Monitoring treatment response to an anti-angiogenic therapy in experimental breast cancer bone metastases using DWI, DCE-MRI and VSI

M. Merz[1], D. Komljenovic[1], W. Semmler[1], and T. Bäuerle[1]
[1]Medical Physics in Radiology, German Cancer Research Center, Heidelberg, Germany, Germany

Introduction: In patients suffering from bone metastases imaging treatment response is essential for the clinical management. Current classification systems recommend the determination of the osteolytic lesion size by CT and the respective soft tissue component by MRI. Morphological changes in these osseous lesions often occur months after the initiation of treatment and are difficult to quantify. Using non-invasive imaging techniques from MRI such as diffusion-weighted imaging (DWI), dynamic contrast-enhanced MRI (DCE-MRI) and magnetic resonance vessel size imaging (VSI) changes in tumor cellularity and vasculature upon therapy can be assessed and quantified *in vivo*. In our study we evaluated treatment response to sunitinib malate in experimental breast cancer bone metastases by comparing morphological data from CT and MRI with functional parameters derived from DWI, DCE-MRI and VSI.

Materials and Methods: Rats bearing site specific breast cancer bone metastases in the right hind leg (1) were imaged at days 30, 35, 45 and 55 after tumor implantation in a clinical MRI scanner (1.5T Symphony, Siemens) using a home-built coil for radiofrequency excitation and detection as well as in an experimental flat-panel volume CT (VCT, Volume CT, Siemens). Animals of the treatment group (n=8) received sunitinib malate (20mg/kg p.o., daily from days 30 to 55 after tumor implantation) and were compared to an untreated control group (n=10). Volumes of the osteolytic bone lesions and the corresponding soft tissue tumors were determined on unenhanced VCT and T2-weighted MR images, respectively. For DCE-MRI T1w saturation recovery turbo FLASH sequences were acquired while infusing 0.1mmol/kg Gd-DTPA. Parameters *amplitude A* and *exchange rate constant k_{ep}* were calculated according to the two-compartment model by Brix (2). Mean vessel diameters in osseous lesions were determined by VSI (3). Therefore T2 and T2* weighted MR images were obtained before and after intravenous injection of ultra small paramagnetic iron oxide particles (USPIO, 200µmol Fe/kg). DWI was performed using half-Fourier acquisition single-shot turbo spin echo sequences (HASTE; b = 0, 50, 100, 200, and 600 s/mm^2) to measure *apparent diffusion coefficients* (*ADC*) within bone metastases. For statistical analysis the Wilcoxon test was applied; p-values <0.05 were considered significant.

Results: Animals treated with sunitinib malate showed significantly reduced osteolytic lesion sizes (OLS) and soft tissue components (STC) at days 45 and 55 (OLS: 35.3T/C%, day 45 and 19.0T/C%, day 55; STC: 19.3T/C%, day 45 and 10.5T/C%, day 55). Using DCE-MRI, DWI and VSI functional information was assessed non-invasively in osseous lesions. For the group treated with sunitinib malate, significantly decreased values for *A* and k_{ep} were found as early as from day 35 on compared to untreated animals (*A*: 81.9T/C%, day 35; k_{ep}: 39.4T/C%, day 35) until the end of the observation time (*A*: 54.4T/C%, k_{ep}: 46.8T/C% day 55). Significantly increased *ADC*s indicating decreased cellularity and necrosis in bone metastases were found on days 45 and 55 (*ADC*: 145.5T/C%, day 45 and 148.2T/C%, day 55) and mean vessel diameters increased significantly from day 35 (148.7T/C%) to day 55 (169.5T/C%) as assessed by VSI.

Conclusions: In the present study we show that sunitnib malate is effective in experimental breast cancer bone metastases. Treatment effects were assessed and quantified earliest with non-invasive MRI techniques such as DWI, DCE-MRI and VSI before a change in morphology was observed.
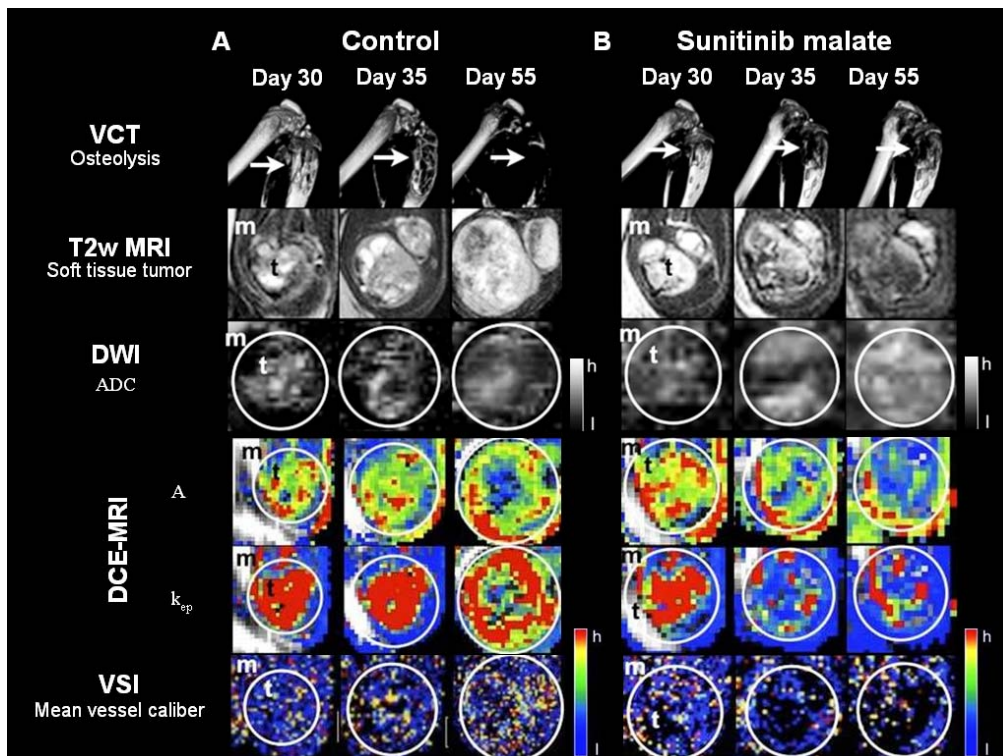

Figure legend: Morphology of bone metastases as imaged by VCT (3D reconstructions in first row) and T2w MRI (axial slices in second row) on days 30, 35 and 55 after tumor cell inoculation (A: untreated control; B: treatment with sunitinib malate; m = muscle t = tumor).
In *ADC* maps from DWI (third row, high values in white, low values in black), color maps for *A* and k_{ep} from DCE-MRI (fourth and fifth row) and maps for the mean vessel caliber derived from VSI (sixth row) white circles delineate bone metastases. Color maps in axial orientation for all parameters ranging from high values (h, red) to low values (l, blue).

References:
(1) Bäuerle T et al, Int J Cancer 2005
(2) Brix G et al, J Comput Assist Tomogr 1991
(3) Tropres I et al, Magn Reson Med 2001