Assessing Changes in Tumor Vascular Function Using DCE-MRI: A Tale of Two Analysis Algorithms

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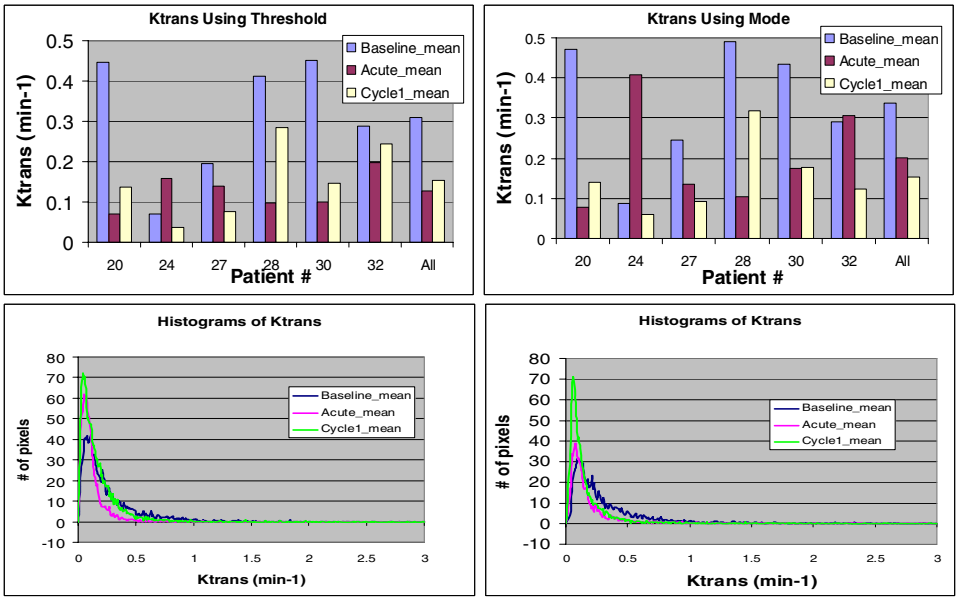
Background: Contemporary progress in our conception of the cancer genome, and the control of molecular processes significant to the growth and regulation of cancer cells, are leading to the identification of several innovative targets for cancer therapeutics [(1)]. Tumor vasculature represents one such critical target with agents directed against neoangiogenesis [(2)] and the vascular endothelium [(3)]. The enhanced specificity of these classes of drugs, however, emphasizes the necessity of surrogate end-points offering indirect evidence of desired biological activity. Quantitative dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) has shown considerable potential for monitoring the effect of these medications on tumor microvasculature [(4, 5)]. However, user-defined, whole tumor regions of interest (ROIs) are unable to evaluate tumor heterogeneity [(6)] in malignant lesions and thus may be insensitive to drug action. We consequently sought to compare two threshold-based, whole tumor ROI analysis algorithms based on ipsilateral, pre-contrast baseline signal intensity (tumor heterogeneity unaccounted), and contralateral, pre-contrast mode-based signal intensity (tumor heterogeneity accounted), respectively, with regard to the resulting endothelial transfer constant (K^{trans}) measures obtained from two-compartment pharmacokinetic modeling**.**

Materials & Methods: This preliminary analysis was performed on DCE-MRI datasets obtained from six subjects (2 males + 4 females) with histopathologically proven glioblastoma multiforme. They were participants in an open-label, Phase I, dose escalation study of an orally administered (1500 mg, once daily continuous) receptor tyrosine kinase inhibitor. Scans were performed (1.5T GE LX EchoSpeed, GE Healthcare, Waukesha, WI) at baseline, 24-48 hours post-first dose, and at one month. Before, during, and following bolus administration of 0.1 mmol / kg Gd-DTPA, axial T_1-weighted images were acquired using a custom 2D multiphase FSE sequence (TR / TE = 400 / 14 ms; ETL = 4; 256 x 128 matrix; 22 cm x 16 cm FOV; 5 mm section; 1.5 mm gap; 25 phases; 5:01 min). Prior to the acquisition of the DCE-MRI data, T1 mapping was performed using variable TRs (3500, 2000, 1500, 1000, 750, 500, & 250ms). Between the scans at three different time-points in each subject, there were no other therapeutic interventions that could have potentially altered the quantitative measures of vascular permeability. A generalized kinetic model [(7)] was implemented in the Functool environment (GE Healthcare, Waukesha, WI) to quantitatively analyze the DCE-MRI data. The arterial input function was obtained by manually drawing an ROI in the superior sagittal sinus. A second ROI was drawn to encompass the entire tumor. The endothelial transfer constant (K^{trans}) was calculated on a pixel-by-pixel basis. To exclude the necrotic unenhancing area within the whole tumor ROI, two thresholding approaches were utilized. While the first method used the pre-contrast, averaged baseline signal intensity of the whole tumor ROI, the second one used the 120% percentile mode value of pre-contrast signal intensity obtained from an essentially identical location in the contralateral hemisphere. The histogram of the K^{trans} distribution of the whole tumor in each patient at each different time point was generated for each method. The mean K^{trans} of the tumor was also calculated**.**

Results:



Per patient and average K^{trans} values indicating an acute decrease followed by a rebound when using the baseline signal intensity of the whole tumor ROI as the threshold (left top) in contrast to a consistent decreasing response noted using the 120% mode-based signal intensity threshold (right top).

Histograms of K^{trans} distribution using the baseline signal intensity of the whole tumor ROI (left bottom) and the 120% mode-based signal intensity threshold (right bottom) suggest differential therapeutic efficacy post-drug administration.

Discussion: Recent recommendations for the analysis of DCE-MRI data [(8)] suggest that the outer limit of the lesion should act as the boundary of the ROI to minimize partial volume effects, areas of necrosis should be excluded, and that the ROI should be constant in position and size for each image in the series under analysis. However, user-defined whole tumor ROIs while yielding graphic outputs with a good SNR, lack spatial resolution, are prone to partial volume averaging errors, and are thus unable to evaluate tumor heterogeneity. They may consequently not mirror small areas of rapid change and thus be insensitive to therapy. To negate the effect of these pitfalls, we used a pixel-by-pixel analysis technique in our study to evaluate the inhomogeneous vascular permeability of tumor and monitor its response to treatment. Two different thresholding techniques were utilized: ipsilateral, pre-contrast baseline signal intensity in comparison with a pre-contrast mode-based signal intensity derived from the unaffected contralateral hemisphere. Our data reinforce how critical thresholding criteria are to the evaluation of therapeutic response with different analysis algorithms and underscore once again the necessity to develop standardized analytical approaches for the measurement of parameters reflecting therapeutic respons**e.**

References: (1) Kohn EC et al: Seminars in Oncology; 31:39-53; 2004. (2) Bicknell R et al: Current Opinion in Oncology; 8:60-65; 1996. (3) Thorpe PE: Clinical Cancer Research; 10:415-427; 2004. (4) Morgan B et al: Journal of Clinical Oncology; 21:3955-3964; 2003. (5) Padhani AR: Journal of Magnetic Resonance Imaging; 16:407-422; 2002. (6) Parker, GJ et al: Journal of Magnetic Resonance Imaging; 7:564-574; 1997. (7) Tofts PS et al: Journal of Magnetic Resonance Imaging; 10(3):223-32; 1999. (8) Leach MO et al: British Journal of Cancer; 92:1599-1610; 2005.