An international, multi-institutional trial of DCE-MRI in children treated for osteosarcoma

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PURPOSE: Osteosarcoma (OS) is the most common malignant bone tumor in youth with an average age at diagnosis of 15 years. Response to neoadjuvant chemotherapy is associated with increased survival but conventional static imaging methods are of limited utility in assessing response primarily due to the lack of significant change in tumor size. Dynamic contrast-enhanced MR imaging (DCE-MRI) has the potential to non-invasively assess tumor response but has historically lacked standardized methods for image acquisition, processing, and analysis, which made comparisons across institutions difficult. The current study prospectively evaluated the use of DCE-MRI to non-invasively evaluate tumor response to neoadjuvant chemotherapy in pediatric patients treated on a phase II trial conducted at three institutions.

METHODS: Serial DCE-MRI was performed to assess tumor response in patients with OS treated on a phase II trial of multiagent chemotherapy conducted from 1999 to 2006 at three institutions (2 in the USA and 1 in Chile). It has been shown in a previous single institutional trial that the measure of k_{ep} at completion of preoperative chemotherapy was useful in assessing OS response to neoadjuvant chemotherapy[1]. Sixty-three subjects (median age, 14.1 years; 37 male, 26 female) with non-metastatic OS of the extremity (41 femur, 16 tibia, 3 humerus, 2 fibula, and 1 ulna) underwent one or more DCE-MRI examinations and had histologic assessment of tumor response.

DCE-MR images were acquired on a Siemens 1.5 T imager at presentation (before course 1 of chemotherapy [week 0]), at week 9 (after 3 courses of chemotherapy), and at week 12 (after 4 courses of chemotherapy before definitive surgery). After selection of the single section 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, 256 phase encodes, 10 mm thickness, 40-50 cm FOV, 2 acquisitions) were collected over a 6.5 minute period. Rosen/Huvos grade of tumor response was determined by histologic review of the resected specimen[2]. DCE-MRI parameters were produced by fitting a two-compartment pharmacokinetic model to the concentration time curve for each voxel within the tumor using the Tofts model[3]. This analysis assumes that the signal intensity is proportional to the contrast agent concentration.

Quantitative DCE-MRI measures (**Figure 1**) reflecting regional contrast transfer (K_{trans}, k_{ep}) between the plasma and extracellular / extravascular spaces as well as the relative size of the compartments (v_p, v_e) were analyzed in relation to histologic response. Logistic regression was used to examine the association between histologic response and DCE-MRI parameters at each time point.

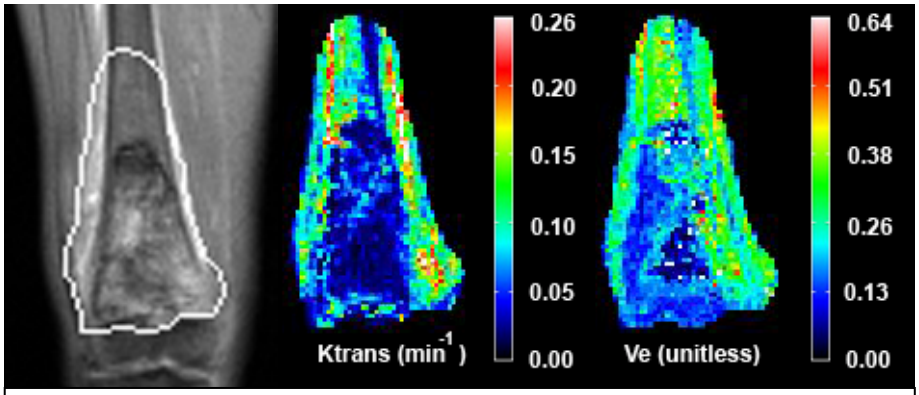

Figure 1. From left to right: Post contrast T1 image of distal femur with radiologist selected ROI followed by color-coded parameter maps of K_{trans} and v_e from the ROI.

RESULTS: Forty patients were histologic responders to the neoadjuvant therapy (>90% tumor necrosis) and 23 were non-responders. K_{trans} and v_e for each time point are summarized in **Figure 2**. Decreased K_{trans} and v_e at week 9 relative to presentation was significantly associated with good histologic response to preoperative chemotherapy (ΔK_{trans}, P=0.01; Δv_e, P=0.04). Patients with higher K_{trans} and v_e at presentation [week 0] were more likely to have good histologic response (K_{trans}, P=0.06; v_e, P=0.03).

CONCLUSIONS: It is feasible to use DCE-MRI as a non-invasive measure to assess tumor response to neoadjuvant chemotherapy in OS trials conducted at multiple institutions. Early decreases in K_{trans} and v_e, and greater K_{trans} and v_e at baseline correspond to good histologic response to preoperative chemotherapy.

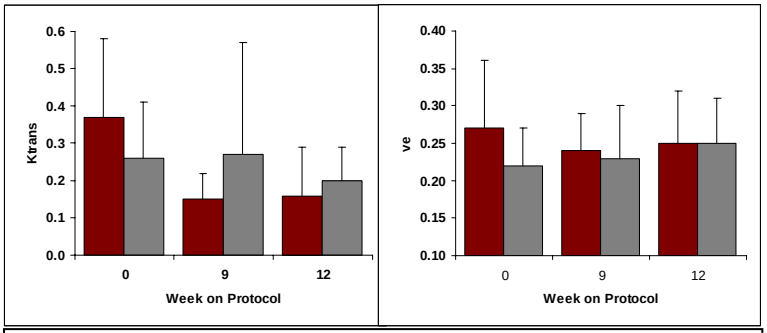

Figure 2. K_{trans} and v_e for responders (red) and non-responders (gray) at each of the three time points during preoperative chemotherapy.

REFERENCES

1. Reddick WE, *Cancer*, 91:2230-2237, 2001.
2. Huvos AG, *A Path Lab Med*, 101:14-18, 1977.
3. Tofts PS, *JMRI*, 10:223-232, 1999.