MONITORING METASTASES IN A MOUSE MODEL OF EWINGS SARCOMA USING DWIBS

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Introduction: Ewings sarcoma is the second most frequent primary bone cancer, with a characteristic age peak in adolescents and young adults. While modern treatment is able to cure the majority of patients with localized disease systemic relapse frequently occurs in patients, with disease that involves bone or bone marrow even after complete tumor responses to therapy. Novel treatment strategies are urgently needed, the development of which requires studies in animal models and appropriate means to monitor tumor growth and metastasis formation. While a mouse model of metastasis forming Ewing Sarcoma cells has been developed recently, monitoring of the disease in the mouse is challenging. MRI provides a number of contrasts that may be used to identify metastases. In particular diffusion weighting has been shown to be valuable for this purpose in humans. We have implemented DWIBS (Diffusion-weighted Whole-body Imaging with Body background signal Suppression(1,2)) for application in a mouse model to test whether metastasis detection is feasible.

Methods: DWIBS acquires several thin slice averaged during free breathing with STIR fat suppression and b-values of 1000, to reach suppression of normal body signal. 3D reconstructions are displayed as maximum intensity projections (MIP) with inverted gray scale to mimic the appearance of PET images. In humans it has been shown that DWIBS is in some cases equal to PET for metastasis detection (2,3). Measurements were performed on a Philips Achieva 3 T scanner equipped with a 4 cm solenoidal mouse coil. DWIBS (87 slices, slice thickness 0.8 mm, gap 0.2mm, FOV: 50 x 50 mm, NA: 1, single axis gradient in phase encoding direction, STIR fat suppression TI: 240 ms, TR: 16550 ms, TE: 63 ms), for comparison STIR (25 slices, slice thickness 1 mm, gap 0.1mm, FOV: 70 x 29 mm, NA: 16, fat suppression TI: 200 ms, TR: 2363 ms, TE: 87 ms), T1 weighted scans (3D GE: 56 slices, voxel size: 0.5 mm isotropic, FOV: 70 x 35 x 28 mm, NA: 6, TR: 5.9 ms, TE: 2.6 ms, Flip angle: 35 deg.) and T2 weighted scans (axial: 47 slices, slice thickness 1.5 mm, FOV: 30 x 30 mm, NA: 3, TR: 3758 ms, TE: 75 ms; sagittal: 27 slices, slice thickness 1 mm, FOV: 70 x 35 mm, NA: 3, TR: 2177 ms, TE: 75 ms) were performed. Six sub-lethally irradiated mice having received either 0.5, 2, or 6 million Ewings Sarcoma cells intra venously in the tail vein were imaged from week 3 after transplantation longitudinally over four weeks. Mice were anesthetized with 1.5% isoflurane and positioned roughly with the liver in the center of the coil. Total scan time was 38 min.

Results: DWIBS was successfully implemented and yielded images covering the animal from brain to the hind limbs (Fig. 1). Background signal was suppressed efficiently. Only fluids with long T2 (in the bladder and kidney) resulted in not fully suppressed residual signal (T2-shine-through-effect). Artifacts from breathing motion was satisfactorily averaged out, only peristaltic motion in the gut region produced residual artifacts (Fig. 1). Tissue with lower diffusion coefficients (brain and spinal cord) were also visible in the images. Metastasis were detected in DWIBS images due to the low diffusion coefficient, at the same time point as they were detectable in STIR or T1 weighted images (Fig. 1). Additionally acquired images with b-values of zero allowed for estimation of the apparent diffusion coefficients in the observed lesions, which was on average 0.45 mm^2/s compared to 2.8 mm^2/s in the bladder. Thus, DWIBS provided additional information to unambiguously identify lesions in STIR or T2 weighted images as tumors.

Applying all three sequences, analysis of the group of mice showed that the focus of metastasis formation was in the kidneys and further metastasis were detected in different locations without obvious focus.

Conclusion: DWIBS is feasible in mice and yields even with a clinical 3 T scanner additional data for identification and monitoring of metastasis forming cancers. Since DWIBS data are reconstructed as 3D MIP, metastasis become conspicuous and can be identified more easily than in multi slice imaging data. Artifacts from unsuppressed signal will be further reduced at higher magnetic field strength (due to shorter T2) and motion artifacts may be reduced with stronger gradient systems. Thus, DWIBS can be expected to perform even better on dedicated small animal scanners and to become a powerful tool in studies of animal models of cancer.

Literature: 1. Takahara T, et al. (2004) Radiat. Med. 22:275. 2. Kwee TC, et al. (2008) Eur. Radiol. 3. Mürtz P et al. (2007) Eur. Radiol. 17:3031.

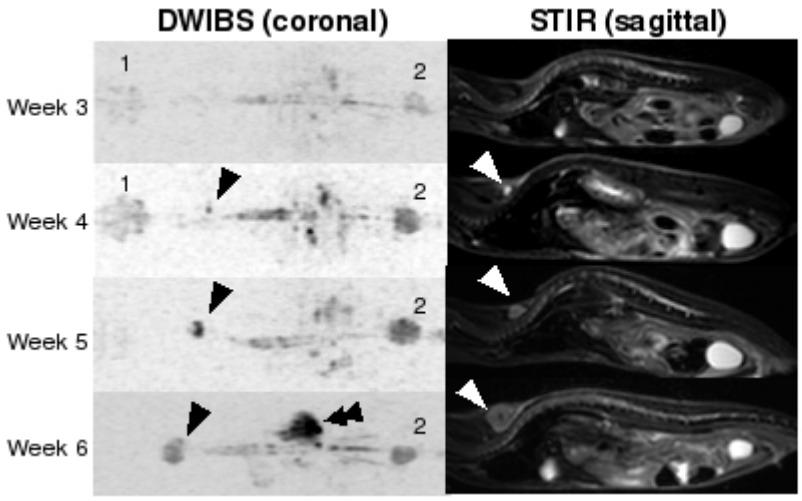

Figure1: Comparison of DWIBS and STIR images of one examplary mouse. Brain (1) and myelon are visible in DWIBS images due to lower diffusion values. Kidneys and bladder (2) are visible due to long T2, leading to residual signal (shine-through-effect). One metastasis in the neck (arrowhead) could be followed from week 4 to week 6. A large metastasis in the kidney was observed in week 6 (double arrow head).