

Phospholipid metabolism before and during bevacizumab therapy in recurrent glioma

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Introduction

MR spectroscopic imaging (MRSI) investigates metabolism of membrane lipids which has been shown as one of the major indicators for tumor growth [1]. We investigated in vivo ³¹P MRS to monitor recurrent glioblastomas (GBMs) before and during antiangiogenic treatment with Bevacizumab (BVZ) measuring the ethanolamine (Eth) and choline (Cho) related lipid metabolism as well as the high-energy metabolites phosphocreatine (PCr) and ATP.

Methods

¹H and ³¹P MRSI was performed as described in [2]. We examined 32 patients with recurrent GBMs before and every 2 months after the first BVZ cycle until the tumor recurred again. Patients were grouped into long and short overall survival (OS) times referring to the median overall survival measured from start of BVZ therapy. For both groups, parameters from tumor tissue were compared to the contralateral hemisphere (control tissue). Detectable metabolites within the tumor area were quantified in terms of concentrations and concentration ratios. The ratios of membrane lipid anabolites (PCho, PEth) to their respective catabolites (GPC, GPE) were assumed as indicators for tumor growth while the ratios of ATP and PCr to inorganic phosphate (Pi) characterized high-energy tumor metabolism. In addition, the longitudinal changes were evaluated.

Results

Before BVZ, recurrent GBMs showed significant increases for ¹H MRS detectable choline (which includes GPC and PCho) and also for the PCho/GPC ratio compared to control tissue. Significantly higher PCho/GPC ratios were found in patients with short-OS and PCho/GPC ratios before BVZ inversely correlated with the survival days. Both groups showed significantly elevated PEth/GPE compared to control tissue (Fig.1). Decreased ratios of PCr/Pi and ATP/Pi compared to control indicated impaired energy metabolism for both groups.

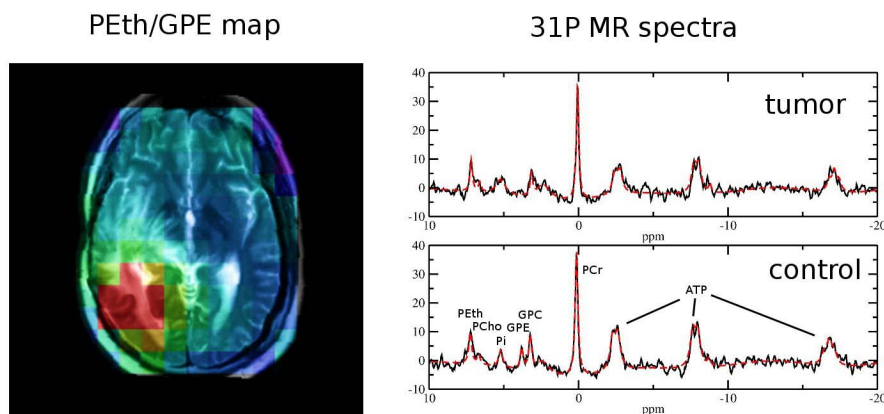


Fig. 2: ³¹P MR spectra and map of PEth/GPE ratio. The broken red line indicates the fit with jMRUI.

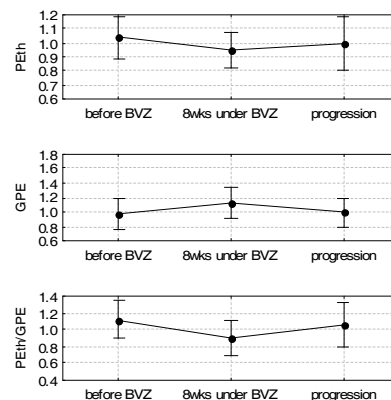


Fig. 2: Longitudinal changes during treatment for ethanolamine compounds in tumor tissue.

Under BVZ, the ratios of membrane anabolites to catabolites significantly decreased (Fig.2). At the time of progression under BVZ, PCho/GPC re-increased significantly, exceeding initial values. In normal appearing tissue there was an initial decrease of PEth/GPE followed by an increase concomitant with tumor progression.

Discussion

The PCho/GPC increase in the short-OS group suggests that it is a negative predictive marker for BVZ efficacy. Gliomas with increased PCho/GPC ratio may represent a malignant phenotype which is refractory to anti-VEGF treatment. Increased PEth/GPE represents a novel biomarker of recurrent GBMs in vivo. The PEth/GPE ratio might be a sensitive marker of tumor infiltration in “normal-appearing” brain regions.

References

1. Podo, F. (1999), *NMR Biomed* **12**(7), 413-439.;
2. Hattingen, E, et al., *Neuro Oncol* **13**(12), 1349-1363.