DCE-MRI as a Prognostic Factor in Osteosarcoma

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Introduction: Osteosarcoma (OS) is one of the most common malignant bone tumors in children in the United States. However, there is no robust prognostic factor reported to stratify OS patients for risk-adapterd therapy. Dynamic contrast enhanced (DCE) MRI has been investigated as a potential biomarker for histologic response to the preoperative chemotherapy in a small group of osteosarcoma patients [1]. In this study, DCE-MRI data from pediatric OS patients at three institutions were analyzed to investigate whether DCE-MRI could be used to evaluate tumor histological response to preoperative chemotherapy, and provide possible prognostic factors for event-free survival (EFS) and overall survival on a single phase II trial.

Method: Seventy-two eligible patients with high-grade nonmetastatic osteosarcoma of the extremity were enrolled and 69 patients met the inclusion criteria. Three serial DCE-MRI examinations at week 0 before any treatment, week 9 and week12 before definitive surgery were performed on a 1.5 T Siemens Symphony scanner (Siemens Medical Solutions, Erlangen, Germany). After selection of the single slice that best showed the tumor, images were acquired before, during, and after bolus injection into a central line of a 0.1 mmol/kg dose of Gd-DTPA, followed by a saline flush. Thirty sequential FLASH images (TR/TE=23/10 ms, 40° flip angle, Nk/Ny = 256/256, 10 mm thickness, 40-50 cm FOV, 2 acquisitions) were collected over a 6 minute period.

Tumor region of interest (ROI) was drawn in red line as shown in Fig. 1 by a pediatric radiologist. Tumor ROI was then divided by computer software into inner and outer 50% by the black line as shown in Fig. 1. DCE-MRI data were analyzed using a two-compartment pharmacokinetic model [2] with an average T_i0 (1100 ms) and an assumed AIF, bi-exponential decay curve [3], to calculate kinetic parameters $k_{trans}$, $k_{ep}$, $v_p$ and $v_o$ and corresponding differences ($\Delta k_{trans}$, $\Delta k_{ep}$, $\Delta v_p$ and $\Delta v_o$) between outer and inner half of tumor ROI for all the patients.

Average values of each of eight DCE-MRI parameters ($k_{trans}$, $k_{ep}$, $v_p$, $v_o$, $\Delta k_{trans}$, $\Delta k_{ep}$, $\Delta v_p$ and $\Delta v_o$) in the region of interest were determined for each patient at each time point of examination (week 0, week 9, and week 12). All the results from three different institutions were pooled to investigate associations between DCE-MRI parameters with histologic response, event-free survival (EFS) and overall survival. Logistic regression was used to examine the association of each of eight DCE-MRI parameters at each time point between responder and nonresponder. Cox proportional hazards models were used to explore the association between outcome (EFS and overall survival) and each of eight DCE-MRI parameters. Probabilities of EFS were estimated using the method of Kaplan and Meier. All reported $P$ values are statistically significant when $P < 0.05$ and are trending significant when $P$ values are from 0.05 to 0.1.

Results: Fig. 1 shows DCE-MRI parametric maps ($k_{trans}$ and $v_o$) of two pediatric patients with osteosarcoma of distal femur in the baseline examination are displayed as an example. The first patient in the upper row is an EFS responder, and the second patient in the lower row is a nonresponder with event that expired. Fig. 2 shows bar plots of $k_{trans}$ and $v_o$ for responder and nonresponder at three time points. $k_{trans}$ and $v_o$ at week 9 were significantly different between two groups with $P = 0.046$ and 0.021, respectively. $\Delta k_{ep}$ at week 9 with $P = 0.008$ was significantly different too. No significant difference of other parameters between two groups was found at any time points. $k_{trans}$, $v_p$ and $\Delta k_{trans}$ at week 9 may be the promising early biomarkers for histologic response. The association between EFS and each of all eight parameters was examined using Cox proportional hazards models. $\Delta k_{trans}$ and $\Delta v_o$ at week 0 were two parameters with possible prognostic significance. EFS survival curves shown on Fig. 3 using the median value of $\Delta k_{trans}$ and $\Delta v_o$ of total 62 patients as a threshold were compared at week 0 with the log-rank test. Fig. 3a shows two survival curves of $\Delta k_{trans}$, which were trending towards significance with $P=0.0585$; Fig. 3b shows two survival curves of $\Delta v_o$, which were prognostic significance with $P = 0.0387$. $\Delta k_{trans}$ and $\Delta v_o$ at week 0 could be possible prognostic factors for EFS before any treatment. Also, $\Delta k_{ep}$ and $\Delta v_o$ were two parameters with possible prognostic significance for overall survival.

Conclusion: We investigated the role of DCE-MRI in tumor response to preoperative chemotherapy and predicting overall and event free survival of pediatric OS patients. We found that DCE-MRI parameter $k_{trans}$, $v_o$ and $\Delta k_{trans}$ at week 9 could serve as a surrogate biomarker for histological response. DCE-MRI parameter $\Delta v_o$ at week 0 may be a true early prognostic factor for EFS and overall survival, which eventually, could contribute to the development of risk-adapted therapy.

Reference:
1. Reddick WE, et al. JMRI, 10, p277,1999
2. Tofts PS, et al. JMRI, 10, p223, 1999