The effect of oligodendroglial -1p/-19q genotypes on glioma grading from MR perfusion imaging

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Purpose: To evaluate whether oligodendroglial tumors with combined loss of short arm of chromosome 1p (-1p) and long arm of chromosome 19q (-19q) influences the result in glioma grading from MR-derived cerebral blood volume maps and propose a way to potentially reduce this influence.

Background: The value of normalized cerebral blood volume (nCBV) ratio 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'). A well-known problem with this method is that most oligodendroglial tumors exhibit a higher hot spot value than astrocytomas irrespective of WHO grade. A recent study suggests that the -1p/-19q genotype might be the reason for this, consequently leading to an inconclusive hot spot grading result [2]. We have investigated how the -1p/-19q genotype influences the result of a traditional hot spot method and evaluated whether an alternative grading method based on histogram analysis of nCBV values from total glioma volume [3] might reduce this influence.

Methods: Twenty-two patients with histologically confirmed oligodendrogliomas and oligoastrocytomas (aged 9-62 yrs, mean age 43; 10 males, 12 females) have so far been included. The study has been approved by the local ethics committee and an informed consent was obtained from all patients. Loss of heterozygosity (LOH) at 1p and 19q were analyzed using a standard polymerase chain reaction (PCR) technique. Imaging was performed at 1.5 T (Siemens Sonata or Avanto, Germany) prior to surgery. rCBV maps were generated using established tracer kinetic models [4] applied to the first-pass data obtained by i.v. bolus injection of 0.1 mmol/kg of Gadovist (Schering AG, Germany). The time resolution of the first-pass gradient echo (GRE)-EPI sequence was 1.5s and the voxel size was 1.8x1.8x6.5mm^3. Normalized (n)CBV maps were created by dividing each rCBV value in each slice with a white matter rCBV value obtained from an contra-lateral unaffected region. An experienced neuroradiologist was blinded to the histopathological diagnosis and defined the glioma areas based 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. For each glioma, a hot spot (rCBV max) value was also selected using a 16 pixel ROI. All image analysis was performed using nICE^{TM} (NordicImagingLab, Norway). The results from the histogram method were compared to the results from the hot spot method using a Mann-Whitney test and a coefficient of variation test.

Results: The -1p/-19q genotype was found in 9 of the twenty-two included tumors. Four gliomas were histologically confirmed as high-grade (grade III), which included two of the nine -1p/-19q genotypes. Figure 1 shows examples of nCBV maps of low-grade oligodendroglial tumors with and without the -1p/-19q genotype. Both the histogram method and the hot spot method were able to differentiate between the low-grade oligodendroglial tumors with and without the -1p/-19q genotype (p=0,003 [histogram] vs p=0,02 [hot spot]). Figure 2 shows examples of this when using the histogram method. Neither methods showed any difference between the four high-grade gliomas, of which two had -1p/-19q genotype. Both methods achieved a statistical significant difference between the low-grade gliomas *without* the -1p/-19q genotype and the high-grade gliomas (p=0,008 [histogram] vs p=0,05 [hot spot]), whereas neither could differentiate between the low-grade gliomas *with* the -1p/-19q genotype and the high-grade gliomas. Including both oligodendroglial tumors with and without the -1p/-19q genotype in the low-grade cohort, only the histogram method achieved a statistically significant difference between the high- and low-grade gliomas (p=0,04). The coefficient of variation was lower for the two low-grade cohorts using the histogram method compared to the hot spot method (with -1p/-19q genotype: 0,33 [histogram] vs 0,44 [hot spot], without -1p/-19q genotype: 0,16 [histogram] vs 1,31 [hot spot]).

Discussion: Our results suggest that the presence of -1p/-19q genotype in oligodendroglial tumors strongly influence the results of glioma grading from MR-derived nCBV maps. The hot spot method was less specific than the histogram method for grading high- and low-grade gliomas in the presence of -1p/-19q genotypes, A reason for this might be that even though the low-grade -1p/-19q genotypes show signs of increased vascularity, the distribution of nCBV values in the total glioma volume is still relatively homogeneous. Although the current method so far is tested in a limited number of patients only, these preliminary results suggest that the histogram method provides a more robust approach to glioma grading than the traditional hot spot method.

Conclusion: The presence of oligodendroglial tumors with -1p/-19q genotype was shown to reduce the specificity of MR-derived nCBV analysis in glioma grading. When -1p/-19q genotypes are present, the histogram approach holds promise as a more robust method for grading high- and low-grade gliomas than a traditional hot spot method.
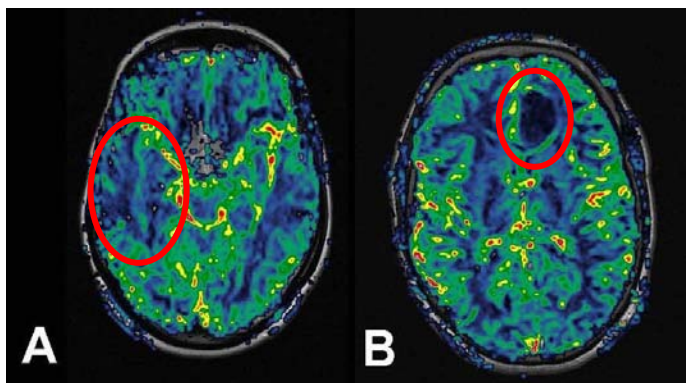
Figure 1: *rCBV maps as overlays on T2-w SE images. A: low-grade oligodendroglioma with -1p/-19q genotype. B: low-grade oligodendroglioma without -1p/-19q genotype. Note the low rCBV values in (B), typical of gliomas without -1p/-19q genotype.*
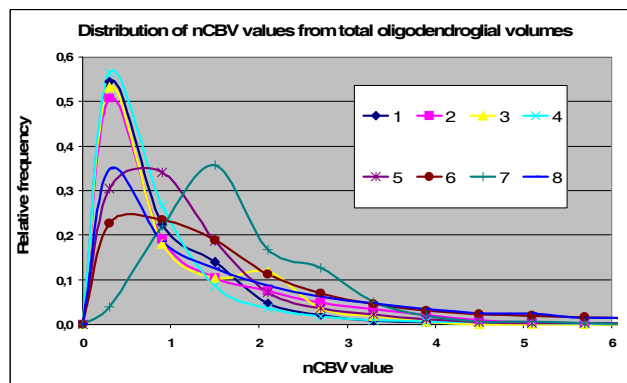
Figure 2: *Distribution of normalized nCBV values from total glioma volume in four low-grade oligodendroglial tumors without -1p/-19q genotype (1-4) and four with -1p/-19q genotype (5-8). Note the lower peak values of the gliomas with the -1p/-19q genotype attributed to increased vascular heterogeneity.*

References:
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