Effects of Arterial Input Function Determination on Pharmacokinetic Modeling of Osteosarcoma DCE MRI Data

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Introduction A unique aspect of pharmacokinetic modeling of dynamic contrast enhanced (DCE) MRI signal time course is the requirement for an arterial input function (AIF). The absolute accuracy of the pharmacokinetic parameters, K^{trans} (transfer rate constant) and v_e (interstitial fluid space volume fraction), depends on the AIF accuracy (1). The determination of the latter has been considered extensively (2). Recently, significant progress has been reported for the reference tissue method (3).

Using a semi-quantitative approach, we reported that the histogram amplitude of initial slope of DCE MRI signal time course correlates significantly with necrosis percentage of osteogenic and Ewing sarcoma, which is an important indicator of the effectiveness of chemotherapy (4). In determination of AIF for absolute quantitation of K^{trans} and v_e, however, it is often not possible to obtain reliable AIF in each individual osteosarcoma DCE MRI experiment, due to data acquisition constraints or lack of visible artery anatomically adjacent to the tumor. In a clinical environment, the contrast injection rate may not be consistent because of variations in location and size of IV catheters that are already in place before patients undergo DCE MRI. In this preliminary study, we sought to assess the feasibility of using an average AIF obtained from a limited population of osteosarcoma patients for kinetic modeling of DCE MRI data of a larger population, as well as the effects of different injection rates (1cc/sec and 2cc/sec) on determination of pharmacokinetic parameters. A recent study (5) has shown that use of population-averaged AIF improves reproducibility of kinetic modeling of DCE MRI data.

Methods Prior to definitive surgeries, 16 patients with osteosarcomas in the knee area underwent a clinical MRI protocol that includes DCE MRI. All the MRI studies were performed with 1.5T GE Excite systems. For DCE MRI data acquisition, a fast multiplanar SPGR sequence was employed with 30° flip angle, 2.9 ms TE, 7.5-9.0 ms TR, 20-24 cm FOV, and 256x128 matrix size. The entire tumor was imaged with 8-11 sections of 10-12 mm thickness. The total DCE MRI acquisition time was about 5-10 min with 7-10 sec temporal resolution and 30-60 time course data points. At the beginning of the sixth image set acquisition, GdDTPA contrast agent at a dose of 0.1 mmol/kg was administered intravenously with a rate of 1 cc/sec or 2 cc/sec by a programmable power injector. The variation in injection rate was due to the location and the size of the IV catheter. In order to calculate the longitudinal relaxation rate constant, R_1, for each DCE MRI data point, proton density images were acquired prior to DCE MRI using the same pulse sequence with 30° flip angle, 2.0 ms TE, 350 ms TR, and DCE MRI-matching section number, thickness and location.

Reliable ROI signal time courses were obtained from visible femoral arteries only in 5 patients with 1 cc/sec contrast injections and 5 patients with 2 cc/sec injections, respectively. Fig. 1 shows an example of a study with 2 cc/sec injection rate. For AIF measurements, the signal time courses were converted into GdDTPA concentration time courses using the linear relationship between R_1 and GdDTPA concentration (example shown in Fig. 1b), and then fitted with a biexponential decay function (6). Average AIFs (Avg-AIFs) for the two injection rates were then obtained from 5 individual AIFs (Ind-AIFs) of 1 and 2 cc/sec injection rates, respectively. The Ind- and Avg-AIFs were used for pharmacokinetic modeling of the tumor tissue signal time courses according to the Toft's model (7). For the purpose of this study, only the image section that included the center portion of the tumor was used for data analysis. The tumor tissue signal intensity was measured from an ROI manually drawn circumscribing the contrast enhanced tumor. Student t test was used to evaluate differences in pharmacokinetic parameters resulted from the use of Ind- and Avg-AIFs, as well as differences resulted from the use of Avg-AIFs of the two injection rates.

Results Fig. 2a shows a scatter plot of tumor tissue ROI K^{trans} parameters obtained from kinetic modeling with the Ind-AIFs and the Avg-AIF for the 5 patients who had 2 cc/sec contrast injection rate, while Fig. 2b demonstrates the same type of plot for the 5 patients who had 1cc/sec contrast injection rate. The straight lines connect the data points from the same patient. At either injection rate, there is no statistically significant difference between K^{trans} parameters derived with Ind-AIFs and those derived with the Avg-AIF ($p = 0.45$ for 2 cc/sec and $p = 0.56$ for 1 cc/sec injection rate, paired t test). Fig. 3 shows a scatter plot of tumor ROI K^{trans} parameters obtained with the two Avg-AIFs for all 16 patients. There is no significant difference between these two sets of K^{trans} parameters ($p = 0.92$). Similar results were obtained for the v_e parameter (plots not shown here).

Discussion Our preliminary results suggest that it is reasonable, as well as practical, to use a limited-population-based Avg-AIF for pharmacokinetic modeling of osteosarcoma DCE MRI data from a large population when it is not possible to measure Ind-AIF in each patient. This approach also provides opportunity to quantitatively analyze osteosarcoma DCE MRI data that were acquired in the past without AIF measurement in mind, but otherwise with the same data acquisition scheme and contrast injection setup as the current study. Use of Avg-AIFs of 1 and 2 cc/sec injection rates respectively does not seem to cause significant changes in derived pharmacokinetic parameters. This may be due to the small difference in the injection rate. Nonetheless, for osteosarcoma DCE MRI data analysis, this finding indicates that Avg-AIF derived from the more commonly used 2 cc/sec contrast injection rate may be used for kinetic modeling of the data obtained with the less commonly used 1 cc/sec injection rate when AIF measurement for the latter is not feasible.

References 1. T.E. Yankeelov *et al. Magn. Reson. Med.* 50: 1151-1169 (2003). 2. R.E. Port *et al. Magn. Reson. Med.* 45: 1030-1038 (2001). 3. C. Yang *et al. Proc. Intl. Soc. Magn. Reson. Med.* 384 (2006). 4. J.P. Dyke *et al. Radiology* 228: 271-278 (2003). 5. G.J. Parker *et al. Proc. Intl. Soc. Magn. Reson. Med.* 382 (2006). 6. H.J. Weinmann *et al. Physiol. Chem. Phys. Med. NMR* 16: 167-172 (1984). 7. P.S. Tofts *JMRI* 7: 91-101 (1997).

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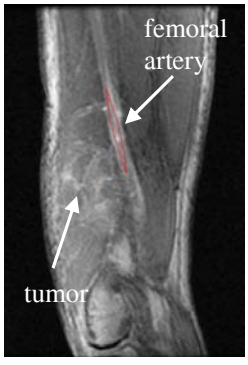
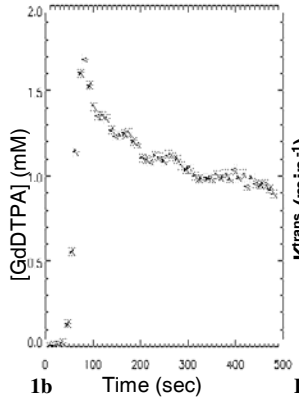


Fig. 1a



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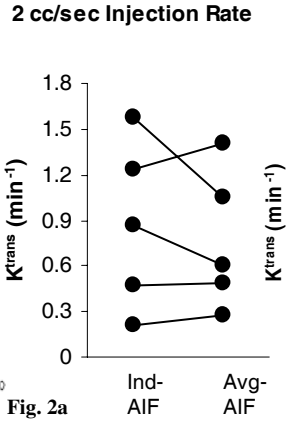
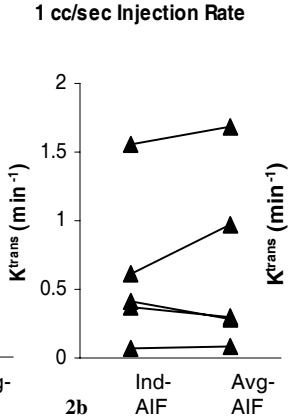


Fig. 2a



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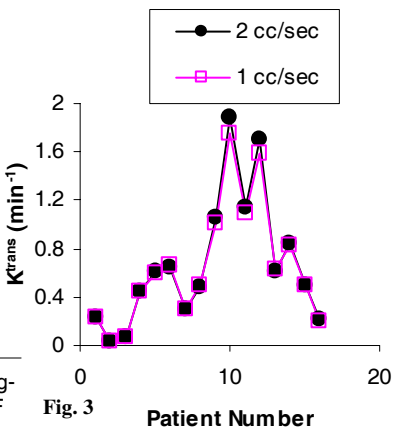

Fig. 3