Histogram Analysis of Saturation Time Dependent Amide Proton Transfer MRI in Brain Metastases

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Purpose - In recent years, saturation transfer MRI techniques based on endogenous contrast of exchangeable amide protons of intra-cellular proteins and peptides (amide proton transfer, APT)[1,2,3] have been developed successfully and applied in initial clinical studies for oncology and neurology applications. For the analysis of the obtained APT measures, specifically in different tumor types and contralateral normal appearing white matter (NAWM), ROI averages of the magnetization transfer asymmetry (MTR_{asym}) are typically used. But tumor tissue is often very heterogeneous and may contain different tissue compartments like the solid tumor, necrosis, edematous or cystic areas. The high spatial resolution of the APT MRI techniques (e.g. 2 mm in plane) allows a detailed analysis of the amide concentrations found within the apparent tumor boundaries. In this work, histogram analyses were performed in an exemplary study in human brain metastases cases. Different durations of the sensitizing RF saturation pulse were chosen to analyze potential differences on a multi-compartment APT signal.

Methods - The study was performed on a 3.0T clinical whole-body scanner (Achieva TX 3.0T, Philips Healthcare, NL) using an 8-channel head coil for signal reception and 2-channel RF transmission via the body coil. Five cancer patients with confirmed brain metastasis from different primary origin (esophageal, urethral, breast) were enrolled, from whom informed consent was obtained. The protocol was approved by the institutional review board. Pulsed RF saturation with an overall duration T_{sat} = 0.5, 1.0 or 2s was used consisting of 50 ms single lobe sinc-gaussian pulse elements with $B_{1,rms}$=2.0μT. 100% RF duty cycle was achieved by alternate transmission via two RF channels[3]. RF shimming was applied for both, image homogeneity (excitation/refocusing pulses) and for saturation homogeneity (amplitude of saturation pulse elements) via a B_1 calibration measurement. 2D fast spin-echo sequences with driven equilibrium refocusing were used: TR/TE=5s/6ms, FOV (230 mm)^2, matrix 168^2, resolution 1.8×1.8×5 mm^3. 25 Z-spectral images S[ω], ω=−6 to 6 ppm (step 0.5ppm) and S_0 were measured with 2 minutes total acquisition time. B_0 field maps for off-resonance correction were acquired separately (identical geometry, 2D GRE, ΔTE=1ms, TR/TE=15ms/8ms, 16 averages, 33 sec). For B_0 mapping, low gradient strength was used to minimize eddy current effects. The resonance frequency reference and the B_0 shimming were carefully fixed among the APT and B_0 acquisitions. APT maps based on MTR_{asym}=(S[−3.5ppm]−S[+3.5ppm])/S_0 were calculated using Z-spectral interpolation for B_0 correction[3]. Tumor ROIs covering the metastases and contralateral NAWM ROIs were manually defined by a trained radiologist based on the clinical gadolinium contrast-enhanced T1w and T2w images. The APT data was analyzed in histograms (−3 to +10% MTR_{asym}, 150 bins), and single-peak as well as multi-peak (2-/3-peak) Gaussian fits were performed on the histogram data.

Figure 1: Histogram analysis of the APT measurement in a selected brain metastases case (primary tumor: breast) using different durations of the RF saturation: (a,d) T_{sat}=0.5 sec, (b,e) 1.0 sec, (c,f) 2.0 sec. Graph (g) shows a three component Gaussian fit to the histogram (f).

Results and Discussion – Exemplary histogram data from a brain metastasis patient with primary diagnosis of breast cancer is shown in Figure 1: T_{sat}=0.5 sec (a, d; red), 1.0 sec (b, e; green) and 2.0 sec (c, f; blue). NAWM based MTR_{asym} closely follows single-peak Gaussian distributions for any duration (for clarity of the graph, only fits shown for a/b). A nearly single-peak distribution is found for Fig1.d, but with longer duration of the RF saturation, the distributions spread and show 2 or 3 distinguishable components (Fig.1e/f). Fig1.g shows the individual components of a 3-peak fit for T_{sat}=2.0s (f). The center values of the NAWM distributions are clearly

Figure 2: Summary of the ROI histogram findings in the group of 5 subjects with brain metastases for 3 durations of the RF saturation T_{sat}: (a) Average of center MTR_{asym} values from single-peak fits. (b) Average of the highest MTR_{asym} components found in multi-peak fits. (c) Average NAWM center values. A clear contrast gain is observed for long T_{sat}.

diminishing for a longer saturation. The mean values in the tumor ROI are increasing with T_{sat}, and the increase is in particular pronounced for the compartment with highest MTR_{asym} values. On the other hand, some compartments with low MTR_{asym} remain mostly unchanged resulting in a particular large spread at long T_{sat}. The average findings from all subjects are summarized in Figure 2. While the single-peak values (a) reflect the mean increase of APT signal, the T_{sat} mediated MTR_{asym} increase in the 3rd compartment (b) from the multi-peak fit is more pronounced. Initial anatomical correlations indicate, that this compartment is related to protein-rich cystic areas in the metastasis. Overall, a clear gain of APT contrast is observed for increasing RF saturation time. Based on these findings, histogram type analysis is strongly recommended for further investigation of APT contrasts for tumor tissue characterization.

References - **1**. Zhou J et al., Using the amide proton signals of intracellular proteins and peptides to detect pH effects in MRI. Nat Med. 2003; 9(8):1085-90. **2**. Wen Z et al., MR imaging of high-grade brain tumors using endogenous protein and peptide-based contrast. Neuroimage. 2010; 51(2):616-22. **3**. Keupp J et al., Parallel RF Transmission based MRI Technique for Highly Sensitive Detection of Amide Proton Transfer in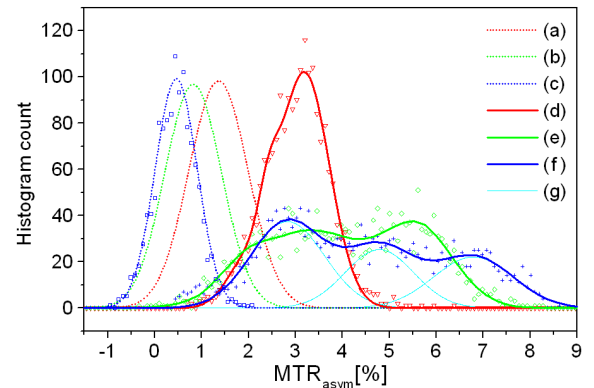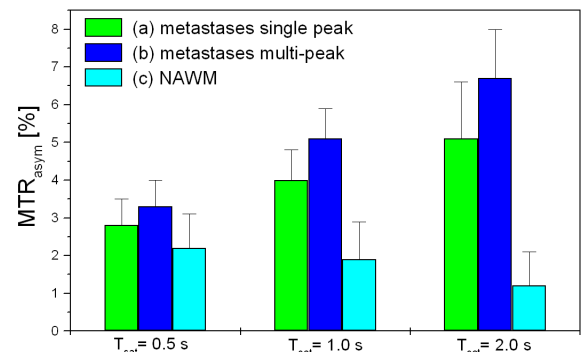 the Human Brain at 3T. Proc. ISMRM 19:710 (2011).