NUCLEAR OVERHAUSER ENHANCEMENT (NOE) MEDIATED CHEMICAL EXCHANGE SATURATION TRANSFER (CEST) IMAGING AT 7 TESLA IN GLIOBLASTOMA PATIENTS

Daniel Paech[1,2], Jan Eric Meissner[3], Johannes Windschuh[3], Benedikt Wiestler[4], Jan Oliver Neumann[5], Heinz Peter Schlemmer[6], Wolfgang Wick[4], Armin Nagel[3], Marc Ladd[3], Martin Bendszus[1], Peter Bachert[3], Moritz Zaiss[3], and Alexander Radbruch[1,2]

[1]Department of Neuroradiology, University of Heidelberg Medical Center, Heidelberg, BW, Germany, [2]Neurooncologic Imaging, Department of Radiology, German Cancer Research Center (Deutsches Krebsforschungszentrum, DKFZ), Heidelberg, BW, Germany, [3]Department of Medical Physics in Radiology, German Cancer Research Center (Deutsches Krebsforschungszentrum, DKFZ), Heidelberg, BW, Germany, [4]Department of Neurooncology, University of Heidelberg Medical Center, Heidelberg, BW, Germany, [5]Department of Neurosurgery, University of Heidelberg Medical Center, Heidelberg, BW, Germany, [6]Department of Radiology, German Cancer Research Center (Deutsches Krebsforschungszentrum, DKFZ), Heidelberg, BW, Germany

Target Audience: Researchers and clinicians in the field of MRI who are interested in the use of chemical exchange saturation transfer (CEST) contrast in oncology.

Purpose: Diagnosis of glioblastoma is usually based on T1-weighted gadolinium contrast enhanced MRI in combination with T2-weighted images. However, established MRI sequences suffer from limitations in particular concerning the determination of tumor infiltration area and identification of most malignant portions with high tumor proliferation [1]. Initial examinations at 7T showed for one glioblastoma patient that NOE mediated CEST effects significantly drop in tumor tissue [2]. The purpose of this study was to investigate if CEST contrast with high 3D spatial resolution at 7T MRI can provide additional information about glioblastoma pathophysiology, specifically the visualization of tumor infiltration and tumor hot spots compared to T1 contrast enhanced (ce-T1) and T2-weighted images.

Methods: Eleven patients (2 female, 9 male) with newly diagnosed and histologically proven glioblastoma were enrolled in this prospective study before surgery. Approval of the local ethics committee after written informed consent was obtained. CEST contrast was acquired with a modified three-dimensional gradient-echo sequence (~09 min 30 sec) and a 24-channel head coil on a 7T whole body MRI scanner (Magnetom 7T; Siemens Healthcare, Erlangen, Germany). Asymmetry calculation defined as MTR_{asym}= Z(Δω = -3.3 ppm) - Z(Δω = +3.3 ppm) yields the CEST contrast. At the applied saturation field amplitude of 0.7μT CEST effects are predominantly NOE mediated [3]. Contrast enhanced T1 (ce-T1) and T2-weighted images at 3 Tesla were used for data co-registration. Six regions of interest (ROI) were selected for each patient in a representative slice for quantitative analysis: 1) tumor enhancement according to ce-T1, 2) hot spots within tumor enhancement, 3) tumor necrosis, 4) surrounding tumor edema on CEST according to T2, 5) cerebrospinal fluid and 6) contralateral normal appearing white matter (Fig. 1A-C).

Results: NOE-effects in all contrast-enhancing parts, as well as in the necrosis and the surrounding edema of glioblastoma were decreased in comparison to contralateral white matter. Thus average MTR_{asym} in contrast enhancing regions, surrounding edema and necrosis were significantly higher than in contralateral white matter ($p<0.001$). MTR_{asym} in edema was significantly lower than in ce-T1 tumor parts ($p=0.027$) and tumor necrosis ($p<0.001$). Edema extension in nine out of 11 patients was smaller on CEST than on T2 weighted images, while two displayed at equal size. Furthermore, stria like substructures could be identified within the edema on CEST images that extended to the edema periphery. Hot spots on CEST displayed within the contrast enhancing tumor that were not discernible on ce-T1. Average MTR_{asym} in hot spots was significantly higher than in ce-T1 tumor ($p<0.001$) and tumor necrosis ($p=0.002$). Even though CEST contrast showed a comparable asymmetry as parts of the tumor and cerebrospinal fluid (Fig. 1E), Z-spectrum analysis revealed that they can still be distinguished by the width of the direct water saturation (Fig. 1D). Figure 2 illustrates the quantitative ROI analysis as boxplot.

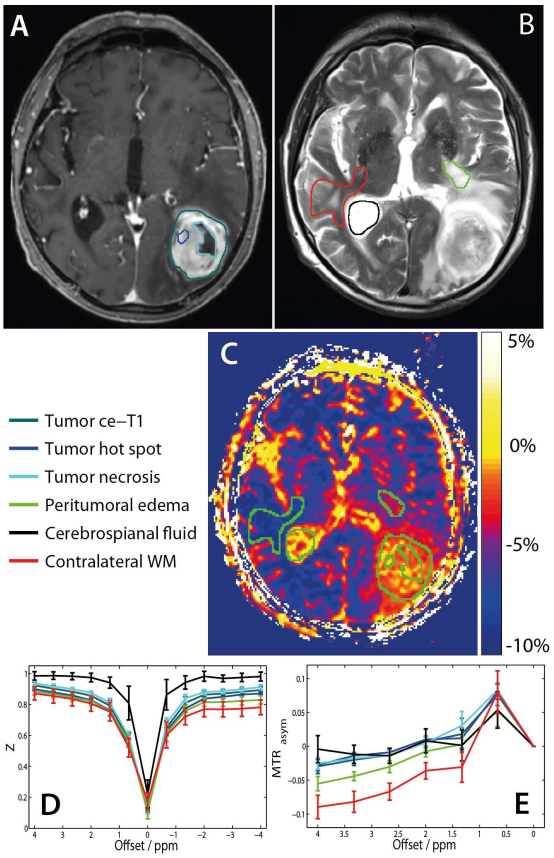

Figure 1 ROI analysis of a 53 year old patient with a left occipital glioblastoma. Co-registrated ce T1-weighted (A), T2 weighted images (B) and CEST asymmetry contrast at 3.3 ppm with color coded ROIs (C); Z-spectrum (D) and asymmetry analysis (E).

Discussion: Our study provides evidence that a contrast in glioblastoma can be obtained by NOE mediated CEST imaging in terms of infiltrative behaviour and hot spot imaging that cannot be acquired with conventional MRI. A major problem in glioblastoma imaging within daily clinical decision making is that it is not possible to differentiate a T2-signal increase caused by tumor infiltration and a non-specific cause of T2-signal increase (e.g. edema, radiation effects, decreased corticosteroid dosing, seizures, postoperative changes) [1]. As edema extension on CEST tends to be smaller than on T2- weighted images a potential explanation for this finding might be, that CEST contrast displays tumor infiltration more accurately than non-specific T2 weighted images. Furthermore hot spots on CEST might contribute to identify the most malignant tumor parts by adding information about protein concentration or protein folding as NOE mediated CEST effect is potentially caused by protein content, protein folding or pH-value [2] [3].

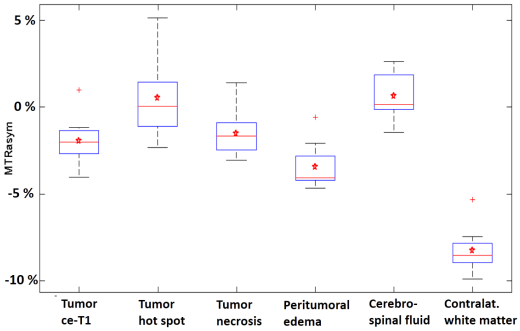

Figure 2 Boxplot of ROI analysis, mean values (red stars).

Conclusion: CEST offers a new contrast, different to T1- and T2-weighted imaging, which has the potential to identify the most malignant tumor portions as well as tumor infiltration and may therefore be further assessed as additional imaging technology for biopsy guidance, radiotherapy planning and therapy-assessment in neuro-oncology. Further research is needed to determine the pathophysiological origin of NOE mediated CEST effect and the clinical benefit of CEST contrast still needs to be proven within larger patient collectives, including follow up examinations and bioptical correlations.

References:

[1] Wen, P.Y., et al., Updated Response Assessment Criteria for High-Grade Gliomas: Response Assessment in Neuro-Oncology Working Group. JCO, 2010. 28(11): p. 1963-1972.

[2] Zaiss, M., et al., MR imaging of protein folding in vitro employing Nuclear-Overhauser-mediated saturation transfer. NMR in Biomedicine, 2013: p. n/a-n/a.

[3] Zhou, J., et al., APT-weighted and NOE-weighted image contrasts in glioma with different RF saturation powers based on magnetization transfer ratio asymmetry analyses. MRM, 2013. 70(2): p. 320-327.