Advanced MRI techniques in the evaluation of Low-Grade Gliomas – Summary of Research Findings November 2008

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(The information contained in this summary is research data only. The author should not be approached for advice on individual cases.)

This summary complements a lecture given at the recent Low-Grade Glioma Information Day held at the Royal Free Hospital on November 21st 2008.

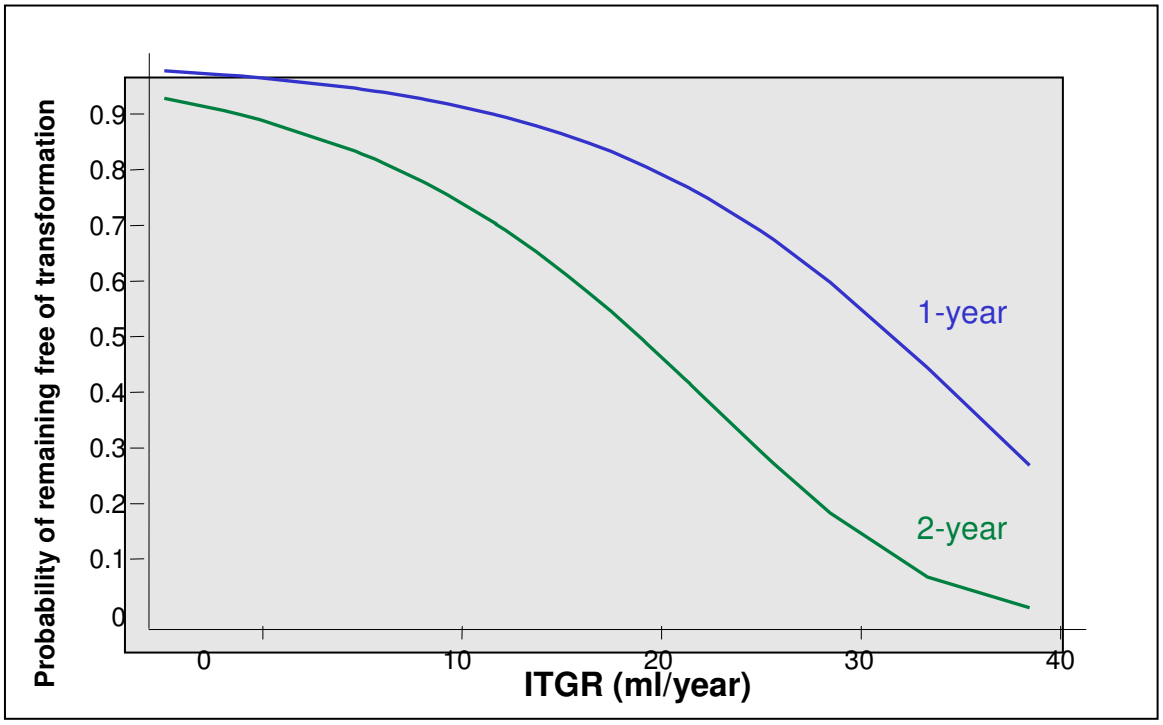
Results of research project investigating advanced MRI techniques in the evaluation of adult low-grade glioma (sponsored by the Samantha Dickson Research Trust)

In all 75 patients have been recruited, 63 of whom were eligible for long term study. Unfortunately all but 23 patients have transformed and have required further surgery, radiotherapy or chemotherapy. Because of the active surveillance protocol, we were picking up transformation before the majority of patients developed neurological problems, which we feel is beneficial for all the patients in the study. The long-term benefit of such a proactive approach is unknown but 14 out of 18 transformers who had been studied for at least one year before transformation are still alive and well. The majority of patients whose tumours have transformed are still alive, some up to six years after transformation.

Results

Tumour volume measurements in 27 patients showed that even so called 'stable' tumours were growing steadily at around 13%/year while tumours that eventually transformed grew even faster at 26%/year and then at 56%/year just before transformation occurred. This work has been accepted for publication in the *European Journal of Radiology*. Because of the highly significant differences in growth rates between the non-transformers and the transformers, we have now extended this work to examine the relationship between 'Initial Tumour Growth Rate' (ITGR) i.e. the absolute growth rate in ml/year measured over the first six months of scanning and the

subsequent probability of 'Transformation-Free Survival'. We have shown that ITGR is a highly significant independent predictor of early transformation and will give us a 'head start' on the tumour so we can advise the patient up to two years beforehand what their individual probability is of transformation. These data can be summarized in the following graph which shows that given an absolute Initial Tumour Growth Rate, the probability of remaining free of Transformation one or two years later can be predicted with reasonable accuracy.



We have developed the use of histogram analysis which allows different parameters from the whole tumour to be plotted in graphical format and which permits comparison between patients and between studies from the same patient across time. This powerful methodology has been applied to our diffusion-weighted imaging, perfusion imaging and permeability data. We have now published two papers incorporating histogram analysis showing that it is possible to distinguish between astrocytoma and oligodendrogliomas on the basis of ADC (Apparent Diffusion Coefficient) measurements (1) and to predict early transformation on the basis of 'subtle' gadolinium enhancement through analysis of post-contrast images (2).

We have also completed our Perfusion analysis and have shown that relative Cerebral Blood Volume (rCBV) maps predict progression by as much as twelve to eighteen months (3). We believe that this technique will probably turn out to be the most useful method of monitoring low-grade gliomas (See Figure below). We have collaborated with doctors at Mount Sinai Hospital in New York, and grouped our perfusion data to bolster the datasets. These data have now been accepted for publication in *European Journal of Radiology*.

Finally we have demonstrated that when these two main techniques are compared, tumour growth rate is even better than perfusion in predicting malignant transformation. These data have also been accepted for publication by *Radiology*.

Further research

We have now closed the MRI study to recruitment. Nevertheless the interest that this study has generated has resulted in more patients with LGG being referred and we are developing a neurosurgical research programme with preoperative fMRI and intraoperative cortical stimulation during awake craniotomy for suitable patients. We are hoping to implement some of these research protocols into the clinical sequences that LGG patients should be having. The analysis however is time-consuming and additional resources are required which do not have NHS funding at present.

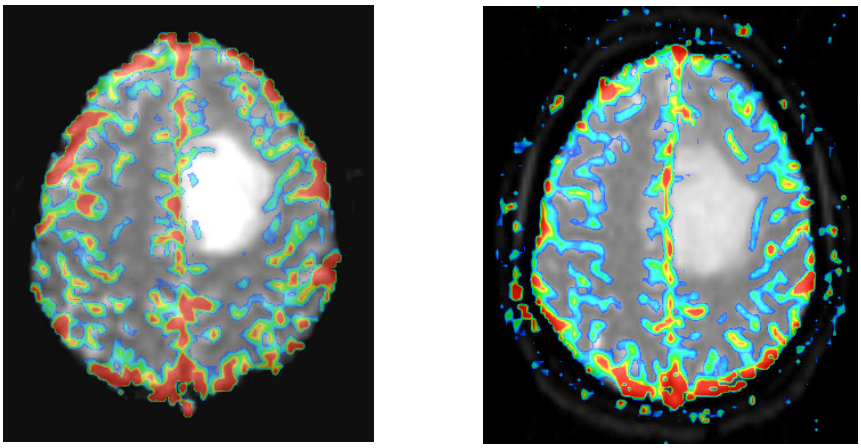
We are also in preliminary discussions with a large pharmaceutical company to set up a Phase II study of an oral anti-angiogenesis agent to be used in patients with LGG who are deemed to be at 'high risk' of malignant transformation by virtue of their growth rates. This study will recruit patients from three centres in London (NHNN/UCH, Royal Free Hospital and Royal Marsden Hospital.)

We are beginning to examine the genetic correlates of our tumour samples from patients recruited into the LGG study, thanks to a further grant from the SDBTT Astro fund, in collaboration with Dr Tracy Warr, Department of Molecular Neuro-oncology, Institute of Neurology UCL.

Perfusion Maps

Non-transformer

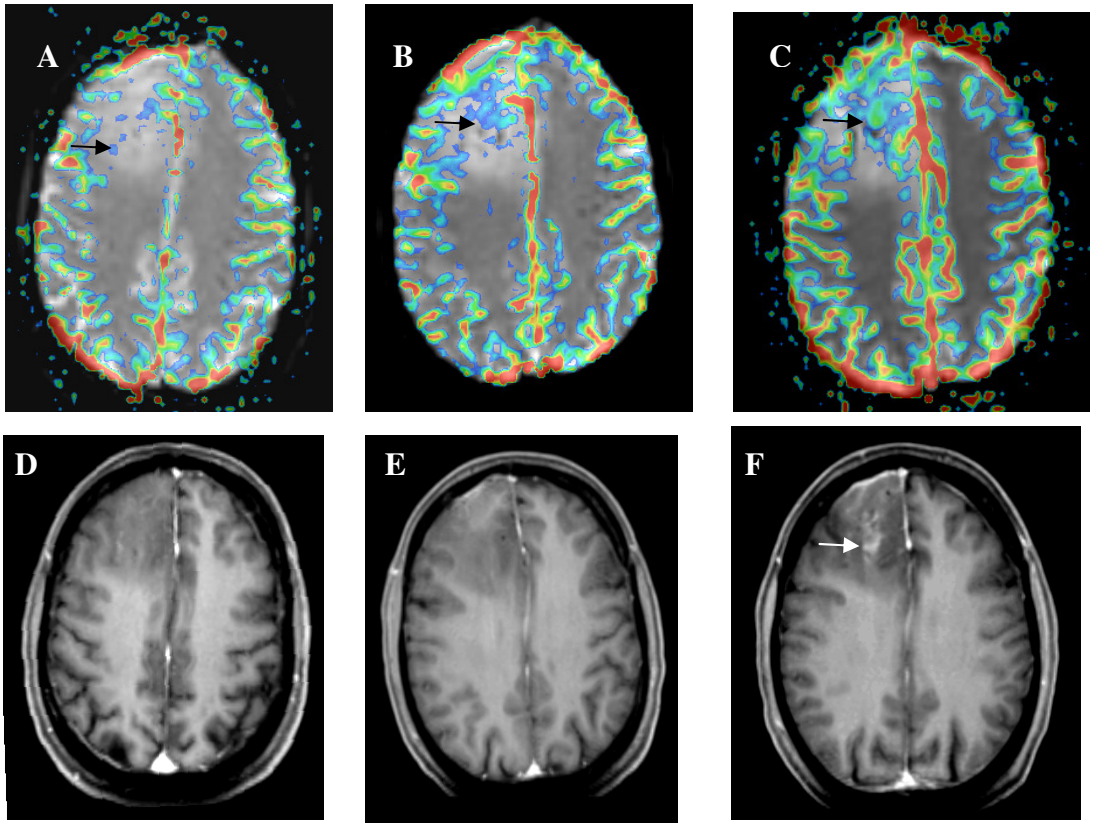
Serial MR perfusion study in a 29-year-old patient with a left frontal low-grade astrocytoma which did not undergo malignant transformation during an observation period of 30 months. The rCBV color overlay maps (using the more T2- weighted first image of the perfusion series as background) are windowed to show areas with a greater rCBV than white matter. *A*, The rCBV map at study entry shows a tumor of a low rCBV, with a maximum measured rCBV of 0.76. *B*, after 30 months there has been some increase in tumor volume but the maximum rCBV remains low (0.96).



Transformer

Serial MR perfusion studies with CBV overlay images (*A*-*C*) and axial reformatted images of a double dose contrast-enhanced volumetric T1-weighted sequences (*D*-*F*) in a 30-year-old patient with an oligodendroglioma who showed progression to a high grade tumor 18 months after study entry. *A*, the rCBV map at baseline shows a small area of elevated rCBV (black arrow) measuring up to 4.52. *B*, rCBV map six months before transformation shows a lager area of increased rCBV (black arrow) measuring up to 8.32. *C*, rCBV map at transformation shows a further increase of area with an elevated rCBV (black arrow) which now reaches maximum values of 12.04. *D*, the baseline contrast-

enhanced T1 weighted images shows a hypointense tumor without pathological enhancement. *E*, six months before transformation there is no evidence of pathological intratumoral enhancement despite a significantly increased rCBV. *F*, at transformation there is irregular enhancement in the centre of the tumor (white arrow), the area of pathological enhancement being much smaller than the region of increased rCBV.



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