Short echo time ^{1}H Magnetic Resonance Spectroscopic Imaging in the differentiation of high grade gliomas and metastases in the human brain.

J. P. Wijnen[1], M. W. Lagemaat[2], P. Krooshof[3], A. J. Idema[4], G. J. Postma[3], L. C. Buydens[3], T. W. Scheenen[1], and A. Heerschap[1]

[1]Radiology, Radboud University Nijmegen Medical Centre, Nijmegen, Gelderland, Netherlands, [2]Radiology, Radboud Universtiy Nijmegen Medical Centre, Nijmegen, Netherlands, [3]Analytical Chemistry, Radboud University Nijmegen, Nijmegen, Netherlands, [4]Neurosurgery, Radboud Universtiy Nijmegen Medical Centre, Nijmegen, Netherlands

Introduction:

^{1}H Magnetic Resonance Spectroscopy (MRS) has been widely used to characterize and grade human brain tumors [1,2]. Glioblastoma multiforme (GBM) and solitary brain metastases (MET) are both highly malignant grade IV tumors but originate from different organs. GBMs mostly present as heterogeneous lesion with a focal part surrounded by infiltrative growth in the brain, e.g. along white matter tracts [3], whereas METs are assumed to be more focal lesions without a strong infiltrative growth pattern. On conventional MR images, these two tumor types are hard to distinguish from each other. In this study we investigate the metabolic differences as found in MR spectra of GBMs and METs obtained with short echo time MRSI at 3T. We focus on the regions outside the tumor contrast enhancing area, since these regions show different pathology and growth patterns which we would like to characterize by ^{1}H MRS.

Methods:

14 Patients with newly diagnosed GBM and 9 patients with newly diagnosed MET were examined on a 3T whole body system (Magnetom TRIO, Siemens, Erlangen), the body coil was used for excitation and a 12-channel receive only head coil was used for reception of the MR signal. The MRI protocol included T2-weighted axial images (0.6x0.6mm, slice thickness 5mm, TR/TE 4040/102ms), T1 weighted 3D images (1x1x1mm, TR/TE 2300/4.71ms) before and after contrast administration (15ml 0.5mM Dotarem (Guerbet,France)), and 3D ^{1}H-MRSI using a semi-LASER sequence [4] (TR/TE 1500/30ms, nominal voxel size 1-1.7cc, hamming filtered weighted acquisition,, acquisition time 12 min.). MRSI data was analyzed by LCModel with a basis set with simulated metabolite profiles and a macromolecular profile that was measured in the normal brain. Metabolite maps of the concentrations calculated by LCModel were overlaid on MR images using an in-house developed software package MRCAD. The following regions of interest (ROIs) were selected: the non-enhancing necrotic tumor core (NE tumor), the contrast-enhancing tumor on T1-weighted post Gd image (CE tumor), the peritumoral region hyperintensive on a T2-weighted image (peritumoral T2h), the region normal appearing on T1 and T2-weighted images, at most 2 voxels away from the tumor (peritumoral) and contralateral normal appearing brain tissue (NAWM) (Figure 1). The quality of all MR spectra from the voxels inside the ROIs was manually assessed. Voxels with artifacts or bad fit results from LCModel (CRLB's of NAA+NAAG, Cre+PCr, PCho+Cho+GPC, mI+Gly or Glu+Gln >20%) were excluded from further analysis. For each ROI in each patient, metabolite concentrations were averaged over de number of voxels in the ROI and normalized to their averaged concentration in the NAWM ROI. Unpaired t-test were performed for all metabolites between the two patient groups and ROIs.

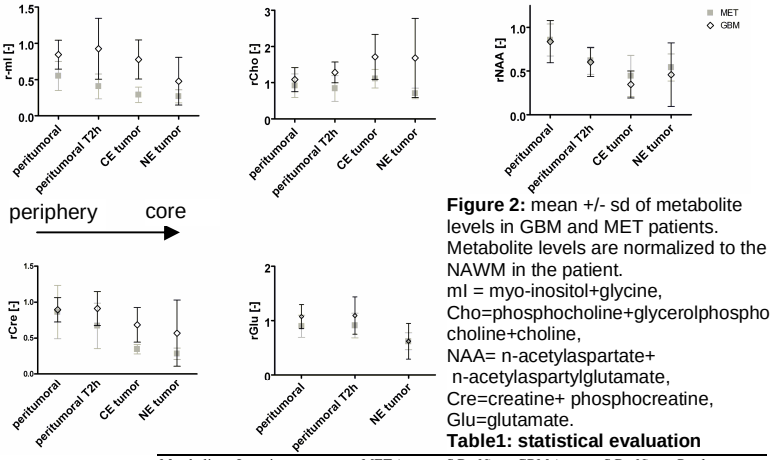

Figure 2: mean +/- sd of metabolite levels in GBM and MET patients. Metabolite levels are normalized to the NAWM in the patient.
mI = myo-inositol+glycine,
Cho=phosphocholine+glycerolphosphocholine+choline,
NAA= n-acetylaspartate+ n-acetylaspartylglutamate,
Cre=creatine+ phosphocreatine,
Glu=glutamate.

Table1: statistical evaluation

Metabolite	Location	MET (mean ± S.D., N)	GBM (mean ± S.D., N)	P value *t* -test
rCre	Peritumoral	0.86 ± 0.37 , 4	0.89 ± 0.17 , 12	0.812
	Peritumoral T2h	0.67 ± 0.32 , 6	0.91 ± 0.24 , 14	0.073
	CE tumor	0.35 ± 0.07 , 5	0.69 ± 0.24 , 9	0.011
	NE tumor	0.28 ± 0.08 , 4	0.57 ± 0.46 , 10	0.251
rCho	Peritumoral	0.92 ± 0.33 , 4	1.09 ± 0.33 , 11	0.400
	Peritumoral T2h	0.84 ± 0.35 , 5	1.28 ± 0.29 , 13	0.014
	CE tumor	1.11 ± 0.25 , 4	1.71 ± 0.62 , 9	0.094
	NE tumor	0.70 ± 0.15 , 4	1.68 ± 1.09 , 9	0.110
rNAA	Peritumoral	0.86 ± 0.18 , 4	0.84 ± 0.24 , 12	0.890
	Peritumoral T2h	0.62 ± 0.16 , 6	0.60 ± 0.17 , 14	0.838
	CE tumor	0.44 ± 0.23 , 4	0.35 ± 0.15 , 7	0.422
	NE tumor	0.54 ± 0.16 , 4	0.46 ± 0.36 , 8	0.682
r-mI	Peritumoral	0.55 ± 0.20 , 4	0.85 ± 0.20 , 12	0.023
	Peritumoral T2h	0.41 ± 0.17 , 6	0.93 ± 0.42 , 13	0.010
	CE tumor	0.29 ± 0.11 , 2	0.78 ± 0.27 , 8	0.042
	NE tumor	0.27 ± 0.09 , 2	0.48 ± 0.33 , 6	0.429
rGlu	Peritumoral	0.90 ± 0.20 , 3	1.08 ± 0.22 , 9	0.250
	Peritumoral T2h	0.91 ± 0.23 , 5	1.09 ± 0.34 , 11	0.299
	NE tumor	0.62 ± 0.15 , 4	0.62 ± 0.33 , 5	0.996

Results and Discussion:

The *t*-tests found significant differences between GBM and MET in rCre and r-mI in the CE tumor ROI (p = 0.011 and p = 0.042 resp.), in rCho and r-mI in the peritumoral T2h ROI (p = 0.014 and p = 0.010 resp.) and in r-mI in the peritumoral ROI (p = 0.023) (Table 1). Furthermore a decrease in rCre and rNAA towards the tumor core is observed in both patient groups (Figure 2). The increase of rCho in the peritumoral T2h region in GBMs, but not in METs corresponds with previous findings [2,5]. However, the stronger decrease in r-mI in METs compared to GBMs has not been reported before. A higher choline signal outside the tumor core in GBM has been related to tumor infiltration [6]. The reason that we only detected a small increase in rCho could be the random selection of peritumoral ROIs around the CE tumor region, averaging active infiltrating parts of the tumor with regions without infiltration, as infiltration can be local and directional. The pronounced difference in r-mI signal between GBM and MET was caused by a decrease in r-mI in MET. Since this effect was larger than that of rCho, we hypothesized that this change in myo-inositol in MET is a more general peri-tumoral effect (as opposed to directional infiltration), possibly related to an increased interstitial pressure around the tumor. If indeed related to pressure-induced edema, the difference between the tumor types could point to differences in edema or osmolarity between GBM and MET.

Conclusion: In this study we observed differences in metabolite levels in GBMs and METs as measured by short echo time ^{1}H MRSI. A significant difference in relative mI+Gly levels and relative Cho levels in the peritumoral T2 hyperintense regions was found. More detailed research in which metabolite levels are related to specific regions in the tumor and pathological phenotype is necessary to understand the biological processes that underly our observations.

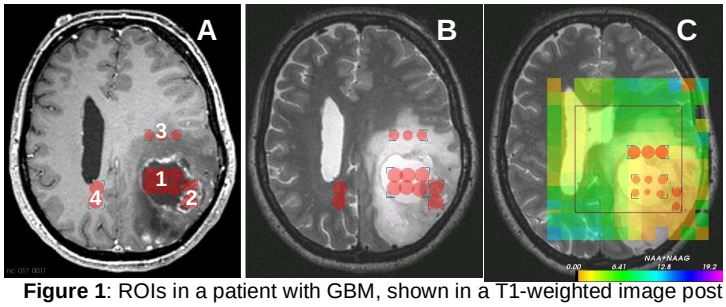

Figure 1: ROIs in a patient with GBM, shown in a T1-weighted image post Gd (A), T2-weighted image (B) and T2-weighted image overlaid with an metabolite map of NAA+NAAG (C). In A,B,C, ROIs are represented by groups of red circles;1=NE tumor, 2= CE tumor, 3=:peritumoral T2h, 4=NAWM

References: [1] Howe, MRM 2003,49;p223 [2] Nelson, Mol Cancer Ther 2003, 2;p497 [3] Giese, J.Clinical Oncology 2003, 21: p1624 [4] Scheenen, MRM 2008, 59;p1 [5] Law, NeuroRadiology, 2002,222;p715 [6] McKnight, J Neurosurg 2002,97;p794