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# Magnetic resonance spectroscopy metabolite profiles predict survival in paediatric brain tumours

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**Abstract** ***Background:*** Brain tumours cause the highest mortality and morbidity rate of all childhood tumour groups and new methods are required to improve clinical management. $^{1}$H magnetic resonance spectroscopy (MRS) allows non-invasive concentration measurements of small molecules present in tumour tissue, providing clinically useful imaging biomarkers. The primary aim of this study was to investigate whether MRS detectable molecules can predict the survival of paediatric brain tumour patients.

***Patients and methods:*** Short echo time (30 ms) single voxel $^{1}$H MRS was performed on children attending Birmingham Children's Hospital with a suspected brain tumour and 115 patients were included in the survival analysis. Patients were followed-up for a median period of 35 months and Cox-Regression was used to establish the prognostic value of individual MRS detectable molecules. A multivariate model of survival was also investigated to improve prognostic power.

***Results:*** Lipids and scyllo-inositol predicted poor survival whilst glutamine and N-acetyl aspartate predicted improved survival ($p < 0.05$). A multivariate model of survival based on

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three MRS biomarkers predicted survival with a similar accuracy to histologic grading ($p < 5e–5$). A negative correlation between lipids and glutamine was found, suggesting a functional link between these molecules.

***Conclusions:*** MRS detectable biomolecules have been identified that predict survival of paediatric brain tumour patients across a range of tumour types. The evaluation of these biomarkers in large prospective studies of specific tumour types should be undertaken. The correlation between lipids and glutamine provides new insight into paediatric brain tumour metabolism that may present novel targets for therapy.



## 1. Introduction

Of the solid tumours typically occurring in childhood, brain tumours are the most common and have the highest mortality rate.[1] Surgery, chemotherapy and radiotherapy are commonly used in isolation or combination to treat these tumours but advances in clinical management are required to improve survival rates and reduce long-term morbidity such as effects on cognitive development.[2,3]

Diagnosis remains the most important determinant of treatment and whilst this is available from a major surgical resection in many cases, in others, a diagnosis is made from a small biopsy or on clinical and imaging appearances alone. Molecular tests on the tumour tissue are providing new prognostic markers[4,5] and these are starting to be incorporated into clinical management strategies. Novel non-invasive biomarkers would add to this improved tumour characterisation and would have the advantage of being available for cases where surgery was not performed.

$^{1}$H magnetic resonance spectroscopy (MRS) is a non-invasive technique that measures the concentration of variety of biomolecules from a volume of interest.[6] The technique is widely available clinically and easily appended to a standard magnetic resonance imaging (MRI) examination, which is routinely performed at diagnosis on children with brain tumours. The two main MRS protocol choices are duration of echo time and single versus multi voxel acquisition. Short echo time MRS is the most suitable investigation for detecting the maximum amount of metabolite information, provided suitable analysis methods are used.[7,8] Single voxel MRS is generally preferred over multi-voxel spectroscopic imaging where disease is localised since it generally provides better quality data at shorter echo times for metabolite quantification.[9]

Abnormal metabolism in tumours has been recognised for many years[10] and this area of research continues to provide new insight into tumour biology.[11] MRS is a powerful method for the detection of tumour metabolism *in-vivo* and metabolic profiles have been shown to characterise brain tumours non-invasively.[12,13] Classification methods based on MRS profiles have also been shown to be effective in both adult[14] and childhood brain tumours[15] providing information on tumour characterisation useful for clinical management. High-resolution *in-vitro* MRS analysis of tumours has also identified a number of potentially useful metabolites that may be detectable on future clinical MR platforms.[16,17]

In addition to metabolites, MRS is effective at measuring the level of mobile lipids (MLs),[18] which are often present at high levels in brain tumour tissue. A number of studies have shown a significant correlation between the level of MRS detectable lipids and tumour grade in adult gliomas[19–21] and similar findings have been found in a more limited number of studies in childhood brain tumours.[22]

The primary aim of this study was to determine whether metabolite levels measured by MRS are able to predict the survival of paediatric brain tumour patients in a clinical setting. Single voxel, short echo time MRS was used to ensure quantification of both small molecular weight species and MR detectable lipids.

## 2. Patients and methods

### 2.1. Patients

All patients undergoing MR imaging at Birmingham Children's Hospital as part of their clinical investigations for a suspected brain tumour were eligible to be enroled on this study. The accrual period was between September 2003 and July 2009 and patients were followed up until January 2010. Dates of death and progression were determined from the West Midlands tumour registry database and clinical records. Histopathologic, clinical and radiological features, as available, were used to form a diagnosis and reviewed by a multidisciplinary team. All graded tumours were biopsy proven. Ungraded tumours were either unbiopsied or biopsied and found to have a WHO diagnosis with no associated grade. Approval was obtained from the research ethics committee and informed consent given by parents/guardians.

### 2.2. MRI/MRS

MRI and MRS were carried out, prior to the patient receiving treatment, on a 1.5 T Siemens Symphony