Prediction of Response to Chemotherapy in Patients with Osteosarcoma and Ewing's Sarcoma

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Introduction

Osteosarcoma (OS) and Ewing's sarcoma (ES) are aggressive bone cancers found primarily in pediatric patients. The standard of care for nonmetastatic OS and ES includes neoadjuvant chemotherapy followed by surgery providing 60–70% long-term survival. MRI has shown promise in predicting early response to chemotherapy in patients with OS [1]. The purpose of this study was to assess the ability of DCE MRI to predict the histological response to chemotherapy in patients with OS and ES.

Methods

This prospective, HIPAA-compliant study was approved by the Institutional Review Board and informed consent was obtained from all patients. Between 2004 and 2010, patients were enrolled into the study if they were recently diagnosed with osteosarcoma (OS) or Ewing's sarcoma (ES) and received no prior treatment. Each patient underwent MRI before, during, and after the completion of chemotherapy (MRI1, MRI2, MRI3, respectively) followed by surgery or radiation therapy (RT). In patients who underwent surgery, tumors were histologically analyzed and percent necrosis was determined on a central slice. Follow-up was established based on the results of the last clinical examination (up to 6 years after imaging). MRI was performed at 1.5 T (Signa Excite; GE Healthcare, Waukesha, WI) and included anatomical sequences followed by T1-weighted DCE MRI (SPGR sequence; TR = 7–9 ms; TE = 1.7–1.9 ms; acquired matrix 256x128 interpolated to 256x256; field of view, 24x24 cm^2 to 50x50 cm^2; slice thickness/gap , 9–13 mm; number of slices, 6–11; number of time points, 40–60; number of pre-contrast images 5–10; temporal resolution, 10 s. DCE series was acquired after an injection of 0.2 mmol/kg gadolinium dimeglumine (Magnevist, Bayer HealthCare Pharmaceuticals, Wayne, NJ) over 6–10 min. Image analysis was performed in Matlab (Mathworks, Natick, NJ). Voxel enhancement was converted to change in relaxation rate (ΔR_1) using the gradient echo sequence formula and a fixed T_1 = 1150 ms [2]. Voxel-wise analysis was performed with Tofts compartmental model [3] with two parameters (K^{trans} and v_e) implemented in linearized form [4] and the appropriately scaled population-based arterial input function (AIF) from literature [5]. Regions of interest were drawn around the tumor on all slices and the mean parameters were obtained and were compared across the time points using Wilcoxon signed-rank test and between subsets of the data using Mann-Whitney U-test. The correlations between model parameters and histological percent necrosis were assessed using Spearman's correlation coefficient ρ.

Results

A total of 37 patients with leg tumors were included into the study; three patients were excluded because of motion artifacts (n=2) or lack of tumor enhancement (n=1). Among the final 34 patients, 28 had OS and 6 had ES. Femur was the most common tumor site (n=23), followed by tibia (n=9) and other locations (n=2). The median age of the patients was 13 years (range, 7–30 years). All patients except one were treated with chemotherapy and surgery; one patient with ES was treated with RT. The median interval between the start of chemotherapy and surgery was 12 weeks (range, 9–17 weeks). By the end of the study, 28/34 patients (82%) showed no evidence of disease (NED) and 6/34 (18%, OS, n=4; ES, n=2) suffered an adverse event (AE), death from disease (n=5) or metastasis (n=1). The median time between surgery and AE was 22 months (range, 18–36 months). Good quality voxel model fits to DCE data were obtained in all patients (Fig. 1). The mean tumor K^{trans} decreased on average at MRI2 by 7% (p=0.083) and by 31% at MRI 3 (p<0.001) relative to MRI1, but v_e did not show significant changes (Table, Fig. 2). In 24/34 patients, the histological percent necrosis was under 90% (45±26%) and in 10/34 patients it was above 90% (96±4%). The mean K^{trans} at MRI3 in patients with percent necrosis ≥90% was significantly different from patients with less than 90% necrosis (0.03±0.02 min^{-1} vs 0.06±0.03 min^{-1}, p=0.008) There was a moderate, but significant negative correlation between percent necrosis and the percent decrease in K^{trans} between MRI1 and MRI3 and (ρ=-0.47, p=0.006) and between MRI2 and MRI3 (ρ=-0.56, p=0.0012). Neither the percent necrosis nor the K^{trans} values appeared to be correlated with survival.

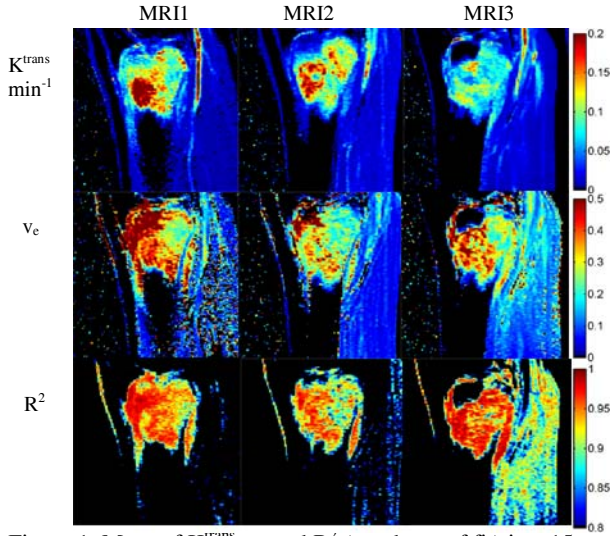

Figure 1: Maps of K^{trans}, v_e and R^2 (goodness of fit) in a 15-year-old patient with OS of proximal tibia at MRI1–3 (histological necrosis, 80%).

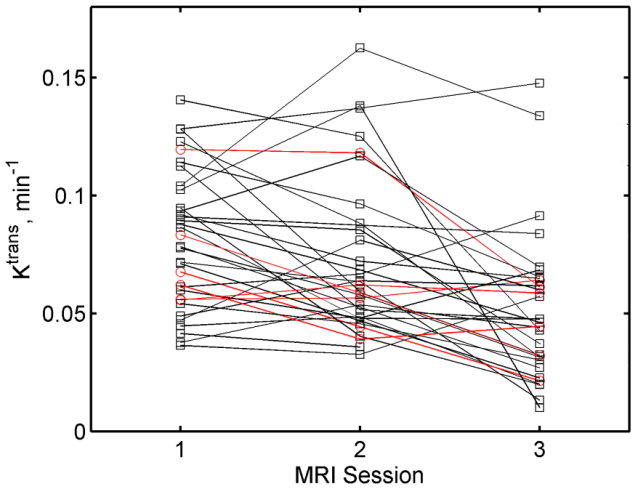

Figure 2: The mean tumor K^{trans} values in all patients at MRI1–3. Data from patients who suffered an AE are shown in red.

Table: Tofts model parameters derived from DCE MRI performed before, during and after chemotherapy (MRI1-3) and Wilcoxon test p-values for comparison between time points

Parameter	MRI1	MRI2	MRI3	p-value MRI 1 vs 2	p-value MRI 1 vs 3
K^{trans}, min^{-1}	0.081±0.029	0.067±0.039	0.050±0.031	0.083	<0.001
v_e	0.20±0.08	0.18±0.09	0.17±0.06	0.47	0.69

Discussion

The majority of patients showed a decrease in K^{trans} values at the completion of chemotherapy. The percent decrease in K^{trans} and the mean K^{trans} at MRI3 were predictive of histological response, in agreement with Guo et al. [1]. However, the model parameters did not appear to be correlated with survival, possibly because of the small and heterogeneous dataset.

References

[1] Guo et al. Cancer 2012;118:3776-85. [2] Huang et al. Magn Reson Imaging 2009;27:852-58. [3]. Tofts et al. J Magn Reson Imaging 1999;10:223-32. [4] Murase. Magn Reson Med 2004;51:858-62. [5] Parker et al. Magn Reson Med 2006;56:993-1000.