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

Vitaliy Khlebnikov[1], Daniel Polders[2], Dennis Klomp[1], Jeroen Hendrikse[1], Piere Robe[3], Eduard Voormolen[3], Peter Luijten[1], and Hans Hoogduin[1]
[1]*Department of Radiology, University Medical Center Utrecht, Utrecht, Netherlands,* [2]*Philips Healthcare, Best, Netherlands,* [3]*Brain 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 T_1 relativity (T_{1w}) 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 (MTRasym) 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-actrocytoma 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 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 mm^3, isotropic resolution 2mm, time per volume 20.3s, inter-volume delay 2s, total scan time 6min40s. Water T_1 (T_{1w})-corrected APT [2] was quantified as an area between CEST-spectrum and continued baseline in the region from 3 to 4 ppm. Asymmetry was calculated as MTRasym=CEST(-ώ ppm)/M_0-CEST(ώ ppm)/M_0 in the region from 3 to 4 ppm. Both APT and MTRasym were linearly corrected for B_1. Fluid attenuated inversion recovery (FLAIR) [3] was used to visualize edema and cystic regions. T1map was obtained as described in [4]. B_1map was based on the dual TR sequence [5]. The 3T protocol included a T1-weighted post gadolinium (Gd, 0.1 ml/kgm Gadobutrol, Gadovist 1.0 mmol/mL, UK) scan with 3D fast field echo (FFE) readout, TR/TE=475/14 ms, FOV 240x240x180 mm^3 and reconstructed voxel size 1 mm^3. All images were co-registered to the FLAIR space in FSL (FMRIB 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.

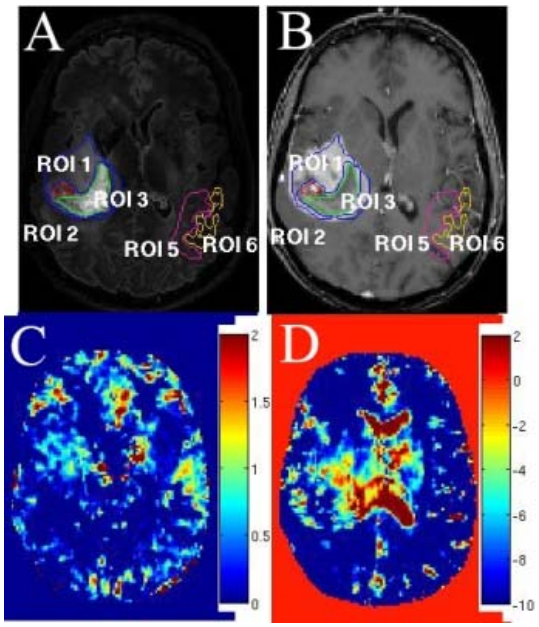

Fig. 1. ROI-based tumor tissue analysis of a patient with glioblastoma (WHO grade 4). (A) FLAIR, (B) post Gd-T1w, (C) APT and (D) MTRasym. The colored masks are defined in the methods. Edema region was not identified.

Results and Discussion. A representative case is shown **Fig. 1**. APT (**Fig. 1 C**) and MTRasym (**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 T_{1w}-corrected 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, MTRasym (**Fig. 2 B**) differentiated tumor tissues fairly well. Since MTRasym 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 this work because NOE offsets used 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, MTRasym in this pilot study could distinguish Gd-enhanced tumor from non-enhanced solid tumor without contrast agent administration.

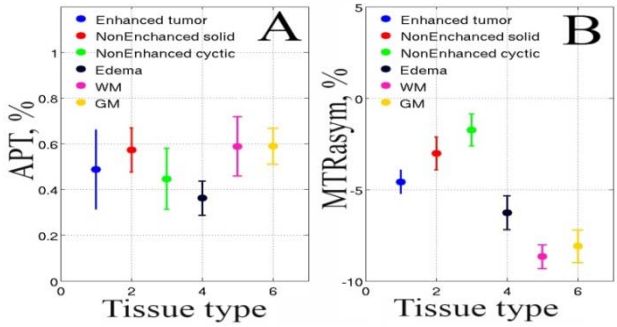

Fig.2. Average ROI-based tumor tissue analysis of all patients. (A) APT and (B) MTRasym. ROI 1 - Gd-enhanced tumor, ROI 2 - non-enhanced solid tumor, ROI 3 - non-enhanced cystic, ROI 4 – edema, ROI 5 - normally appearing white matter and ROI 6 - normally appearing gray matter.

Conclusions. Average T_{1w}-corrected 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, MTRasym 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.

References. [1] Jones C et al. Magn Reson Med 2012. [2]. Zaiss M et al NMR Biomed 2014. [3].Visser F et al. Magn Reson Med. 2010. [4]. Ordidge RJ et al. Magn Reson Med. 1990. [5] Yarnykh VL, Magn Reson Med. 2007. [5]. Nelson SJ. NMR Biomed. 2011. [6] Griffiths JR. Br J Cancer. Sep 1991. [7] Paech D et al. PloS one. 2014.

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