Preliminary experience with 3D DCE-MRI evaluation of children treated for osteosarcoma with chemotherapy plus bevacizumab

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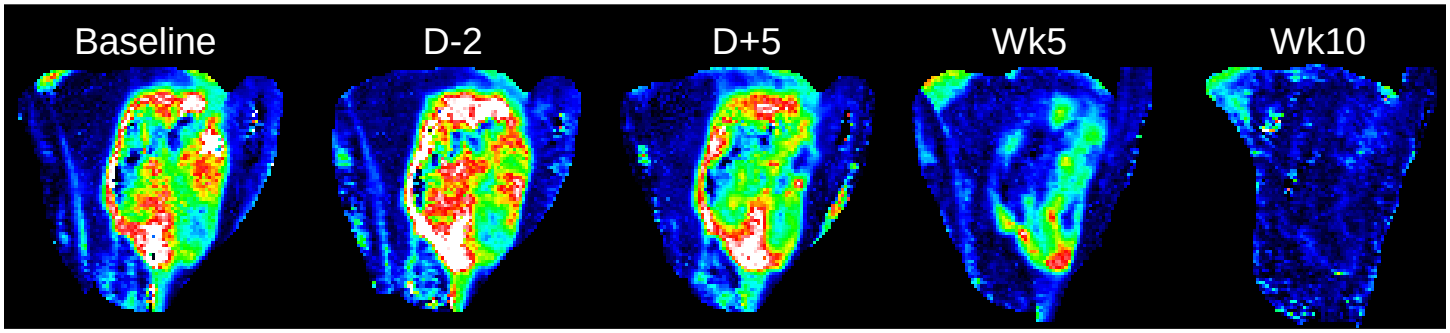
PURPOSE: Osteosarcoma (OS) is the most common malignant bone tumor of childhood with a median age at diagnosis of 13 years. Our new treatment protocol for OS is investigating the addition of an anti-angiogenic agent (bevacizumab) to standard chemotherapy. Dynamic contrast-enhanced MR imaging (DCE-MRI) has the potential to non-invasively assess tumor response to neoaduvant chemotherapy. In a previous single institutional trial, k_{ep} measurement at completion of preoperative chemotherapy was useful in assessing OS response to neoadjuvant chemotherapy[1]. The current study presents the design and incorporation of DCE-MRI in the treatment protocol and preliminary results of changes in dynamic pharmacokinetic parameters in response to neoadjuvant chemotherapy and bevacizumab in children treated for osteosarcoma.

PATIENTS & METHODS: Serial DCE-MRI was performed to assess the effect of therapy on tumor in patients with OS treated on a phase II trial of multiagent chemotherapy and bevacizumab. Preliminary data were analyzed for the first six subjects enrolled (aged 6.8–14.4 years; 5 male, 1 female) with OS of the extremity (2 femur, 2 tibia, 2 humerus). Bevacizumab was administered three days before the first cycle of chemotherapy (day-3) and on the first day of subsequent cycles. Two blocks of neoadjuvant chemotherapy each consisting of one cycle of cisplatin/doxorubicin and two doses of methotrexate were administered over 10 weeks before definitive surgery. DCE-MRI was performed on a Siemens 1.5 T scanner at baseline, on day-2 (one day after bevacizumab alone), day+1 (3 days after bevacizumab before starting chemotherapy), and day+5 (after starting chemotherapy) during the first cycle, and then at week 5 (after block 1), and week 10 (after block 2 and before definitive surgery).

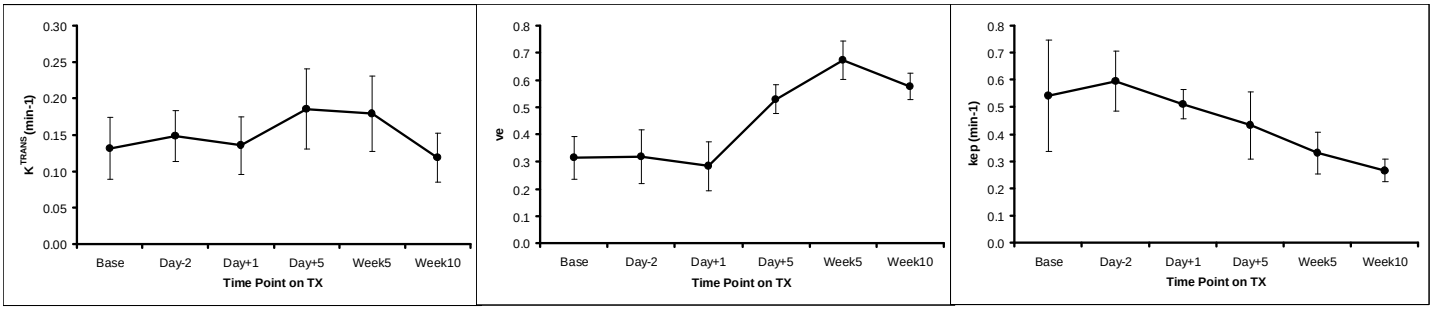
Before contrast, a baseline T1 estimation was performed using an inversion recovery 3D-HASTE acquisition (TR/TE=4000/78 ms, 5 mm thick, 16 sections) with 6 different inversion times (TI=100, 300, 900, 1500, 2200, 3300 ms) requiring 5 minutes total. DCE-MRI was acquired using a 3D-FLASH acquisition (TR/TE=3.5/1.32 ms, 20° flip angle, 5 mm thick, 16 sections, 50 measurements) collected over a 5:50 minute period. Kinetic 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[2]. Quantitative DCE-MRI measures 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. A series of k_{ep} maps from one patient are shown in **Fig 1**.

Fig 1. k_{ep} maps of one section from first patient demonstrating the change during therapy. Patient missed the day+1 examination.



RESULTS: Mean values of kinetic parameters throughout the tumors of six patients were assessed at each time point during therapy (**Fig 2**). K^{trans} and v_e did not change substantially at the initial two time points (with bevacizumab alone), but k_{ep} increased at day-2 and returned to baseline at day+1. After the start of chemotherapy, K^{trans} initially increased and then returned to baseline. However, v_e increased and k_{ep} decreased throughout therapy which may reflect increased necrosis in response to therapy.

Figure 2. From left to right, mean K^{trans}, v_e, and k_{ep} plots at each of time point during neoadjuvant chemotherapy for 6 patients.



CONCLUSIONS: It is feasible to use 3D DCE-MRI as a non-invasive measure to assess the effect of chemotherapy and bevacizumab on tumor in OS trials. Measures of k_{ep} and v_e may provide the most reliable measures of change in tumors.

REFERENCES: [1] Reddick WE, *Cancer*, 91:2230-2237, 2001. [2] Tofts PS, *JMRI*, 10:223-232, 1999.