Translating MRS into clinical benefit for children with brain tumours

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Childhood Cancer – The Facts

• Cancer is the most common cause of death from disease in childhood

• Brain tumours are
  – the most common solid tumours in children
  – the most common cause of cancer death in children

• 50 years ago 10% of children with cancer survived now more than 80% survive

• Improvements have not been so good in brain tumours
MRI and its limitations

Key component of the care for children with solid cancers

Exquisite structural detail

BUT:

• Is it a tumour?
• If so what type?
• Is it aggressive?
• Will it respond to treatment?
Harry’s Story

Presented 8 years old, visual problems

Biopsy 1/1,000 of the tumour

Chemotherapy – failed
Radiotherapy - stable

4 years later tumour reactivated, intratumoural bleed

“The complete doctor”
Non-invasive diagnosis

10 hospitals from 7 countries
98% accuracy in determining the diagnosis,
100% accuracy for broad tumour categories

“This study is the proof that MRS is useful and comparable even in a multicenter and multimodal setting in children.”

Vincente et al. EJC, 2013
Prospective Evaluation

- Accuracy ~ 91% (vs 93% predicted)
- 3/33 incorrect:
  2 anaplastic ependymomas
  1 medulloblastoma with very unusual features
- Some cases classified correctly but with low confidence estimate
But can’t we diagnose them with MRI?

- **Medulloblastoma**
- **Pilocytic Astrocytoma**
- **Ependymoma**

Different morphological appearances but significant overlap
Establishing improved diagnostic accuracy
How do we use it? Added value and application in a clinical environment

Radiologist evaluation

Wilson and Reynolds
Prognostic Biomarkers

MRS at diagnosis in 155 children with brain tumours

Kaplan-Meier curves

A. Lipids (prior hypothesis)
B. Glutamine
C. N Acetyl Aspartate
D. Scylloinositol

Significant in Cox regression and likelihood ratio tests.
Objective: incorporation into international clinical trials

Wilson et al. EJC, 2013
High Citrate indicates poor prognosis in diffuse astrocytomas
Glutamate as a biomarker of poor prognosis in medulloblastoma

Subtle changes in vivo – need high quality signal processing

Tumour Heterogeneity and spectroscopic imaging

Thalamic diffuse astrocytoma

mIns – low grade

Cho – high grade

Peet Nature Reviews 2012
Distinguishing relapse from pseudo-progression

MRS at diagnosis very similar to that at relapse even when relapse is at a distant site

Enhancing lesion post treatment uncertain on MRI if relapse but MRS very different to diagnosis

Gill et al Neuro-oncology 2013
State of the art facilities for paediatric research embedded in the NHS
An Eye to the future
Functional Imaging combine rather than compete:

Metabolite profiles

Quantitative imaging

Investigating children’s cancer using functional imaging

Diffusion imaging

Metabolite maps

Perfusion

Tractography

Poppy’s Story

Diagnosed as an infant

Surgery 4 times
Chemotherapy multiple courses
Radiotherapy

50 MRI scans - each decision is made on a complex set of information

10 years later
Conclusions

• New imaging methods can greatly enhance the management of patients

• Physics and engineering advances are required in many areas to enable their translation to clinical practice

• Collaboration between fundamental scientists, clinical scientists and clinicians is required in the translation.
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• The children and families who have supported and contributed to the research
• Harry and Poppy’s families.
In vivo clinical studies in adults with brain tumours

Single Centre – Pruel, Nature Medicine 1996
Multi centre – INTERPRET, Tate MRM 2003
Diagnosing Childhood Brain Tumours MRS Classifier Development

- Cerebellar tumours with pre-treatment MRS at 1.5T
- N=34 (after QC)
- 12 PA, 18 MB, 4 EP on histopathology
- Spectral fitting: LCModel
- PCA ⇒ LDA
- Cross-validation
- Accuracy ~ 93%

Davies et al, NMR in Biomed 2008