Incorporation of Explicit Arterial Input Function for DCE-MRI Quantification: Use in Human trial of Sorafenib in Renal Cell Carcinoma

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Background: Dynamic contrast-enhanced MRI (DCE-MRI) has been utilized as a means of assessing tumor microvasculature, and has been incorporated into human clinical trials of vascular-targeted therapies (1). Quantification of DCE-MRI tumor enhancement requires an arterial input function (AIF), in order to calculate the serum-tumor 1st order transfer constant, Ktrans(2). Often, a population-based AIF (3) is assumed. However, this model neglects the 1st pass effect of gadolinium bolus. We demonstrate a semi-automated method for deriving an empiric AIF from DCE-MRI images using an arterial region of interest, ROI and incorporate this function in a clinical trial of DCE-MRI for monitoring tumor therapy.

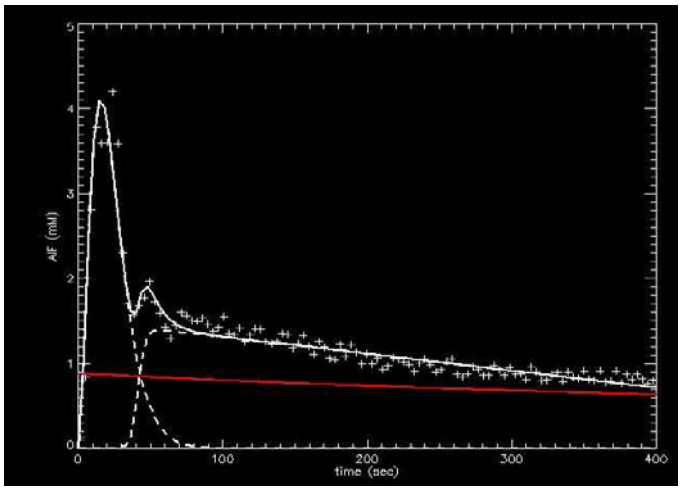

Figure 1: Arterial gadolinium vs. time curve, and resulting fitted AIF function. The comparison standard bi-exponential ("Weinmann") function is in red.

Methods: Seventeen patients with locally advanced or metastatic RCC were enrolled in a prospective study of the Raf kinase inhibitor Sorafenib (Bayer, Inc., Hartford, CT). DCE-MRI was performed prior to initiation of therapy, and between day 21 and 72 of therapy to assess for anti-vascular effects on tumors. DCE-MRI was performed on a 1.5T magnet (Symphony©, Siemens, Erlangen, Germany). The study was approved by the local IRB. Arterial ROIs were selected to generate an averaged arterial enhancement curve for each DCE-MRI exam. From these curves, an empiric AIF of the form AIF = G + L*W, where G is a gamma variate function, and L*W is a linear washout function modified by a logistic function was generated (Figure 1). This "explicit" AIF was then used as input for the two compartment model to derive whole tumor Ktrans values. Results were compared to those using the population standard ("Weinmann") function.

Results: Median Ktrans values pre-therapy were lower using the explicit AIF (0.93 min-1) than using the Weinmann AIF (1.31 min-1). Post-therapy changes were less pronounced between the two methods (0.44 and 0.47 min-1, respectively). The rank correlation of tumor Ktrans values between the two methods was significant pre-therapy (R=0.65, p=0.005), but not post-therapy R=0.43, p=0.11). Kaplan-Meir survival curves for time to progression were evaluated based on percent change in Ktrans post therapy either method. Using a cutoff of ΔKtrans <>30%, survival was significantly correlated with ΔKtrans using explicit AIF method, but not the standard AIF method (Figure 2).

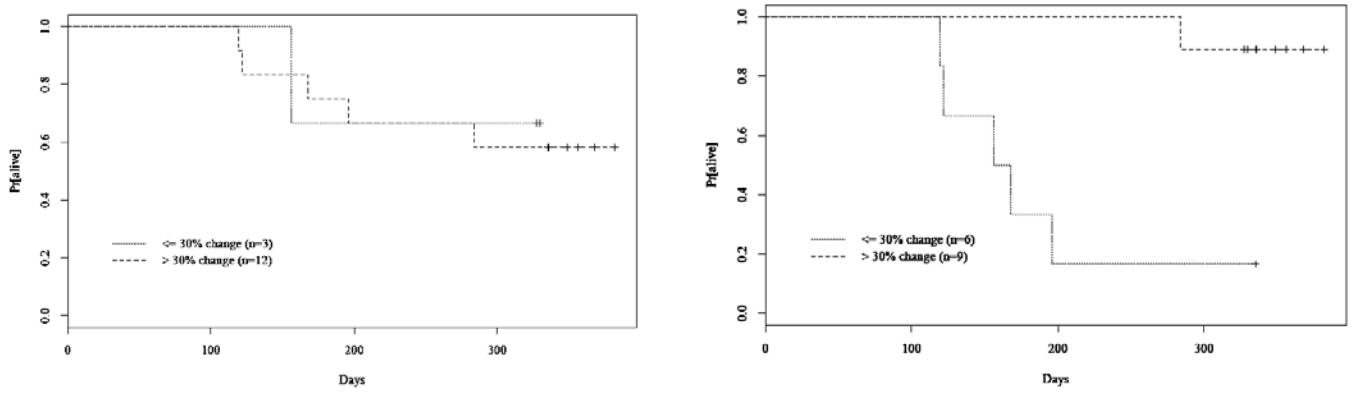

Figure 2: Kaplan-Meier curves (progression free survival) using the percent change in tumor Ktrans as derived with either a population based AIF (left) or the patient-explicit AIF (right). Progression is highly correlated with ΔKtrans using explicit AIF (p=0.025), but not population-based AIF (p=0.87).

Conclusion: Use of measured AIFs during DCE-MRI studies can dramatically alter the derived whole tumor Ktrans values. These values are more likely to be reflective of actual tumor vascular physiology. In a clinical trial of Sorafenib in advanced renal cell carcinoma, the incorporation of individualized AIFs alters the predictive value of percent change of tumor Ktrans for progression free survival.

References:

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