

Areas of necrosis can act as a confounding factor in the functional diffusion map (fDM)

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Introduction: The functional diffusion map (fDM), also known as the parametric response map, has been suggested as a tool for early detection of tumour treatment efficacy [1-3]. In the fDM, a voxel by voxel comparison of pre-treatment and post-treatment apparent diffusion coefficient (ADC) maps is carried out in the tumour areas. An increase in ADC is said to reflect a decrease in tumour cellularity and is associated with a good treatment response. A decrease in ADC is said to reflect an increase in tumour cellularity and hence implies a poor prognosis. Although a lot of work has been devoted to developing this technique, to our knowledge the behaviour of the fDM in necrotic regions of tumour has yet to be examined. Through showing the biological processes involved in the fDM, Moffat et al. [1] have briefly mentioned that necrotic or cystic regions can undergo a displacement of water resulting in a reduction in ADC as cells move into the area. In theory necrotic areas of a tumour can increase in size both as a result of successful treatment (as cells are killed, tumour regions are replaced by areas of necrosis), and also as a result of tumour growth (causing increased hypoxic regions and hence necrosis). Conversely, a reduction in size of necrotic regions can be either due to successful treatment (reduction in tumour size), and also due to an increase in tumour growth through angiogenesis (making the tumour more vascular and hence more cellular in areas which would have otherwise been necrotic). Our hypothesis is that changes in ADC in necrotic regions of tumour do not discriminate between successful and unsuccessful treatment. Due to the already high ADC value in necrotic regions, the fDM is expected to show either no change or a decrease in ADC in most voxels of these areas. We aim to analyse how the fDM is affected by areas of necrosis.

Methods: 11 patients (6 male, 5 female, aged 8.2 to 12.8 years, mean 9.6 years) with brainstem tumours (4 low grade astrocytomas, 4 diffuse intrinsic pontine gliomas, 1 glioblastoma, 2 unconfirmed gliomas) and who had diffusion-weighted imaging (DWI) as part of their clinical imaging, were enrolled in a retrospective study that examined the fDM in areas of necrosis. Necrotic regions were determined by analysing pre-treatment imaging data and identifying areas in the tumour which had an ADC value above $2.0 \times 10^{-3} \text{mm}^2 \text{s}^{-1}$. The fDM, implemented in Matlab (MathWorks), was used to compare baseline pre-treatment ADC maps with ADC maps obtained between 2 and 7 months post-treatment and was constructed as described in [3], performing a voxel by voxel analysis and allowing a threshold for the change in ADC of $0.4 \times 10^{-3} \text{mm}^2 \text{s}^{-1}$. The whole tumour was analysed over all slices by applying a mask onto the T2-weighted baseline images to which all other ADC maps were co-registered using the SPM software package. The percentage area with increased, no change, and decreased ADC between baseline and follow-up imaging was calculated in order to identify any trend between these and survival.

Results: Results show that the major change in ADC for the necrotic areas was a decrease in ADC in 9 cases (5 of whom died) and no change in 2 cases (1 of whom died). The graph in Fig 1 shows the results for all 11 cases. In this cohort, no major difference was apparent between those patients who survived (1-6) and those who died (7-11) and no statistically significant linear correlation was observed between the percentage changes in ADC and survival in days ($p=0.87$, 0.6 and 0.69 for the decrease, no change and increase in ADC respectively).

Discussion: As expected, in 9/11 cases the major change over the whole tumour necrotic area was a decrease in ADC. In applying the fDM to the whole tumour, this decrease in ADC in areas of necrosis is expected to pull down the global results by showing more areas as having a decreased ADC, and hence a worse prognosis. Our results have however shown that in areas of necrosis, a decrease in ADC is not necessarily associated with a lower chance of survival. Inclusion of necrotic regions could therefore confound fDM findings. Although this result was obtained in a small cohort and a specific tumour location, it raises the question of whether areas of necrosis should be excluded in constructing and analysing the fDM. Further analyses are warranted in order to study in more detail what information areas of necrosis can provide and what considerations need to be taken into account in constructing and analysing whole tumour fDMs.

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References [1] Moffat BA et al., PNAS. 2005. [2] Hamstra DA et al., PNAS. 2005. [3] Ellingson BM et al., J Magn Reson Imaging. 2010.

