Non-invasive correlation of 18F-FLT PET and DW-MRI of human lung carcinoma in a xenograft mouse model

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Target Audience: Preclinical scientists and clinicians with an interest in imaging biomarkers for cancer therapy

Purpose:

Diffusion-weighted magnetic resonance imaging (DW-MRI) and molecular imaging techniques, such as positron emission tomography (PET) offer potential imaging biomarkers for evaluating cancer therapy response. They provide complementary information about tumor proliferation from 3´-deoxy-3´-[^{18}F]fluoro-L-thymidine (^{18}F-FLT) PET, and about tissue ultrastructure from DW-MRI. How the latter is influenced by various pathophysiological processes during tumor growth and treatment is a matter of ongoing research[1] and can be addressed e.g. by immunohistochemical analysis. However, a direct overlay of *in vivo* imaging data and histological slides is hampered by a loss of reference points (due to tissue resection), shrinking (fixation) and the big mismatch in section thickness. We performed subsequent *in vivo* MRI and PET examinations of lung cancer cell xenografts without changing the animal position between scans in order to directly relate tracer accumulation to local diffusion coefficients.

Methods:

The human lung cancer cell line H1975 was implanted subcutaneously in the neck region of NMRI nude mice (n=3 tumors per mouse, n=2 mice). Two weeks after tumor implantation, animals were positioned on a custom-built animal cradle. A small canal in the cradle was filled with Magnevist (500 µmol/mL). It served as a landmark for later image coregistration (cf. fig. 1a). T2-weighted morphological images were obtained (9.4 T Bruker Biospec, 2D RARE, TR/TE/Rare factor 3600/40/8, FOV 35 mm, 256 matrix, slice thickness 1 mm) and the apparent diffusion coefficient (ADC) was determined from DW-MRI (EPI-DTI, TR/TE 1000/19 ms, 12 segments, 7 b-values from 0 - 700 s/mm², FOV 35 mm, 128 matrix, slice thickness 1 mm, NEX 6, ECG- and respiration trigger). The reference channel was refilled with radiotracer (1 MBq/mL, cf. fig. 1b). Within the same anesthesia ^{18}F-FLT-PET was performed 70-90 min after tail vein injection of 10 MBq ^{18}F-FLT (quadHIDAC, spatial resolution 0.7 mm FWHM). Quantitative results are reported as mean ± SD. Histology was accomplished after imaging experiments to allow for correlation of imaging data with morphology (HE), tumor proliferation (Ki67), and cell death (caspase 3 and TUNEL).

Results:

On T2w images (cf. fig.2a) tumor tissue appeared heterogeneous, with a dark rim and a central area with medium to high signal intensity. Diffusion coefficients were low (1.1 ± 0.148 mm²/s) at the rim and higher within the tumor core (1.9 ± 0.215 mm²/s). As seen in the overlay (cf. fig. 2d) of ADCmap and PET image, high mean ^{18}F-FLT accumulation was found in the tumor rim (5922 ±1154 Bq/mL) and lower mean uptake values (2399 ± 237 Bq/mL) in the core of the tumor. Immunohistochemistry indicated tumor proliferation at the rim and cell death within the tumor core.

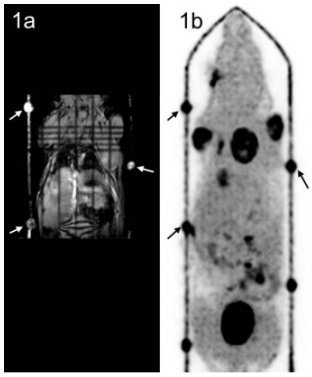

Figure 1: MR scan of the thorax and whole body PET image. The reference canal filled (a) with Magnevist (b) with radiotracer is visible with both modalities. The spheres (arrows) were used as landmarks for coregistration.

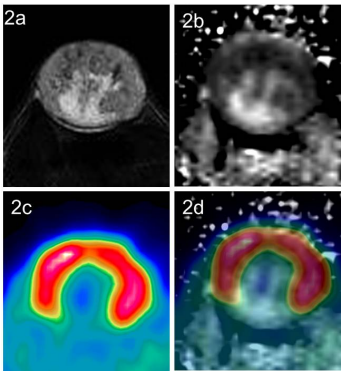

Figure 2: Representative (a) T2w morphological MRI, (b) ADCmap, (c) ^{18}F-FLT-PET, (d) overlay of ADCmap and PET scan.

References:

1. Sinkus R. et al., Apparent diffusion coefficient from magnetic resonance imaging as a biomarker in oncology drug development, *European Journal of Cancer* 2012, **48**, 425-431

Discussion:

Tumor tissue heterogeneity is reflected by regional changes in ADC. ^{18}F-FLT uptake restriction to the proliferative rim of the tumor support the assumption that high ADC values within the tumor core represent necrotic areas[1]. These results accord with bimodal imaging data from our lab from further 20 mice with subcutaneous H1975 tumors, which had been obtained at consecutive days. Accurate coregistration of these tumors was not possible due to time difference (of 1 day) and change in position. However, different tumor areas could be classified by ADC coefficient or tracer accumulation, respectively.

Conclusions:

Successful cancer therapies are expected to kill tumor cells and thereby further increase tissue heterogeneity. The non-invasive correlation between ADC and specific radiotracer accumulation may help to better evaluate therapeutic efficacy in the preclinical and clinical setting.

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