Nonparametric kinetic analysis of DCE-MRI images taken from glioblastoma patients

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Objectives: Contrast agent kinetics, as measured by 5-minute dynamic contrast enhanced (DCE) MRI scans, are used to evaluate the effect of the anti-VEGF monoclonal antibody bevacizumab on tumor vasculature in glioblastoma patients. A one compartment tissue model [e.g., Tofts/extended Tofts (1)] is typically used to quantify contrast agent kinetics, however, a single tissue compartment does not adequately describe data from this study, necessitating the use of more complex kinetic models. Nonparametric (model independent) approaches are currently available, *e.g.* IAUC (2), but may result in loss of kinetic information. Here, our aim is to develop an automated, purely nonparametric method for analyzing DCE-MRI data that retains important kinetic information such as mean residence time and tumor dispersion effects without imposing a particular model structure upon the data, resulting in an analysis method that is objective and flexible. The need to conduct model discrimination for each new study processed would be bypassed, allowing for easier analysis of DCE-MRI data where imaging agents exhibit heterogeneous kinetics across patients.

Methods: 19 glioblastoma patients underwent treatment with bevacizumab plus irinotecan, each receiving two baseline DCE-MRI scans on different days and two scans subsequent to start of treatment. For a linear system, convolution is the process by which an input signal is combined appropriately with the system impulse response function (IRF), yielding the system response. In discrete time space, the convolution operation is written as: $y[n] = \sum_{k=-\infty}^{\infty} h[k]u[n-k]$, where y[n] is the system output (tumor time-activity curve) and u[n] and h[n] are the system input (plasma time-activity curve) and impulse response function (response of the system to Dirac's delta), respectively. Theoretically, for many useful systems the impulse response function can be retrieved via deconvolution if the system input and output are known. In matrix form, the discrete convolution operation can be written as: $\mathbf{U}\bar{h} = \bar{y}$, where **U** is an n×n triangular matrix based on the system input vector, *u(t)*; $\bar{y}$ is an n×1 vector composed of system response measurements, *y(t)*; and $\bar{h}$ is the n×1 IRF, *h(t)*. For this study, the venous input function, measured by drawing an ROI on the reconstructed image in the region corresponding to the sagittal superior sinus, is used as a surrogate for *u(t)*. Since **U** is a triangular matrix, $\bar{h}$ is easily computed by forward substitution. This operation is highly sensitive to noise in the data, so prior to computing $\bar{h}$ we smoothed the VIF and tumor data using a robust locally adaptive smoothing method (3), which captures the peak of the plasma curve (Fig. 1; top panel) and down-weights apparent outlier measurements (Fig. 1; center panel). The plasma portion of the tumor time-activity curve is subtracted using a nominal tissue plasma fraction of 1.5%. The statistical program R was used for data management, computation and plotting (4).

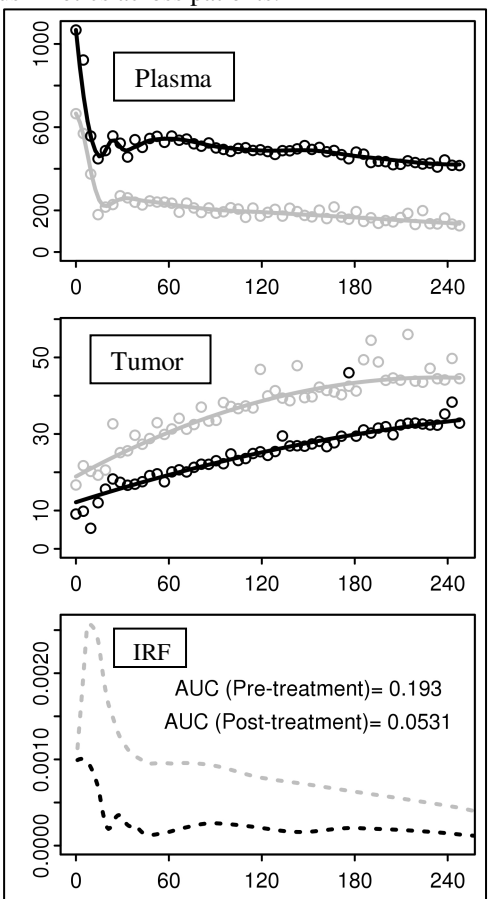

Figure 1. Plasma/tumor concentrations (top/center panels; μmol/L vs. sec) and impulse response function (bottom panel; unitless) 3 days before (grey) and 13 days after (black) start of treatment. Circles represent DCE-MRI data; Solid curves are smoothed DCE-MRI data used for the deconvolution operation.

Results: The IRF (Fig. 1; bottom panel) was successfully retrieved from all 76 (19 patients × 4 visits) scans and the area under the curve (AUC) of each IRF was calculated. Across all patients, IRF AUC decrease from baseline had a median value of 37% one day after start of treatment ($p = 0.0026$, Wilcoxon signed rank test) and a median decrease from baseline of 54% at the second follow-up scan ($p < 0.0001$). These results agree with our compartmental model based estimates of decrease in contrast agent uptake following treatment. Mean residence time (MRT) was also calculated for each IRF and was shown to be relatively constant across all visits for each patient ($p > 0.2$); pre- and post-treatment MRT is approximately 88 and 91 seconds for the patient shown in Figure 1 (bottom panel).

Conclusions: We have developed an automated nonparametric method of analyzing dynamic DCE-MRI data that retains kinetic information, thus providing a robust, model-free approach to evaluation of changes in contrast agent uptake subsequent to anti-tumor therapy. Importantly, the IRF removes the confounding factor of patient plasma concentration, thus facilitating a more accurate comparison of intra- and inter-patient tumor time-activity curves.

References: (1) Tofts, P. Modeling Tracer Kinetics in Dynamic Gd-DTPA MR Imaging. *J Magn Reson Imaging.* 1997;7:91-101. (2) Evelhoch, J. Key Factors in the Acquisition of Contrast Kinetic Data for Oncology. *J Magn Reson Imaging.* 1999;10:254-259. (3) Loader, C. *Local Regression and Likelihood.* Springer; 1999. (4) http://cran.r-project.org/