Quantifying the proportion of enhancement in relation to IAUC thresholds; a comparison with other measures of enhancement in adult gliomas.

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Background: A number of groups have attempted to quantify contrast enhancement in glioma by evaluating the signal intensity in relation to contra-lateral normal appearing white matter on a combination of pre and post contrast T_1-weighted imaging [1, 2]. Although these methods are relatively simple to apply, they have a major disadvantage in their reliance upon signal intensity, which can be unreliable and has poor reproducibility [3]. Dynamic contrast enhanced MRI (DCE-MRI) allows quantification of the concentration of contrast agent over a period of time. The initial area under the concentration curve (*IAUC*) is considered to be a reliable and reproducible measure [4] and gives a quantification of the amount of contrast agent passing through tissue. An assessment of the proportion of a tumour considered to enhance can be made by measuring the proportion of voxels in a given tumour with a measurable *IAUC* (and therefore considered to be enhancing). This measure of enhancing fraction does not quantify the amount of enhancement occurring within a tumour, just whether it is present or absent. To provide some quantification of the degree of enhancement, applying different thresholds values of *IAUC* above which a voxel is considered to be enhancing may be of value. The aim of this study was to examine how enhancing fraction varies in relation to different thresholds of *IAUC* in gliomas of various grade and to compare these measures with other previously described methods for assessing enhancement based upon signal intensity.

Methods: 32 patients with glioma (11 grade II, 2 grade III, &19 grade IV) were imaged on a 3.0T Philips Achieva MR scanner (Philips Medical Systems, Best, NL), prior to surgery. Imaging included T_1W DCE-MRI and anatomical sequences. Tumour volumes of interest (VOIs) were defined on the anatomical images. The DCE-MRI protocol consisted of a baseline T_1 measurement using a variable flip angle 3D T_1-Fast Field Echo (T_1-FFE – RF-spoiled gradient echo) approach, followed by 3D T_1-FFE volumes acquired every 3.4 seconds. A 3ml bolus of gadolinium-based contrast agent was injected after the 5th image volume acquisition at a dose of 0.1mmol/kg of body weight and a rate of 15mls^{-1}.Voxels within a tumour were identified as enhancing if a measure of the initial area under the contrast agent concentration curve ($IAUC_{60}$ - the *IAUC* 60 seconds following the initial bolus of contrast injection) was greater than a specified threshold. Enhancing fraction was calculated for different threshold values of $IAUC_{60}$. An initial analysis on a dataset of 5 grade II and 10 grade IV gliomas was performed to identify the optimum $IAUC_{60}$ threshold for distinguishing between grade II and grade IV gliomas (Fig. 1). Mean curves were generated for the grade II and grade IV gliomas and the maximum difference between the two curves indicated the optimum threshold of $IAUC_{60}$ (2.5 mMol.s). For each tumour the following were calculated; enhancing fraction for $IAUC_{60}$>0mMol.s ($EF_{IAUC60>0}$), enhancing fraction for $IAUC_{60}$ at optimum threshold of $IAUC_{60}$=2.5mMol.s ($EF_{IAUC60>2.5}$), the average gradient (slope) of the thresholded enhancing fraction curve between $IAUC_{60}$=0mMol.s and the optimum threshold of $IAUC_{60}$(=2.5mMol.s) (Fig. 1), median $IAUC_{60}$ and measures of enhancement based on signal intensity using previously described methods [1, 2].

Results: The thresholded enhancing fraction curves demonstrated clear differences between grade II and IV gliomas (Fig. 1). The following variables all discriminated between grade II and IV tumours; slope ($p<0.0001$), enhancing $fraction_{IAUC60>2.5}$ ($p<0.0001$), median $IAUC_{60}$ ($p<0.0001$), and both signal intensity based measures of enhancement (Pronin's, $p<0.0001$ and Tofts %E, $p=0.009$). However, all, apart from slope, showed some overlap between the groups (Figure 2). $enhancing\ fraction_{IAUC60>0}$ did not distinguish between histological grade ($p=0.960$) (Figure 2).

Discussion: We have shown that by optimising the $IAUC_{60}$ threshold used in calculating enhancing fraction provides better discrimination of tumour grade than an enhancing fraction founded on $IAUC_{60}$>0. In addition, we have described a new measure determined by the initial slope of a thresholded enhancing fraction curve. This provides good discrimination between grade II and IV gliomas with no overlap. Insufficient numbers of grade III gliomas were present in this study for formal analysis, though there was a tendency for measured enhancement variables of the grade III tumours to lie amongst those of grade II gliomas. Further analysis with greater numbers is required to evaluate this group of patients. A previous group has shown signal intensity based measures to be sensitive in early prediction of malignant transformation in low grade tumours [2]. Given our measure of slope is based upon the $IAUC_{60}$ and, therefore, is likely to be reliable and reproducible, this may prove to be a more robust measure for identifying tumour dedifferentiation.

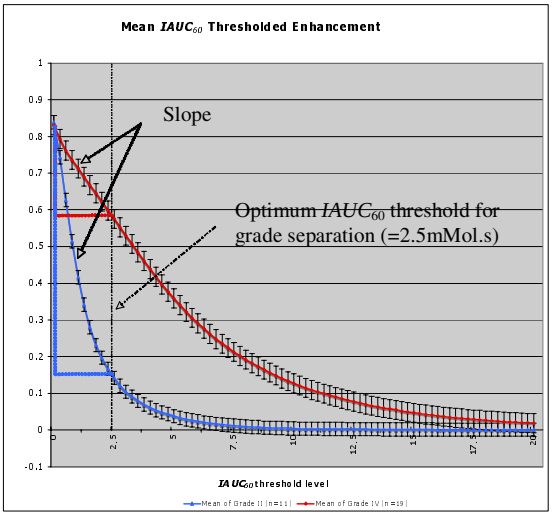

Figure 1. Mean curves of calculated enhancing fraction for different $IAUC_{60}$ thresholds. The black dashed line represents the optimum $IAUC_{60}$ threshold ($IAUC_{60}$=2.5mMol.s) defined on an initial dataset of grade II (n=5) & grade IV gliomas (n=10). The curves clearly demonstrate differences in the average gradient of the initial curve (slope) for grade II (blue, n=11) and grade IV (red, n=19) glioma.

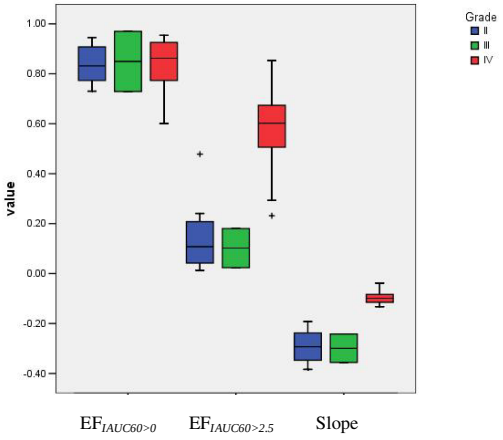

Figure 2. Clustered Boxplots of calculated enhancing fraction for different thresholds of $IAUC_{60}$ - $IAUC_{60}$>0mMol.s ($EF_{IAUC60>0}$) and $IAUC_{60}$>2.5mMol.s ($EF_{IAUC60>2.5}$) – and the initial average gradient of the threshold enhancement curve (Slope) for different grades of tumour. Grade II (blue, n=11), grade III (green, n=2) and grade IV (red, n=19).

References:

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