Combined 31P and 1H MRSI in recurrent glioblastomas prior and post antiangiogenetic therapy

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Introduction:
Bevazizumab, a humanized monoclonal IgG antibody against the vascular endothelial growth factor (VEGF) has been considered as novel agent for treatment of glioblastomas (GBM). The agent blocks tumor neoangiogenesis, which is important for delivering oxygen and nutrition to the proliferating tumor cells. For evaluation of those novel therapeutic agents, discrimination between therapy-induced changes and tumor recurrence is crucial. Choline compounds observable as tCho signal in ¹H MRS, are well established markers in tumor diagnosis but details on the composition of this signal, which are available by ³¹P MRS, provide more specific information on the phosphatidylcholine cycle. Further, ³¹P MRS provides information on phosphorylated compounds of the phosphatidylethanolamine cycle as well as energy metabolism and pH. Thus, we combined ¹H MRSI and ¹H-decoupled ³¹P MRSI to examine patients with recurrent glioblastomas before and following therapy with Bevazizumab, suggesting that phospholipid metabolism may provide important information on tumor malignancy while tumor energy metabolism and pH might be related to hypoxia.

Methods:
Sixteen patients with recurrent malignant gliomas were included in the study. MRSI was performed initially and 6-8 weeks after onset of Bevazizumab therapy. Ten of the 16 patients showed a defined response to the therapy (RANO criteria). For those patients, tumor metabolites and pH were compared before and after treatment. MR examinations were performed on a 3 Tesla whole body system (Magnetom Trio, Siemens Medical AG, Erlangen, Germany) with a double tuned ¹H/³¹P volume head coil (Rapid Biomedical, Würzburg, Germany). For ¹H MRSI a transversal slice (15 mm slice thickness, 7.5 mm in plane resolution) was positioned to cover a maximum of tumor tissue. A 3D MRSI slab (extrapolated matrix yielding 25 mm slice thickness, 19 mm in plane resolution) aligned to the 1H MRSI slice was used for ³¹P MRSI (WALTZ4 proton decoupling). Data were sampled from voxels within the tumor and, as control, from the respective area in the contralateral hemisphere, and analysed with jMRUI (³¹P) or LCModel (¹H). Signal intensities were averaged over the target region and quantified as laboratory units (a.u.). Further, the pH values of tumor and control tissue were determined from the chemical shift difference between inorganic phosphate and phosphocreatine. Significant differences before and during therapy were established using a nonparametric test for paired samples (Wilcoxon-Test).

Results:
Untreated recurrent GBM showed decreased concentrations of tNAA, PCr and an increased Pi/ATP ratio. Following therapy, these parameters did not change. However, for responders a decreased GPE concentration (Fig.1, upper panel) and an increased pH (Fig. 1, lower panel) were reverted to normal values upon treatment (Fig.1).

Discussion:
This is the first in vivo study to investigate changes in membrane and energy metabolism in human recurrent GBM. Experimental in vivo ³¹P MRS of subcutaneous 9L gliosarcoma revealed that tumor growth was associated with a decline in PCr and ATP, which rebounded following chemotherapy (Steen 1988). This is in line with the decrease of Pi/ATP and PCr concentrations in recurrent GBM, indicating tumor hypoxia, which was not reversed under antiangiogenic therapy. A decrease of the phosphomonoster/phosphodiester ratio as response to therapy has been observed in several tumor models including glioma (Mancuso 2005, Valonen 2005). While these studies refer to the phosphatidylcholine cycle, a similar mechanism might affect the phosphatidylethanolamine cycle corroborating our finding that reversion of GPE decrease in treated recurrent GBM serves as an indicator of therapy response.

References: