Characterization of gliomas using MR-derived cerebral blood volume maps in combination with metabolic ratios from proton MR spectroscopy

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Purpose: To evaluate both a histogram based analysis of MR-derived cerebral blood volume maps and metabolite ratios from proton MR spectroscopy in order to exploit the ability of each method to characterize gliomas and to evaluate their combined diagnostic potential.

Background: The value of normalized cerebral blood volume ratio (nCBV) analysis to differentiate high-grade (WHO grade III-IV) from low-grade (WHO grade I-II) gliomas has been shown in multiple studies [1]. This method utilizes first-pass bolus tracking analysis to derive relative cerebral blood volume maps (rCBV) and viable malignant tumor tissue is identified as regions of elevated microvascular blood volume ('hot spots'). Further, it has been shown that histogram analysis of nCBV values from total glioma volume may improve differentiation between these two cohorts [2]. As an alternative to MR perfusion, metabolic ratios from proton MR spectroscopy may be used as a predictor of glioma grade, assessed in combination with anatomical MR images [3]. In this study we have investigated whether a combination of the two methods may improve the differentiation between high- and low-grade gliomas.

Methods: Thirty-six patients with histologically confirmed gliomas, (aged 6-76 yrs, mean age 45; 22 males, 16 females) have so far been included. The study has been approved by the local ethics committee and informed consent was obtained from all patients. Perfusion and spectroscopy data were obtained at the same MR examination, prior to surgery. Imaging was performed at 1.5T Siemens Symphony, Sonata or Avanto (Siemens, Germany). rCBV maps were generated using established tracer kinetic models [4] applied to the first-pass data obtained by i.v. bolus injection of 0.2 mL/kg Gadovist (Schering AG, Germany). The time resolution of the first-pass gradient echo (GRE)-EPI sequence was 1.5 s and the voxel size was 1.8 x 1.8 x 6.5 mm^3. An experienced neuroradiologist (B.N) created normalized (n)CBV maps by dividing each rCBV value in each slice with a white matter rCBV value obtained from an unaffected region in the contra-lateral hemisphere. The nCBV maps were coregistered with T2-w FSE and T1-w SE post-contrast images. Three experienced neuroradiologists, blinded to the histopathologic diagnosis and the MR spectroscopy data, independently defined the glioma areas on the anatomical images (combined with rCBV maps) by drawing freehand regions of interest (ROI's) in each slice. Large tumor vessels were not included in the ROI's. The histogram method assessed the maximum normalized peak height of nCBV distribution from the obtained total glioma volumes, under the hypothesis that a low peak implies a wide distribution of nCBV values illustrating the heterogeneity of a high-grade glioma. All perfusion image analysis was performed using nICE^{TM} (NordicImagingLab, Norway). Multivoxel 2D proton spectroscopy was performed with an echo time of 135 ms. Two experienced neuroradiologists blinded to the MR perfusion findings, reviewed the MR spectroscopy data of the same patient cohort. By consensus, between one and four voxels containing good quality spectra were selected from both gliomas and from normal-appearing brain tissue in the contra-lateral hemisphere. The following metabolic ratios in glioma voxels (choline [Cho]/creatine [Cr] and Cho/N-acetylaspartate [NAA]) were measured, and in addition ratios between metabolites in tumor and normal-appearing white matter (ref), [Cho/Cho ref], [NAA/NAA ref], [Cho/Cr ref] and [NAA/Cr ref]. The results from the histogram method were compared to the spectroscopy results using a Mann-Whitney test and a coefficient of variation test. To evaluate whether a combination of perfusion and spectroscopy might be the optimal way to grade gliomas, a binominal generalized linear model was preformed. Here, the average nCBV peak values of the three observers for each patient were used.

Results: Of the thirty-six gliomas investigated, fourteen were histologically confirmed to be high-grade (eleven glioblastoma multiforme [grade IV] and three anaplastic astrocytomas or oligodendrogliomas [grade III]). Of the twenty-two low-grade gliomas, nine were pilocytic astrocytomas [grade I] and thirteen were astrocytomas, oligodendrogliomas or mixed oligoastrocytomas [grade II]. The MR spectroscopy gave a statistical significant difference between the two cohorts for the ratios [NAA/NAA ref] (p=0.009), [Cho/Cr] (p=0.003) and [Cho/NAA] (p=0.007). Figure 1 illustrates a typical MR spectroscopy result of a high- and low-grade glioma. All three observers obtained statistically significant higher nCBV histogram peak values for the low-grade gliomas compared to the high-grade gliomas (p=0.001, p=0.009 and p=0.003). Figure 2 shows the result of the histogram method in the same gliomas as figure 1. The peak nCBV distribution values of the oligodendrogliomas did not differ from the astrocytomas. For all three observers, the coefficient of variation was lower for the histogram method compared to all the spectroscopy ratios for both the high- and low-grade cohorts. The generalized linear model concluded that high- and low-grade glioma grading based on the statistically most correlated combination of the nCBV peak values and a spectroscopy ratio (Cho/NAA) had a less accurate coefficient estimate than the nCBV values alone (p=0,012 vs p=0,009, respectively).

Discussion: Our results showed that both the histogram method and selective ratios from proton MR spectroscopy were useful in differentiating high- and low-grade gliomas. As in previous studies [5], the correlation between histological glioma grade and histogram analysis was stronger than the correlation to metabolite ratios. In this study, adding the most correlated MR spectroscopy ratio to the nCBV distribution peak values did not contribute to the high- and low-grade glioma grading.

Conclusion: Both histogram based analysis of MR-derived cerebral blood volume maps and metabolite ratios from proton MR spectroscopy were shown to differentiate between high- and low-grade gliomas. Adding the results from the histogram method to the most correlated spectroscopy ratio were shown to improve the glioma grading, whereas adding the most correlated spectroscopy ratio to the histogram method did not.

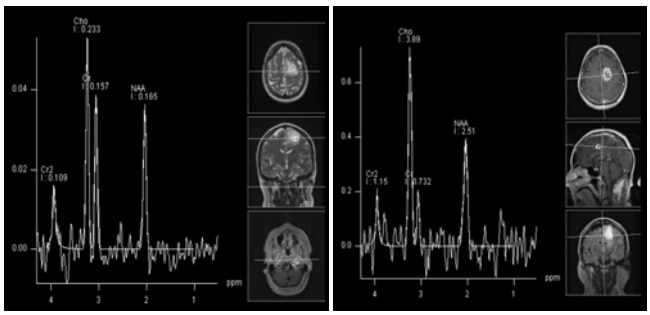

Figure 1: *Multivoxel MR spectroscopy of a low-grade oligodendroglioma (left) and a high-grade glioblastoma (right). Note the increased choline/creatine ratio in the high-grade glioma compared to the low-grade glioma.*

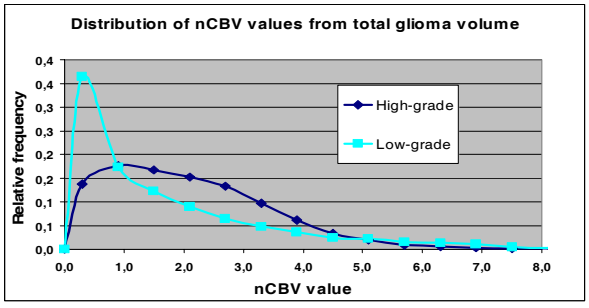

Figure 2: *Distribution of normalized nCBV values from total glioma volume in the high- and low-grade glioma shown in figure 1. Note the reduced nCBV peak value in the high-grade tumor attributed to increased vascular heterogeneity.*

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