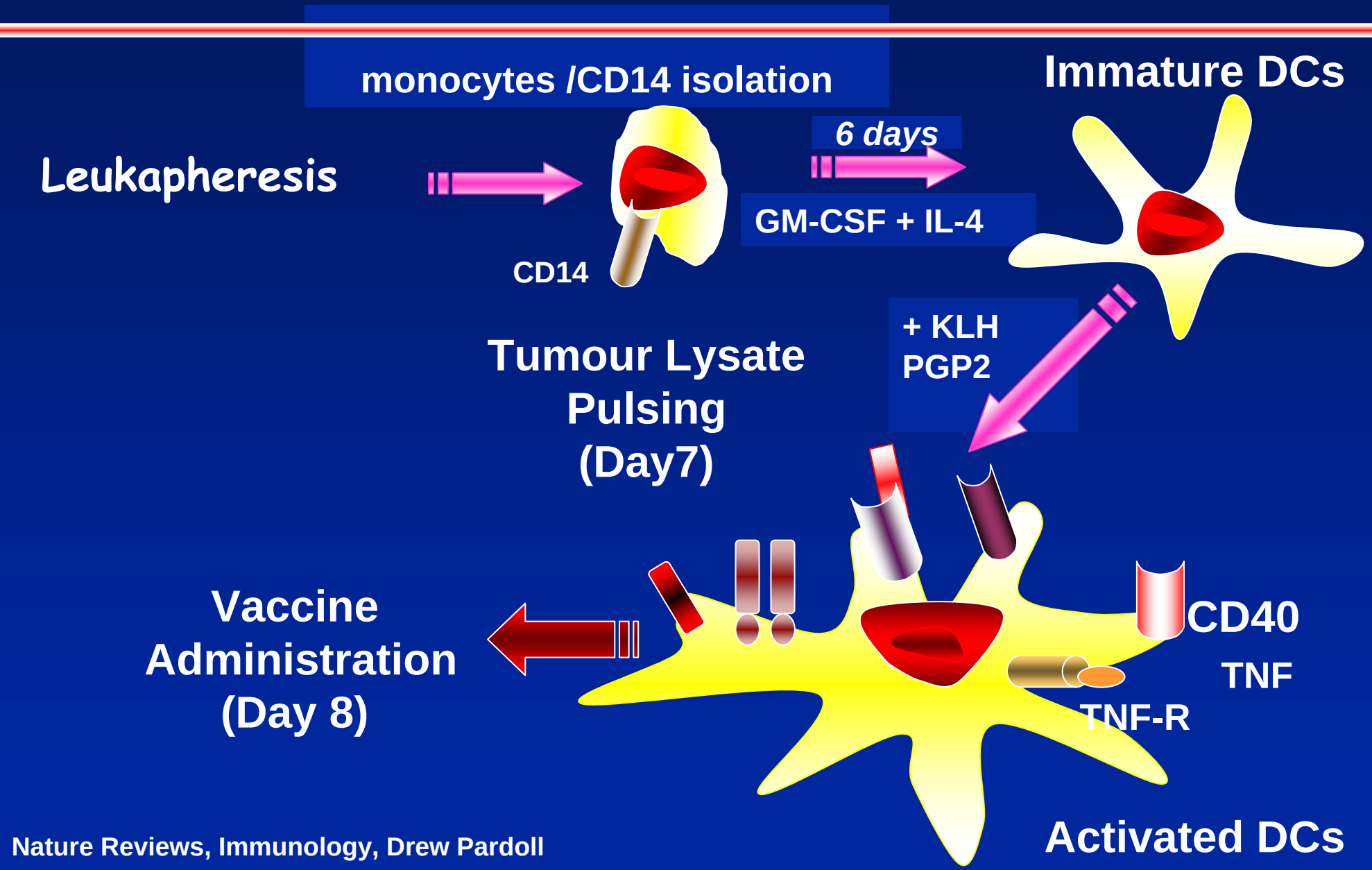


Franklyn Howe, St George's Hospital Medical School

Immunotherapy

Example of getting used to new response criteria

STRATEGIES: *Ex Vivo* GENERATION OF *Ag* PULSED DCs



Nature Reviews, Immunology, Drew Pardoll

Primary Study endpoints of osteosarcoma trial (immunological)

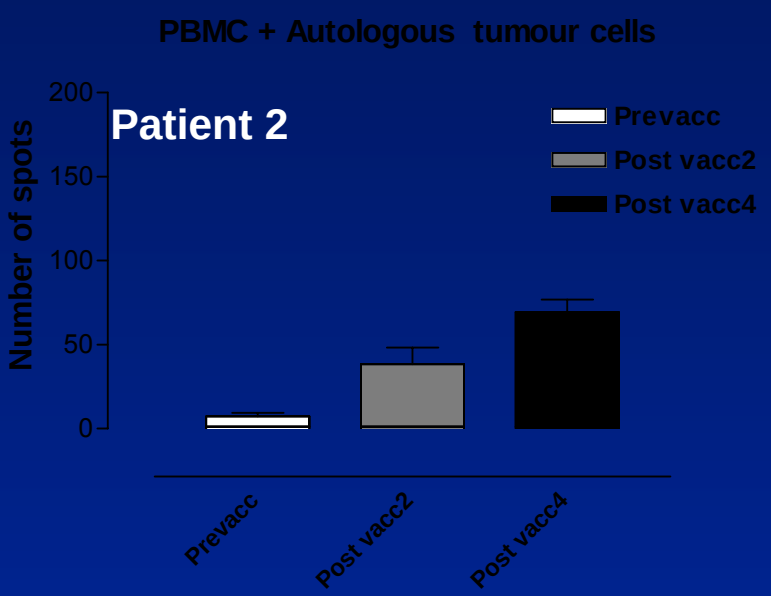
- Specific IFNγ / IL2/ Granzyme B release *in vitro* following addition of autologous tumour cells to PBMC collected pre and post vaccines
- Flow cytometric charcterisation of IFNγ secreting cells
- Local skin reaction to sequential vaccinations

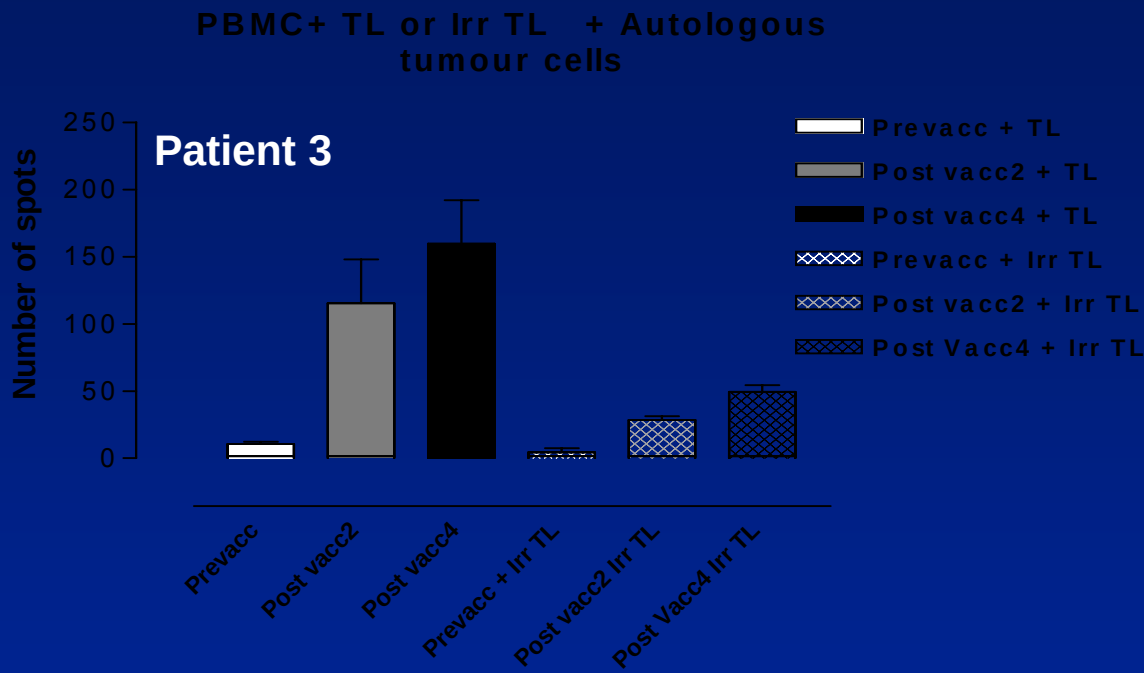
Secondary immunological endpoints

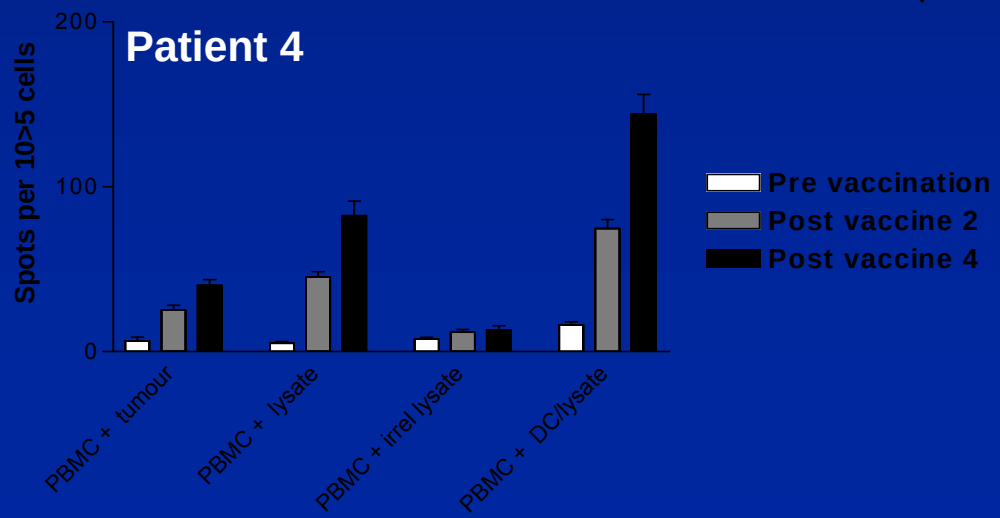
- Immunological environment of osteosarcoma (Treg, NK, NKT cells)
- Isolation of tumour reactive T cell clones for identification of target antigens

Early clinical trial data

IFN-γ ELISPOT







What are the clinical outcomes for immunotherapy?

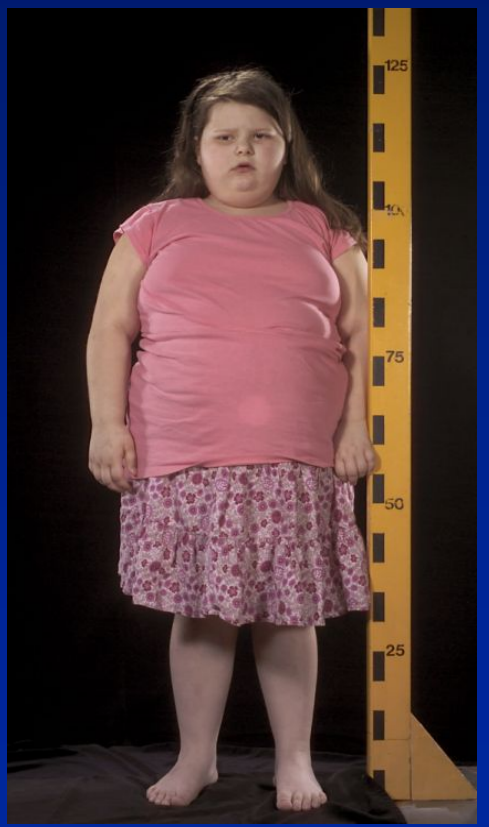
- Early increase in tumour size
- Signs of inflammation
- Later stabilisation and shrinkage of disease in some patients
- How do we define success? Immunology or clinical studies or survival?

Research that changes understanding of disease and therapy

- **Traditional outcomes:**
  - Treatment makes tumour smaller
  - Treatment prolongs life

A success of radical craniopharyngioma surgery?

- 8 years old
- Wt > 99th percentile
- Hyperphagia
- VA 6/60 bilaterally
- Hypothalmic and chiasmatic damage



GOS Experience 1973-94

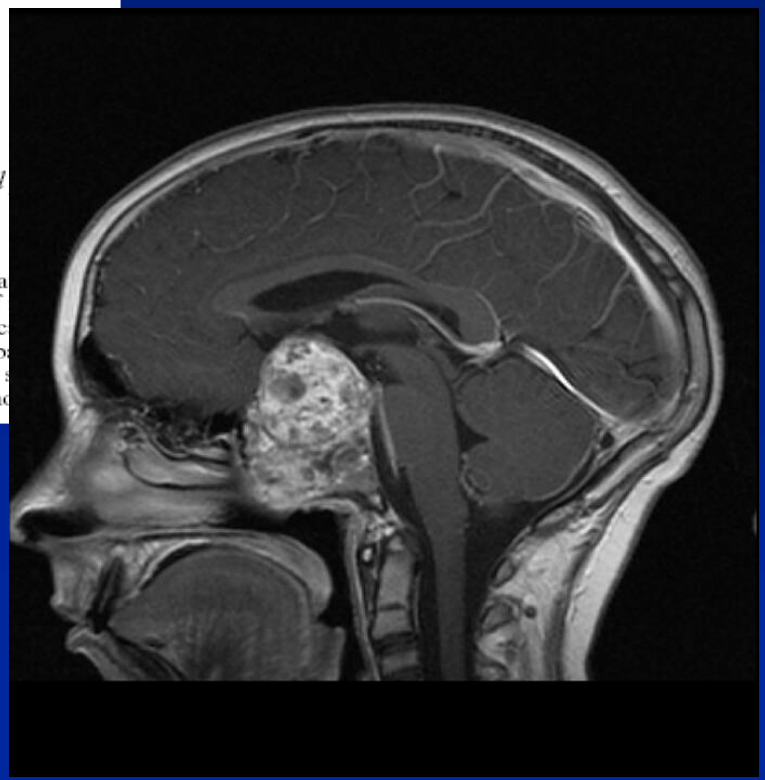
J Neurosurg 85:73–81, 1996

Management of childhood craniopharyngioma: can the morbidity of radical surgery be predicted?

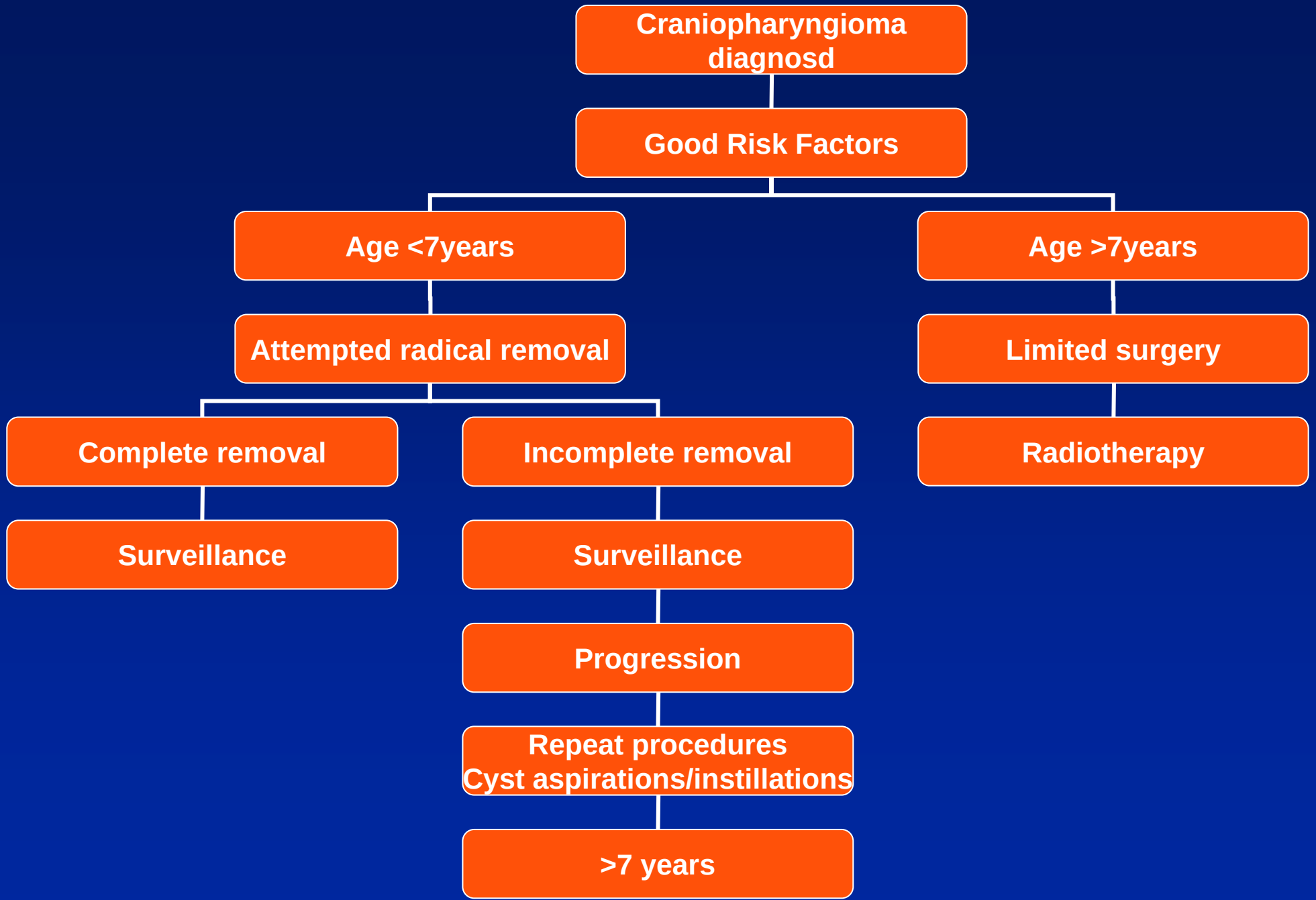
CATHERINE J. DE VILE, M.A., M.R.C.P., DAVID B. GRANT, M.D., F.R.C.P.,
BRIAN E. KENDALL, F.R.C.R., BRIAN G. R. NEVILLE, F.R.C.P.,
RICHARD STANHOPE, M.D., F.R.C.P., KATE E. WATKINS, M.A., M.SC.,
AND RICHARD D. HAYWARD, F.R.C.S.

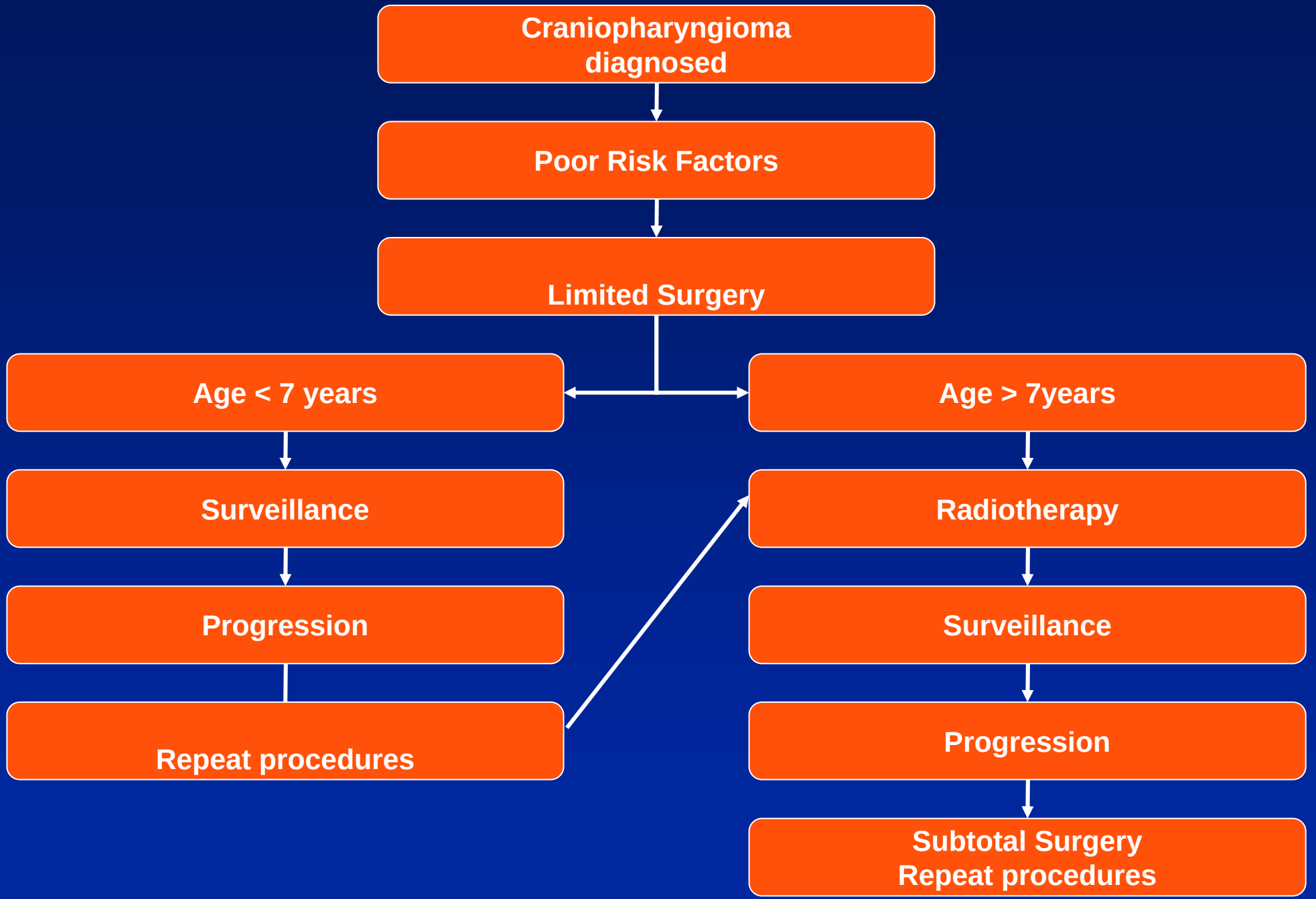
Medical and Neurosciences Units, Institute of Child Health, and Great Ormond Street Hospital Children National Health Service Trust, London, England

Seventy-five children treated for craniopharyngioma between 1973 and 1994 were studied to demonstra pre- and intraoperative factors were indicative of a poor outcome as defined by a quantitative assessment of ty. This involved a retrospective review of 65 patients and a prospective study of 10 patients focused on clinic and cranial imaging and a follow-up "study assessment" of 66 survivors performed over the last 2 years. As p assessment, 63 patients underwent magnetic resonance imaging with a three-dimensional volume acquisition 1.5 to 19.2 years after initial surgery. Predictors of high morbidity included severe hydrocephalus, intra



De Vile et al J Neurosurg 85: 73-81 1996


Craniopharyngioma diagnosd
Good Risk Factors
Age <7years
Age >7years
Attempted radical removal
Limited surgery
Complete removal
Incomplete removal
Radiotherapy
Surveillance
Surveillance
Progression
Repeat procedures
Cyst aspirations/instillations
>7 years


Craniopharyngioma diagnosed
Poor Risk Factors
Limited Surgery
Age < 7 years
Surveillance
Progression
Repeat procedures
Age > 7years
Radiotherapy
Surveillance
Progression
Subtotal Surgery
Repeat procedures

Late Effects and Quality of life

- Moving from descriptive, single institution studies to collaborative studies on homogeneously treated patients.
- Broad agreement on methodologies
- Translation and validation for national norms

QOL studies – challenges to accepted truths

- **Radiotherapy is always bad? – excellent results of conformal RT in ependymoma**

  (JCO 2004 22 3156)
- **Chemotherapy is always good? – neuropsychological late effects of HD salvage (SFOP), leukencephalopathy post IV and IT MTX (HIT), chemo group worse in PNET3**
- **Complete surgery always good? – increased awareness of incidence and severity of posterior fossa syndrome.**

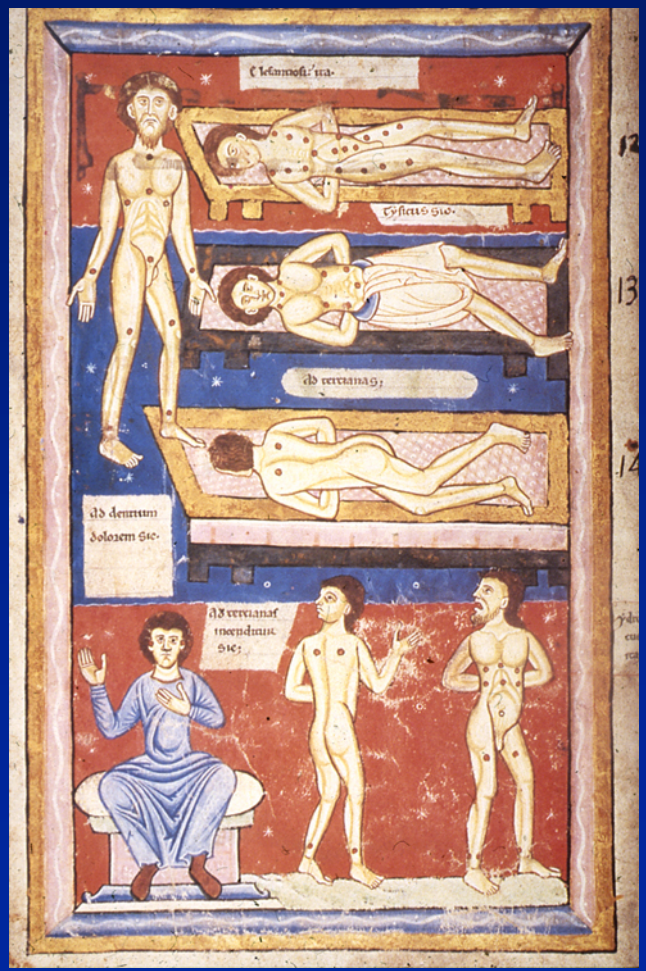
Late Effects studies - future

- So far studies parallel clinical study results
- How do we use results to alter therapy?
- Is there a metric for what % decrease in EFS we would accept for a given % better QOL outcome?
- Who decides this – medics, families, funders?

Palliative Care

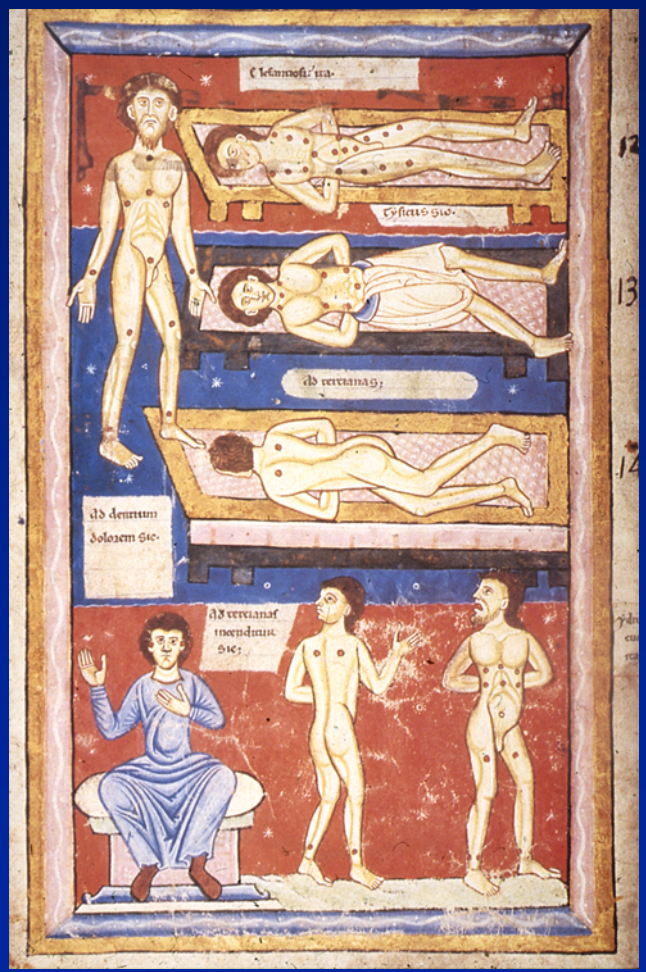
- >30% of children still die of their disease
- Move to palliative care ‘accepted’ part of journey
- What do we understand about what families want?

Great progress – but still loads to do



Great progress – but still loads to do

- Just because you have a protocol it doesn't mean you know what you are doing



Collaborative trials are key

He started fetching the occasional stick and built up the business from there.'

Thanks

- Dr Lannering for invitation
- Drs Clark, Saunders, Anderson, Mr Thompson for slides and data
- You all for your attention