Feasibility of Using Limited-Population-Based Average R_{10} for Pharmacokinetic Modeling of Osteosarcoma Dynamic Contrast-Enhanced MRI Data

W. Huang[1,2], Y. Wang[1], and J. A. Koutcher[1,2]

[1]Medical Physics, Memorial Sloan Kettering Cancer Center, New York, NY, United States, [2]Radiology, Memorial Sloan Kettering Cancer Center, New York, NY, United States

Introduction In pharmacokinetic modeling of dynamic contrast-enhanced (DCE) MRI signal time course, besides the arterial input function (AIF) determination, the measurement of the longitudinal relaxation rate constant, R_1 (= $1/T_1$), is also critical to the accuracy of pharmacokinetic parameters, K^{trans} (transfer rate constant) and v_e (interstitial fluid space volume fraction).

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 (1). For absolute quantitation of K^{trans} and v_e using kinetic modeling, region of interest (ROI) or pixel R_1 measurement for each data point in the DCE MRI time course is needed. The R_1 values are often measured using a two-point T_1 determination method (2, 3) by comparing signal intensities of the T_1-weighted DCE MRI images with those of the proton density images acquired prior to contrast injection. For clinical studies, however, it is often not possible to obtain proton density images due to time constraint on a clinical scanner. Furthermore, possible patient motion between the acquisitions of the proton density and the DCE MRI series may cause errors or require extra work of motion correction when comparing signal intensities of the two image series. In this study, we measured pre-contrast R_1, R_{10}, in a limited population, and sought to assess the feasibility of calculating R_1 values of the DCE series using a limited-population-based average R_{10} for the purpose of pharmacokinetic modeling of osteosarcoma DCE MRI data.

Methods Prior to definitive surgeries, 18 patients with osteosarcomas in the knee area underwent a clinical MRI protocol, in which a DCE MRI scan was added for the purpose of evaluating the efficacy of chemotherapy in inducing tumor necrosis. The DCE-MRI study was IRB-approved, and written consent was obtained from each patient. 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 (α), 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 between 5 to 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 (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 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.

One ROI was drawn on each image section of the DCE MRI series circumscribing the enhanced tumor and spatially registered to the proton density images. The signal intensity time course was converted to the R_1 time course using the two-point T_1 determination method (2, 3) for both the ROI and pixel-by-pixel analysis. To correct for possible errors in R_1 calculation likely caused by imperfect slice profile, a calibration curve of signal intensity ratio of T_1-weighted image over proton density image *versus* T_1 was constructed from a phantom study using a method introduced by Parker *et al* (2). For R_{10} determination, the average signal intensity of the five baseline data points was used to calculate the R_{10} value for each patient, resulting in 0.87 ± 0.29 s^{-1} (mean ± SD) for this population of 18 patients. For the alternative average R_{10} approach for kinetic modeling, the R_1 value for each DCE MRI time point was calculated using the following equation (4), assuming for each patient R_{10} was uniformly equal to 0.87 s^{-1} for each ROI and each pixel within the ROI:

$$S/S_0 = \{(1 - \exp(-TR \cdot R_1))(1 - \exp(-TR \cdot R_{10}) \cdot \cos\alpha)\}/\{(1 - \exp(-TR \cdot R_{10}))(1 - \exp(-TR \cdot R_1) \cdot \cos\alpha)\},$$

where S is the signal intensity for each time point and S_0 is the pre-contrast S. The R_1 time course (obtained through either the two-point T_1 determination method or the average R_{10} approach) and an average femoral artery AIF (obtained from individual measurements in five patients) based on 2 cc/sec contrast injection rate were subjected to kinetic modeling using the Toft's model (5). We have shown that it is feasible and reasonable to use limited-population-based average AIF for quantitative analysis of osteosarcoma DCE MRI data obtained with either 1 or 2 cc/sec contrast injection rate (6, 7). Whole tumor K^{trans} and v_e values were calculated by averaging those of the image section ROIs, weighted by the number of pixels in each ROI. Histogram analysis (1) was performed for the pixel K^{trans} and v_e values. Student paired t test was used to evaluate differences in pharmacokinetic parameters resulted from the two R_1 time course approaches.

Results Fig. 1 shows scatter plots of whole tumor K^{trans} (a) and v_e (b) parameters obtained from kinetic modeling of the R_1 time course measured individually (Ind-R_1) using the two-point T_1 determination method and that calculated using the average R_{10} (Avg-R_1). The straight line connects the data points from the same patient. There is no statistically significant difference between the pharmacokinetic parameters derived with the Ind-R_1 and those derived with the Avg-R_1 ($p = 0.55$ for K^{trans} and $p = 0.64$ for v_e). Fig. 2 shows similar scatter plots of histogram median K^{trans} (a) and v_e (b) parameters. There is no significant difference between the two sets of pharmacokinetic parameters ($p = 0.87$ for K^{trans} and $p = 0.72$ for v_e).

Discussion The average R_{10} was calculated from 18 patients with osteosarcoma in the knee area whose post-surgical pathology analyses revealed a wide range of tumor necrosis percentage (10-100%). Our results suggest that it is feasible, as well as practical, to use a uniform, limited-population-based average R_{10} for pharmacokinetic modeling of osteosarcoma DCE MRI data from a larger population when it is not possible to acquire proton density images for individual R_1 measurement. This study also implicates that the accuracy of the pharmacokinetic parameters obtained from kinetic modeling of DCE MRI data is likely to be more related to the accuracy of the measurement of R_1 change ($R_1 - R_{10}$) during the bolus passage of contrast agent than the absolute R_1 value, as similarly demonstrated by a recent study (8).

References 1. J.P. Dyke *et al. Radiology* 228: 271-278 (2003). 2. G.J.M. Parker *et al. JMRI* 7: 564-574 (1997). 3. G.J.M. Parker *et al. Top Magn Reson Imaging* 10: 130-142 (1999). 4. A. Haase *Magn Reson Med* 13: 77-89 (1990). 5. P.S. Tofts *JMRI* 7: 91-101 (1997). 6. Y. Wang *et al. PISMRM* 2978 (2007). 7. Y. Wang *et al. Magn Reson Med* In Press. 8. E.M. Haacke *et al. Magn Reson Med* 58: 463-472 (2007).

Acknowledgment NIH grant 1 R01 CA104754.

Fig. 1a

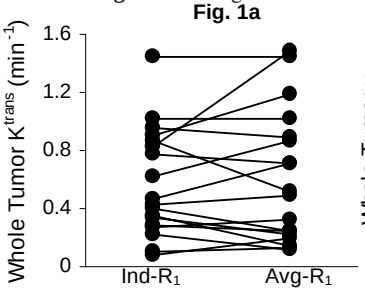

Fig. 1b

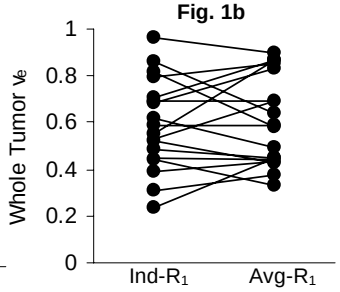

Fig. 2a

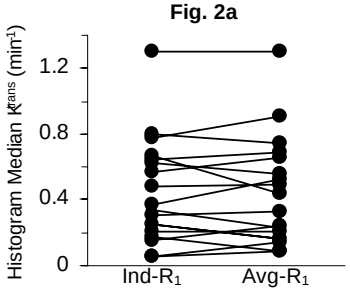

Fig. 2b