T1 relaxation changes of bone and lymph node lesions of metastatic prostate cancer during 4 cycles of antiangiogenic drug therapy

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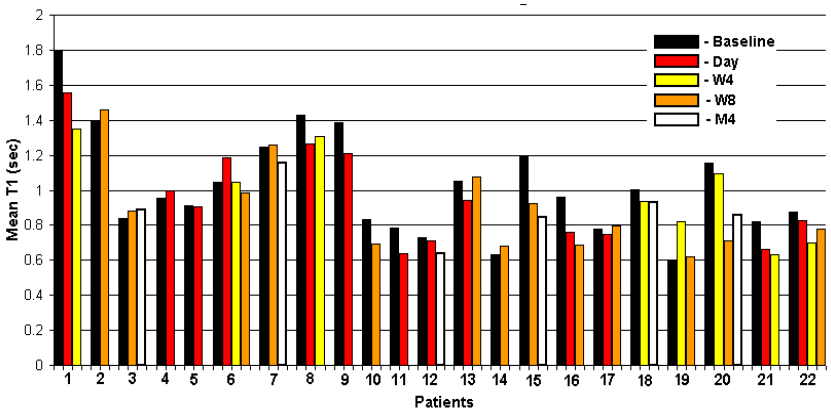
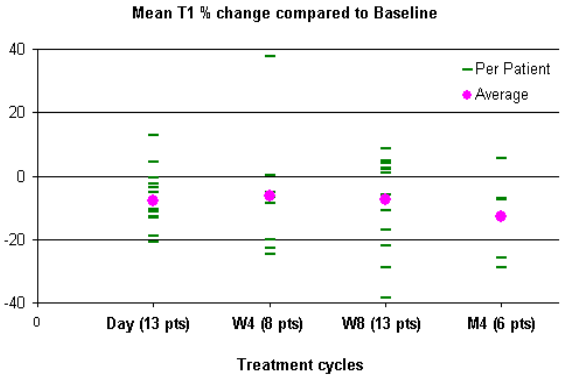
Introduction: Quantitative Dynamic Contrast Enhanced (DCE)-MRI has been used with increasing popularity in phase I and II trials of antiangiogenic agents [1] along with other functional imaging techniques. Quantitative, model based perfusion parameters, such as the transfer constant (K^{trans}) or less often model free initial area under gadolinium concentration curve (iAUGC) have been used to monitor and predict the outcome of these therapies. DCE driven quantitative analyses usually involve conversion of the MR signal into contrast agent concentration. And the T1 relaxation time is commonly used in that conversion process [2] and therefore is an important tissue characteristic to be carefully measured and considered. There is need for more studies addressing those potential changes in various tissues with common treatment options [3]. This study reports T1 changes of bone and lymph node lesions of 22 patients with metastatic prostate cancer through 4 cycles of antiangiogenic therapy.

Methods: Twenty-two patients with metastatic prostate cancer constituted the study population (mean age 65.5 years; range 53-77 years). This prospective study was approved by the local institutional review board and was compliant with HIPAA. An informed consent was obtained from each patient. All patients had MRI exams at baseline and at least at one follow up time point after anti-angiogenic drug regimen therapy, AZD2171 (Cediranib, AstraZeneca), which is an orally available small molecule multikinase inhibitor, with potent activity against VEGF receptor tyrosine kinases. There were 4 follow up time points: 1 or 2 days after the first dose (Day), then at the end of each treatment cycle - 4 weeks (W4), 8 weeks (W8) and 4 months (M4). Target lesions were found in bones (13 patients), lymph nodes (8 patients) and liver (one patient). MR Imaging was performed on two 1.5T MR systems (GE Healthcare, Waukesha, WI, USA and Philips Achieva, Best, The Netherlands) with dedicated receiver only phased array coils. The MR imaging consisted of T2-weighted images (TR/TE = 4600/100msec, slice thickness of 6mm, 40cm field of view, and matrix of 320x320) used to locate the target tumor, unenhanced T1-weighted images (TR/TE=9/3.6msec, with 5° Flip Angle (FA), 5 mm-thick sections, 40cm field of view, and matrix of 256x256) and the dynamic contrast-enhanced MR sequence (TR/TE=9/3.6msec, FA 15°, 5 mm-thick sections through the entire target lesion, 40cm field of view and acquisition time of 15 seconds per phase, matrix of 256x256). Both T1-W image sets were obtained with a three-dimensional spoiled gradient-echo sequence. During the DCE sequence, after three baseline unenhanced phases, an automatic injector (Medrad Spectris, Indianola, PA, USA) was used to intravenously infuse gadopentetate dimeglumine (Magnevist; Bayer Healthcare Pharmaceuticals, Wayne, NJ, USA) at 3mL/sec, for a total of 0.1 mmol per kilogram of body weight (typically 15–20mL), followed by 20mL normal saline flush. Total 23 phases were acquired at 30 second intervals for a total of 8 minutes. Patients were asked to hold their breath during MR image acquisitions. The first T1 weighted (FA 5°) and the pre-contrast baseline phases (FA 15°) were used to calculate the T1 relaxation maps. T1 calculations were performed using CADvue (iCAD, Inc. Nashua, NH), that was also used for manual segmentation of lesions and extraction of T1 mean and standard deviation. The 22 patients were selected from the larger cohort of the study population excluding exams affected by motion or artifacts.

Results: Out of 22 patients, all with pre-treatment exams, 13 had qualifying MR exams right after the first dose (Day), 8 patients - at W4, 13 patients - at W8, and 6 - at M4. There were large variations of lesion T1 values at the baseline (0.5 to 1.8sec) and changes with treatment cycles (the chart below, on the left). And overall decreasing trend was observed with therapy (the chart below, on the right): -7.8% average decrease after the first dose (Day), -6.28% after four weeks, -7.35% after 8 weeks and -12.8% after 4 months.





Summary and Conclusions: The T1 measurements show wide range of values at the baseline and considerable changes with the treatment using antiangiogenic drug in bone and lymph node lesions of metastatic prostate cancer, through 4 cycles of the therapy and as early as after the first dose. A study with more patients would be necessary, however the changes observed in our existing group suggest the need for accurate measurements of the T1 values during each MR session, if those are to be used in further quantitative analyses designed to evaluate the treatment effects.

References:

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