

DCE-MRI and PET imaging as a predictive and prognostic biomarker in Osteosarcoma

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INTRODUCTION: Osteosarcoma (OS) is the most common malignant bone tumor in children in the United States. DCE-MRI is widely used in clinical studies for assessment of cancer treatment response and survival [1, 2]. ¹⁸F-FDG PET also plays an important role in assessment of treatment response in solid tumor including osteosarcoma. The purpose of this study was to assess the role of DCE-MRI and ¹⁸F-FDG PET for evaluation of response to antiangiogenic and neoadjuvant chemotherapy and for prediction of event-free survival (EFS) and overall survival in patients with Osteosarcoma (OS).

METHOD: Total 42 patients with OS untreated were enrolled on a phase II therapeutic trial at three medical centers in United States between May 2008 and April 2012. 31 patients with high-grade nonmetastatic and potentially resectable OS belong to stratum A. 11 patients with metastatic disease at diagnosis belong to stratum B, who were treated differently and excluded for survival analysis. The median age of all the patients (23 males/19 females) was 12.5 years at diagnosis. Protocol treatment was comprised of anti-angiogenic therapy (bevacizumab) and neoadjuvant combination chemotherapy. Two imaging modalities including DCE-MRI and ¹⁸F-FDG PET were used to monitor the treatment before surgery. Patients were eligible for the imaging studies if they completed at least one examination before surgical resection. All 42 patients had at least one DCE-MRI examinations. 34 patients had at least one PET examination.

Six serial DCE-MRI examinations were scheduled at the baseline, on day1, day5, at week 5, and at week 10 before tumor resection. To evaluate the effect of bevacizumab alone, bevacizumab was administered 3 days before the first chemotherapy administration, and DCE-MRI examinations on Day-2 and Day1 were performed with the bevacizumab administration alone. For each subject, three serial ¹⁸F FDG PET examinations were scheduled at the baseline, week 5, and week 10. SUV_{max} in the tumor was measured for further analysis.

DCE-MRI data were acquired on a 1.5 T Siemens MRI scanner. Subjects were given intravenous injections of 0.1 mmol/kg of a gadolinium (Gd) contrast (Magnevist) at a rate of 1 ml/s. DCE-MRI data were acquired using a fast 3D Cartesian gradient-echo pulse sequence (3D FLASH) with radiofrequency spoiling. The protocol was as follows: 16 coronal slices with 75% partial Fourier encoding along k_z , FOVs kept the same for each subject; slice thickness = 5 mm; TE/TR = 1.24/3.5 ms; receiver bandwidth = 390 Hz/pixel; and acquisition matrix = 256 × 192. The total acquisition time was 350 seconds for 50 measurements with temporal resolution of 7 seconds for each measurement. The initial spin lattice relaxation time T_{10} was measured before each DCE-MRI scan using the inversion recovery method. DCE-MRI data were analyzed using a two-compartment pharmacokinetic model to compute the four quantitative measures: K^{trans} , v_e , k_{ep} , and v_p for each voxel [3]. The average values in tumor ROI were calculated for further statistical analysis. The 3D tumor volume (TV) was also calculated in the tumor ROI.

Histologic response was assessed at week 10 after definitive surgery. Responders are defined by the percentage of chemotherapy-induced necrosis no less than 90% and nonresponders less than 90%.

Nonparametric exact Wilcoxon signed rank test was used to examine the difference of each parameter between two time points. Nonparametric exact Wilcoxon rank-sum test was used to examine the difference of each parameter between two groups: responders vs. nonresponders, overall survivor vs. expired patients, and event free survivor vs. non-event free patient. Cox proportional hazards models were used to explore associations between outcome (EFS and overall survival) and each parameters. Reported P-values were considered statistically significant when $P \leq 0.05$. All the statistical analyses were performed using SAS software.

RESULTS: K^{trans} and v_p on Day-2 were significantly lower than their baseline, which indicate a decrease perfusion due to bevacizumab after the first 24 hours, and were consistent with reported results in glioblastoma patients [4]. K^{trans} and SUV_{max} at week 5 and week 10 had a strong positive correlation with Pearson correlation coefficient R equal to 0.56, and 0.5, respectively. Tumor volumes at all three time points strongly correlated with the corresponding SUV_{max} with R equal to 0.67, 0.47, and 0.62, respectively. In assessing tumor histologic response, three parameters (K^{trans} , SUV_{max} , and TV at week10) were significantly different between responder and non-responder. All these parameters were also significantly associated with the percentage of tumor necrosis.

In survival analyses, K^{trans} at week10 and TV on Day-2 and at week5 were significantly associated with EFS, and significantly different between EFS and non-EFS groups in Fig 1. The Kaplan-Meier survival curves in the three cases were plotted in Fig. 2 for the two subgroups stratified by the median of each parameter. All these survival curves were significantly different between two subgroups using the exact log-rank test. These three parameters were also significantly associated with overall survival, and significantly different between survivors and dead patients. Parameters with significance in difference and association tests were summarized in Table 1.

CONCLUSION: We demonstrated significant effects of antiangiogenic therapy alone on tumor perfusion by DCE-MRI in the early stage of the treatment. We also showed that ¹⁸F-FDG PET strongly correlated with DCE-MRI in OS patients, which could provide complementary information to understand the underlying tumor physiology. Both DCE-MRI and ¹⁸F-FDG PET could provide valuable indicators of histologic response. DCE-MRI could also provide potential prognostic factors for both EFS and overall survival.

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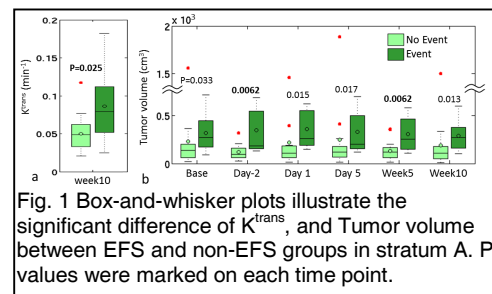


Fig. 1 Box-and-whisker plots illustrate the significant difference of K^{trans} , and Tumor volume between EFS and non-EFS groups in stratum A. P values were marked on each time point.

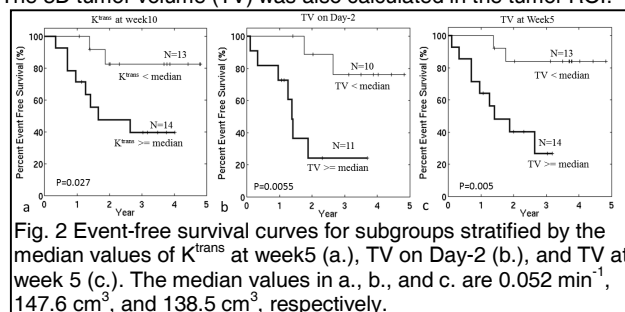


Fig. 2 Event-free survival curves for subgroups stratified by the median values of K^{trans} at weeks (a.), TV on Day-2 (b.), and TV at week 5 (c.). The median values in a., b., and c. are 0.052 min^{-1} , 147.6 cm^3 , and 138.5 cm^3 , respectively.

| Parameters | Difference | Association |
|-----------------------------|------------|-------------|
| Histologic Response | | |
| Ktrans (week10) | 0.029 | 0.026 |
| SUV _{max} (week10) | 0.0055 | 0.018 |
| TV (week10) | 0.021 | 0.032 |
| Event Free Survival | | |
| Ktrans (week10) | 0.025 | 0.028 |
| TV (Day-2) | 0.0062 | 0.0049 |
| TV (week5) | 0.0062 | 0.0029 |
| Overall Survival | | |
| Ktrans (week10) | 0.021 | 0.028 |
| TV (Day-2) | 0.028 | 0.045 |
| TV (week5) | 0.0047 | 0.0054 |

Table.1 Summary of statistically significant difference between subgroups for response, survival, and associations of parametric measures with response and survival.