# DCE-MRI kinetic model and curve pattern analyses for predicting response and survivals in osteosarcoma patients

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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]. Pharmacokinetic modeling analysis is widely used in DCE-MRI since parameters in model have some physiologic significance [3]. Curve pattern analysis (CPA) attempt to extract the important features of contrast enhanced curve without any assumptions or inferences about the underlying physiology [4]. The purpose of this study was to assess the role of kinetic model and CPA methods for evaluation of response to antiangiogenic and neoadjuvant chemotherapy and for prediction of event-free survival (EFS) and overall survival in patients with 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. 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. DCE-MRI was used to monitor the treatment before surgery. Patients were eligible for DCE-MRI imaging study if they completed at least one examination before surgical resection. All 42 patients had at least one DCE-MRI examinations. Six serial DCE-MRI examinations were scheduled at the baseline, on day-2, 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.

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 kinetic Tofts model and the CPA method. Tofts model generates four quantitative measures: $K^{trans}$, $v_e$, $k_{ep}$, and $v_p$ for each voxel [3]; The CPA method calculates four quantitative measures:$\beta_1, \beta_2, \beta_\tau$, and $\kappa$ for each voxel as shown in Fig 1. [4]. The average values in tumor ROI for eight original parameters and their absolute difference (ABD) between two consecutive time points were calculated for further statistical analysis.

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 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. Reported P-values were considered statistically significant when $P \leqslant 0.05$.

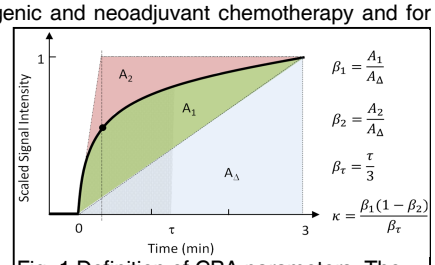


Fig. 1 Definition of CPA parameters. The thick black curve is the normalized signal. $A_1$, $A_2$, and $A_\Delta$ represent the light green, pink, and light blue areas. $\tau$ is the time when the dotted area is one third of the total area of $A_1$ and $A_\Delta$.

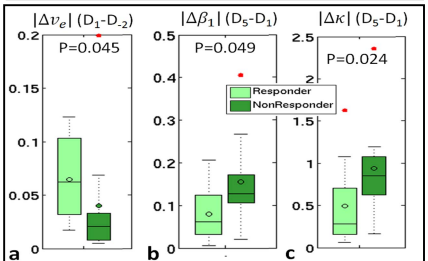


Fig. 2 Box-and-whisker plots illustrate the significant difference of $|\Delta v_e|$, $|\Delta\beta_1|$, and $|\Delta\kappa|$ between responder and non-responders in early time points. $D_{-2}$ represents $Day_{-2}$; $D_1$ represents $Day_1$, $D_5$ represents $Day_5$.

**RESULTS:** In all six examinations, earlier time points with significances are preferred since the individual treatment strategy can be developed in future to improve the clinical outcomes based on those early indicators. Results from week 5 and 10 will be neglected in this study. For response assessment, there are three earlier ABD parameters ($|\Delta v_e|(D_1 - D_{-2}), |\Delta\beta_1|(D_5 - D_1), and\ |\Delta\kappa|(D_5 - D_1)$) were significantly different between responders and non-responders in Fig 2. These results show that subjects who have the larger absolute change of $v_e$ in early antiangiogenic therapy and the smaller changes of $\beta_1\ and\ \kappa$ in early chemotherapy are more likely to be responders.

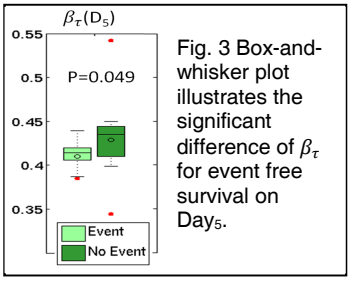


Fig. 3 Box-and-whisker plot illustrates the significant difference of $\beta_\tau$ for event free survival on $Day_5$.

For event free survival, $\beta_\tau$ on Day 5 in Fig 3 is the only early parameter before week 5 to show the significant difference between subjects with and without event. Subjects without event were most likely to have larger $\beta_\tau$ than those with event, which indicates EFS survivors could have slower perfusion on Day5. For overall survival, four ABD parameters ($|\Delta\kappa|(D_{-2} - Base), |\Delta k_{ep}|(D_{-2} - Base), |\Delta k_{ep}|(D_1 - D_{-2})$, and $|\Delta K^{trans}|(D_5 - D_1)$) shown in Fig 4 were significantly different between expired and alive subjects before week5. We can see in Fig 4 that survivors are most likely to have smaller changes of $\kappa$ and $k_{ep}$ at the beginning of antiangiogenic therapy and larger changes of $K^{trans}$ at the beginning of chemotherapy. The CPA parameter $\kappa$ was reported to correlate well with $k_{ep}$ for individual tumors [4]. In this study, the correlation of $\kappa$ and $k_{ep}$ for all 42 subjects was very strong with $\rho = 0.92$, which was much higher than that between $K^{trans}$ $(or\ v_e)$ and $\kappa$.

**CONCLUSION:** We demonstrate that Tofts model and the CPA method could provide prognostic factors for clinical outcome in the early stage of treatment. The CPA parameter $\beta_\tau$ on Day5 is the only potential prognostic factor for EFS before week 5. The CPA parameters could provide additional information to predict clinical outcome besides kinetic parameters and the CPA parameter $\kappa$ strongly correlated with kinetic parameter $k_{ep}$, which indicates that the CPA method could provide complementary information to assess the clinical outcome and understand the underlying tumor physiology. Both pharmacokinetic analysis and Curve pattern analysis (CPA) could provide valuable indicators of histologic response, and potential prognostic factors for both EFS and overall survival.

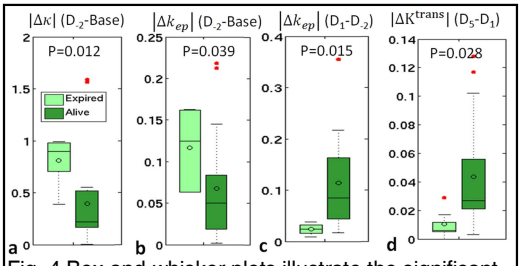


Fig. 4 Box-and-whisker plots illustrate the significant difference of $|\Delta\kappa|$, $|\Delta k_{ep}|$, and $|\Delta K^{trans}|$ between expired and alive subjects for overall survival in early time points. Base represents the baseline.

## REFERENCE:

1. Reddick WE, et al. Cancer, p2230, 2001
2. Guo J, et al. Cancer, p3776, 2012
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4. Guo J. et al. JMRI, v30, p177, 2009