Can brain tumor microenvironment and associated structures be probed by Amide Proton Transfer at 7T?

Vitaliy Khlebnikov1, Daniel Polders2, Dennis Klomp1, Jeroen Hendrikse1, Pierre Robe3, Eduard Voormolen4, Peter Luitjens1, and Hans Hoogduin1

1Department of Radiology, University Medical Center Utrecht, Utrecht, Netherlands, 2Philips Healthcare, Best, Netherlands, 3Brain Division, University Medical Center Utrecht, Utrecht, Netherlands

Target audience. The work will be of interest to anyone interested in the application of Chemical Exchange Saturation Transfer (CEST) imaging in oncology.

Purpose. Any knowledge about differences in microenvironment between normal tissue and tumor can potentially be exploited in therapy. Amide Proton Transfer (APT) imaging is a potentially powerful tool in characterizing tumor microenvironment due to its sensitivity to pH and protein content at high spatial resolution. However, the effects of pH and protein content alteration in tumors can cancel each other out in APT. Moreover, recent correction mechanisms for water T1-relativity and extraction of NOE effects can have a substantial impact on the true APT signal. The purpose of this pilot study was to compare true APT with traditional asymmetry (MTRasymsym) in a variance of brain tumor patients at 7T to investigate the value of APT imaging in tumors.

Methods. 6 patient (3 male, 3 female, average age 49±13.4) with intracranial brain tumors (meningioma WHO grade 1, oligodendroglioma WHO 2, oligo-astrocytoma WHO 2, glioblastoma WHO 4 and 2 glioblastoma-multiform WHO 4) were enrolled in the study. Informed consent was obtained from all patients in agreement with the guidelines set by the local ethical committee. The patients were scanned on a 7T Philips MR system using a 2 channel transmit coil in combination with either a 32 or 16 channel receive head coil (NOVA medical) followed by a standard 3T pre-operative protocol. CEST data was acquired using a 3D segmented EPI readout as described in [1], using 18 frequency offsets (50ms block receive pulse, 1.8 μT) and 3D segmented EPI readout (EPI factor 15 along AP) with a binomial RF pulse for water only excitation,, TR/TE/Fa=106ms/6.4ms/18.5°, FOV 224x224x100 mm3, isotropic resolution 2mm, time per volume 20.3s, inter-volume delay 2s, total scan time 6min40s. Water T1, T2, and MTRasymsym were linearly corrected for B0. Fluid attenuated inversion recovery (FLAIR) [3] was used to visualize edema and cystic regions. T1map was obtained as described in [4]. B0map was based on the dual TR sequence [5]. The 3T protocol included a T1-weighted post gadolinium (Gd, 0.1 ml/kg, Gadobutrol, Gadovist 1.0 mmol/mL, UK) scan with 3D fast field echo (FFE) readout, TR/TE=475/14 ms, FOV 240x240x180 mm3 and reconstructed voxel size 1 mm3. All images were co-registered to the FLAIR space in FSL (FMRI v6.0, UK). Tumor tissues masks, classified as Gd-enhanced tumor (ROI 1), non-enhanced solid tumor (ROI 2), non-enhanced cystic (ROI 3), edema (ROI 4), normally appearing white matter (ROI 5) and normally appearing gray matter (ROI 6), were drawn by an experienced radiologist.

Results and Discussion. A representative case is shown Fig. 1. APT (Fig. 1 C) and MTRasymsym (Fig. 1 D) is significantly enhanced in tumor core, in agreement with a high protein content and slightly alkaline environment [6]. Average ROI analysis from all patients demonstrated that there is no difference in T1corrected APT between different tumor tissues as indicated by the overlapping standard deviations (Fig. 2 A). One explanation of the result is the interplay between the effects of pH and protein content cancelling each other out in pure APT. Interesting, MTRasymsym (Fig. 2 B) differentiated tumor tissues fairly well. Since MTRasymsym is mostly NOE (nuclear overhauser enhancement) [7] dominated, very similar information is to be expected from NOE as well (NOE analysis was not done in our experiments from -4 to -3 ppm were not sufficient for a reliable analysis). While similar information can in principle be obtained from FLAIR and post Gd-T1w images, MTRasymsym in this pilot study could distinguish Gd-enhanced tumor from non-enhanced solid tumor without contrast agent administration.

Conclusions. Average T1corrected APT signal showed very small variation between normal tissue and pathology and is of little clinical use without decoupling of the effects of exchange rate and concentration. Yet, MTRasymsym may distinguish Gd-enhanced tumor from non-enhanced solid tumor as demonstrated by a very good demarcation of different tumor tissues based on average data from 6 patients.


This work was funded by the FP7 Marie Curie Actions of the European Commission (FP7-PEOPLE-2012-ITN-316716).