Dynamic Contrast Enhanced MRI as A Predictor of Long Term Outcome in Pediatric Bone Tumors

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Introduction

Dynamic contrast enhanced MRI (DCE-MRI) has been used to study many diseases and has been shown to have prognostic value in rectal cancer and head and neck tumors. Using semiquantitative analysis of DCE-MRI data, we have previously shown that there are significant correlations between pharmacokinetic parameters and percent necrosis of osteogenic or Ewing sarcomas at the time of surgery (1). The percent necrosis has been used as a prognostic marker in both Ewing and osteosarcoma with patients having ≥ 90% necrosis after chemotherapy defining a good prognostic group. In this study, we have evaluated and compared the merits of using percent necrosis based on pathology vs. combination of pathological percent necrosis and measured K^{trans} (contrast agent extravasation rate constant) and v_e (interstitial fluid space volume fraction) parameters as a predictor of long term survival.

Methods

Patients with osteogenic or Ewing sarcomas were treated according to standard clinical protocols in the Department of Pediatrics. Prior to definitive surgeries, 25 patients 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 study was approved by the IRB. All the MRI studies were performed with a 1.5T GE system (Signa Horizon or LX). For DCE-MRI data acquisition, a fast multiplanar SPGR sequence was employed with 30° flip angle, 2 ms TE, 9 ms TR, 20-24 cm FOV, and 256x128 matrix size. The entire tumor was imaged with 5-9 sections of 10-12 mm thickness. A total of 20-40 time course data points were acquired with 4.8-9.4 sec temporal resolution. At the beginning of the sixth image set acquisition, Gd-DTPA (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. All the DCE-MRI data were collected between November 1998 and May 2001.

One region of interest (ROI) was drawn on each image section of the DCE-MRI series circumscribing the enhanced tumor. The ROI signal intensity time course was converted to the longitudinal relaxation rate, R_1, time course using the longitudinal saturation factor for the employed pulse sequence (2) and a mean pre-contrast R_1, R_{10} (=0.87 s^{-1}) measured from another sarcoma study (3). A recent study (4) shows that it is reasonable to use a uniform average R_{10} for quantitative DCE-MRI data analysis. The R_1 time course and an average arterial input function (AIF) were subjected to pharmacokinetic modeling using the Toft's model (5) to calculate ROI K^{trans} and v_e parameters. The average AIFs (averaged from individually measured AIFs in three to five patients in the visible artery that is nearest to the tumor) were obtained from another study with the same experimental setup (3). We have shown that it is feasible and reasonable to use limited-population-based average AIF for kinetic modeling of osteosarcoma DCE-MRI data of a larger population (3). 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.

We calculated overall survival curves by the Kaplan-Meier method, and statistical significance of comparisons of survival between groups of patients by the log rank test.

Results

Pathologists' estimates of necrosis were not predictive of overall survival when classified as <90% vs 90-100% (Fig. 1) as noted by the Kaplan-Meier survival curves, and were marginally significant if classified as <100% vs 100% (p=0.054). Fig. 2 shows the best linear fit to a plot of v_e vs pathological percent necrosis. When K^{trans} (plot not shown here) and v_e were classified as higher or lower than expected compared to the linear regressions, each was predictive of overall survival (p<0.01, log rank test), though v_e performed better than K^{trans} in such task. We further classified patients with either 100% necrosis or higher than expected v_e as a composite, good prognosis group to illustrate the difference in Kaplan-Meier survival curves. Since all patients with 100% necrosis are alive, we denoted "good risk" patients as those who have 100% pathological necrosis or have a value of v_e above the linear regression line. "Poor risk" patients were defined as those with less than 100% necrosis and having a low (below the regression line) v_e. Fig. 3 shows the Kaplan Meier curves for the "good risk" and "poor risk" categories. v_e by itself (scored as "high/low" relative to % necrosis based on the linear regression analysis) is highly significant (p=0.002) in univariate analysis.

Discussion

With the advent of more intensive chemotherapy, induction of ≥90% necrosis has not been as strong a predictor of outcome as thought previously. Our previous study (1) has shown that pharmacokinetic parameters derived from two-compartment modeling of DCE-MRI data have very good correlations with percent necrosis determined after definitive surgical resection. We have followed the patients from the latter study and found that the DCE-MRI data are predictive of long term outcome whereas percent necrosis was of borderline significance. The combination of pharmacokinetic parameters and percent necrosis significantly improves prediction of outcome from chemotherapy. These patients have been studied for up to 9 years, so although the sample size is only 25 patients, the data warrant further studies including verifying these data on a new cohort of patients and correcting for the transcytolemmal water exchange effects (6) in kinetic modeling of DCE-MRI data. This study suggests that the preoperative DCE-MRI data will provide a strong prognostic marker of long term survival in pediatric bone tumor patients.

References

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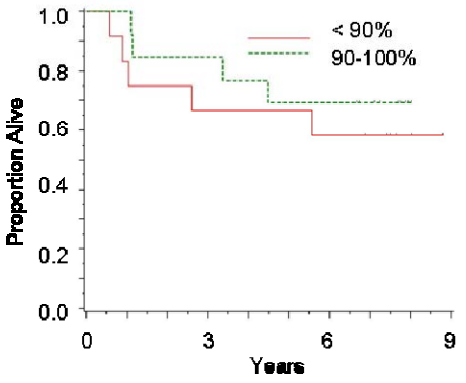

Fig. 1. Plot of proportion of surviving patients vs time as stratified by ≥90% necrosis at surgery vs. <90% necrosis.

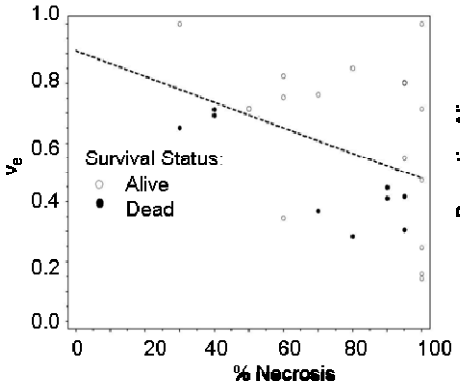

Fig. 2. Linear regression plot of v_e vs. percent necrosis at time of surgery. Patients with higher v_e were more likely to survive.

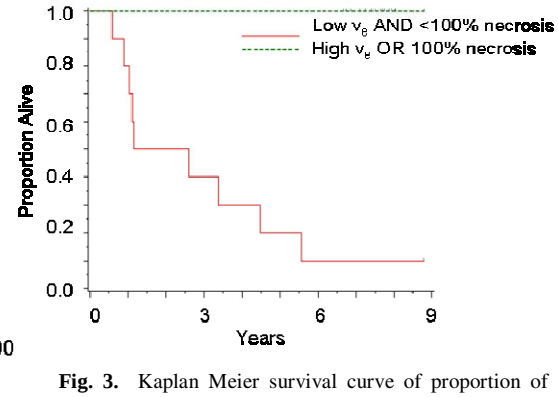

Fig. 3. Kaplan Meier survival curve of proportion of patients surviving after treatment. Patients were stratified based on having a v_e above the regression line or having 100% necrosis at surgery as the good prognosis arm.