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-adapted 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, Nx/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_{10} (1100 ms) and an assumed AIF, bi-exponential decay curve [3], to calculate kinetic parameters K^{trans}, k_{ep}, v_e and v_p and corresponding differences (Δk^{trans}, Δk_{ep}, Δv_e and Δv_p) between outer and inner half of tumor ROI for all the patients.

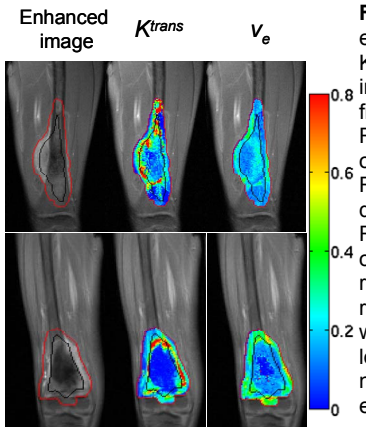

Fig. 1 Contrast enhanced image, K^{trans} and v_e maps in baseline exam from left to right. Red line is the outline of tumor ROI, and black line divided each tumor ROI into inner and outer 50%. Upper row is for the responder alive without event; lower row is for the nonresponder with event that expired.

Average values of each of eight DCE-MRI parameters (K^{trans}, k_{ep}, v_e, v_p, ΔK^{trans}, Δk_{ep}, Δv_e and Δv_p) 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_e) 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_p for responder and nonresponder at three time points. K^{trans} and v_p at week 9 were significantly different between two groups with P = 0.046 and 0.021, respectively. Δk_{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 Δk_{ep} 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. ΔK^{trans} and Δv_e at week 0 were two parameters with possible prognostic significance. EFS survival curves shown on Fig. 3 using the median value of ΔK^{trans} and Δv_e of total 62 patients as a threshold were compared at week 0 with the log-rank test. Fig. 3a shows two survival curves of ΔK^{trans}, which were trending toward significance with P=0.0585; Fig. 3b shows two survival curves of Δv_e, which were prognostic significance with P = 0.0387. ΔK^{trans} and Δv_e at week 0 could be possible prognostic factors for EFS before any treatment. Also, ΔK^{trans} and Δv_e were two parameters with possible prognostic significance for overall survival.

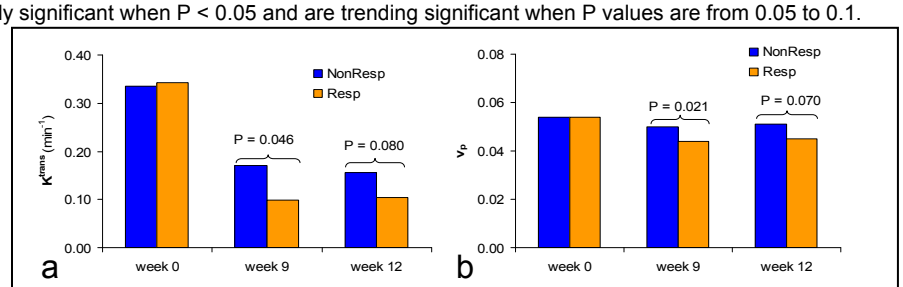

Fig. 2 Bar plots of DCE-MRI parameters K^{trans} (a) and v_p (b) of responder and nonresponder at three time points. Blue represents nonresponders; Orange represents responders.

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_p and Δk_{ep} at week 9 could serve as a surrogate biomarker for histological response. DCE-MRI parameter Δv_e 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.

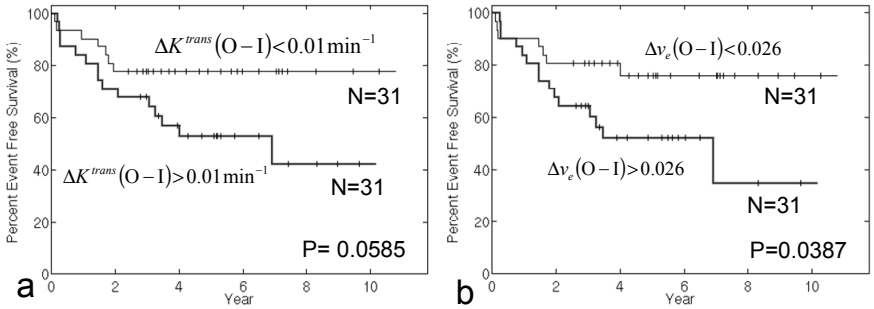

Fig. 3 Kaplan-Meier curves of event-free survival for subgroups stratified by median of variables, ΔK^{trans} (a) and Δv_e (b) at week 0, with possible prognostic significance in univariate analyses. P values are from the log-rank test.

Reference:

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