Determination of hypothetic blood volume and vascular permeability of breast cancer bone metastasis by DCE-MRI in a nude rat model, preliminary results

T. Bäuerle[1], F. Kiessling[2], H-U. Kauczor[1], and S. Delorme[1]

[1]Department of Radiological Diagnostics and Therapy, German Cancer Research Center, Heidelberg, Germany, [2]Division of Medical Physics in Radiology, German Cancer Research Center, Heidelberg, Germany

Introduction. In osteotropic malignancies like breast, prostate, lung, kidney and thyroid cancer, the skeleton is frequently affected as metastatic site. From these cancers, the prevalence of skeletal disease is greatest in patients with breast or prostate carcinoma who in the advanced stage develop skeletal metastases in 70% [1]. According to the WHO and UICC the standard procedure for follow-up examinations of those patients is to assess the extent of bone destruction with bone scintigraphy, skeletal survey or CT [2]. As turnover in bone is slow, a change in bone lesion size is observed in these imaging modalities after several days or weeks. Consequently, there is need for additional radiologic imaging techniques to evaluate the course of bone metastases and their response to treatment.

Material and Methods. In order to induce osteolytic lesions, $1x10^5$ MDA-MB-231 human breast cancer cells were inoculated into the right superficial epigastric artery [3]. At day 30 after tumor cell inoculation bone metastases developed exclusively in the femur, tibia and fibula of the right hind leg. The bone lesions were imaged with a T2 (TR 3240 ms, TE 81 ms, matrix 152 x 256, FOV 90 x 53,4 mm, slice thickness 1,5 mm, 3 averages) and a saturation recovery turbo flash sequence (TR 373 ms, TE 1.86 ms, matrix 192 x 144, FOV 130 x 97.5 mm, slice thickness 6 mm) after intravenous injection of 0.1 mmol/kg Gd-DOTA (Dotarem, Guerbet, Germany). All MR images were acquired on a 1.5T Symphony (Siemens, Germany) with an appropriate animal coil for rats. The analysis according to the model of Brix [4] was performed with Dyna Lab (Mevis, Germany) on a computer based workstation. For statistical analysis the Wilcoxon-Test was applied; p-values <0,05 were considered significant.

Results. Nude rats (n=4) transplanted with MDA-MB-231 breast cancer cells developed osteolytic bone lesions confined to the femur, tibia or fibula of the right hind leg 30 days after tumor cell inoculation. Animals 1 and 2 showed constant lesion sizes at days 30 and 40 (data not shown), bone lesions of rats 3 and 4 increased in size (fig. 1 A-D). The bone metastases can clearly be distinguished in figures 1 A-D at days 30 and 40 after tumor inoculation on T2- weighted MRI. Additionally to the morphologic information of those images, DCE-MRI imaging of these animals revealed necrotic areas in the center of a bone metastasis (fig.1 F, H). Using the model of Brix [4] the parameters A (hypothetic blood volume) and k_{ep} (hypothetic vessel permeability) were determined in the tumor and the surrounding muscle of the hind leg (fig. 2). The A values at days 30 (0.5-1.2) and 40 (0.5-0.7) in the tumor were significantly higher than the respective A values in the surrounding muscle (0.2-0.3 at day 30 and 0.1-0.2 at day 40; fig. 2 A, B). Also the values for the Exchange Constant k_{ep} were significantly higher than the k_{ep} values in muscle (k_{ep} tumor 10.5-17.1 at day 30, 8.1-23.0 at day 40; k_{ep} muscle 1.6-2.3 at day 30, 1.4-2.3 at day 40; fig. 2 C, D). Metastases which were not increasing in size from day 30 to 40 (animals 1 and 2) showed lower A and k_{ep} values at days 30 and 40 than rats 3 and 4, whose lesion sizes increased (fig. 2 A-D).

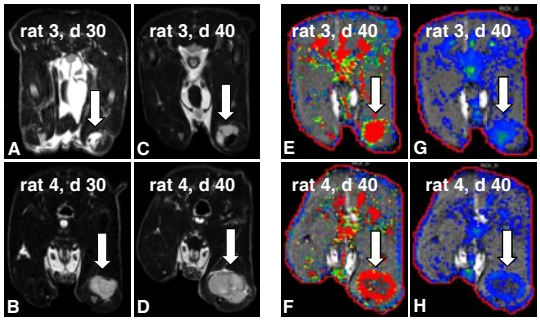

Figure 1. T2 weighted images (A-D) and sr tfl images (E-H) of rat no. 3 (upper row) and no. 4 (lower row) with bone metastases at the right hind leg (arrows). A and B, bone lesions at day 30 after tumor inoculation. C and D, bone lesions at day 40 after tumor inoculation. E-H, parameter maps for rats no. 3 and 4 at day 40 (E and F, k_{ep} parameter map; G and H, A parameter map).

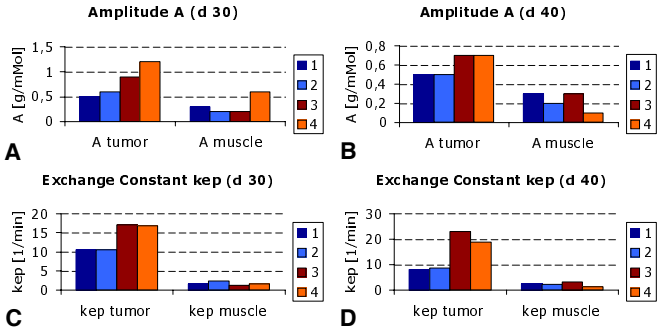

Figure 2. Amplitude A and Exchange Constant k_{ep} for animals 1-4 at days 30 (A and C) and 40 (B and D) after tumor cell inoculation for bone metastases (tumor) and the surrounding muscle.

Discussion. Using the model of Brix, two angiogenic parameters - the hypothetic blood volume (Amplitude A) and vessel permeability (Exchange Constant k_{ep}) - can be determined in bone metastases. The bone lesions were well vascularized and could clearly be distinguished from the surrounding muscles as the A and k_{ep} values in bone metastases were significantly higher. The determination of these angiogenic parameters might be very useful for follow-up examinations and evaluation of new treatments targeting bone metastasis. Interestingly, tumors with constant sizes in bone metastases showed lower values for blood volume and vessel permeability than bone lesions which increased in size. Although the number of animals in this study is low, we demonstrated that hypothetic blood volume and vessel permeability in bone metastases can be evaluated using the Brix model. This technique might be superior to the standard procedure proposed by WHO and UICC determining the area of bone destruction and might predict bone lesions at risk of progression.

References. 1 Coleman RE (1997). Cancer 80**:** 1588-94; **2** Hamaoka T, Madewell JE, Podoloff DA, Hortobagyi GN, Ueno NT (2004). J Clin Oncol 22**:** 2942-53**; 3** Bäuerle T, Adwan H, Kiessling F, Hilbig H, Armbruster FP, Berger MR (2005). Int J Cancer 115**:** 177-86**; 4** Brix G, Bahner ML, Hoffmann U, Horvath A, Schreiber W (1999). Radiology 210**:** 269-76