Cluster analysis from multiple MR image classes can reduce user bias and improve glioma grading

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Purpose: To evaluate whether an automated k-means cluster analysis method can aid in the identification of glioma volume and hence improve the differentiation of high- and low-grade gliomas and reduce user dependence.

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'). Further, it has been shown that histogram analysis of nCBV values from total glioma volume may improve differentiation between these two cohorts [2]. A drawback with the current histogram analysis method is the need to manually define the glioma volume which might be complicated and time consuming. Hence, we propose an alternative approach to region of interest (ROI) analysis by use of k-means cluster analysis of multiple MR images taken from a standard CNS tumor image protocol, including first-pass perfusion imaging.

Methods: Thirty-five patients with histologically confirmed gliomas, (aged 6-76 yrs, mean age 46; 22 males, 13 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. Imaging was performed at 1.5 T (Siemens Sonata or Avanto, Germany) prior to surgery. rCBV maps were generated using established tracer kinetic models [3] applied to the first-pass data obtained by i.v. bolus injection of 0.1mmol/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. An experienced neuroradiologist created normalized (n)CBV maps by dividing each rCBV value in each slice with an unaffected white matter rCBV value. The nCBV maps were coregistered with conventional T2-w FSE, T1-w SE pre-contrast, T1-w SE post-contrast and MR diffusion (b-values = 0, 500, 1000) images. K-means cluster analysis was performed in Matlab 2006a by minimizing the squared Euclidean distance between cluster members [4]. The cluster analysis was performed in three steps. Initially, vessels infiltrating the glioma volume were identified by clustering of composite images generated from T2-w and diffusion (DW) images (b=1000, T2-corrected). The resulting images were then used as a binary mask to exclude vessels from further analysis. Edema and cystic components were identified from cluster analysis of the DW images alone. The result of these two clustering steps were then used as a mask input to a processed difference image generated from the pre- vs post contrast enhanced T1-w images to obtain a final estimation of the glioma volume. Figure 1 shows the result of a cluster analysis as an overlay on a T2-w image. The glioma volumes as identified by the process described above were compared to the glioma volumes independently measured by three experienced neuroradiologists blinded to the histopathologic diagnosis. The glioma ROI's were determined from rCBV maps as overlays on the anatomical MR images. Glioma grading was then performed using the histogram method. The histogram method assesses the maximum normalized peak height of nCBV distribution from the total glioma volume, under the hypothesis that a low peak implies a wide distribution of nCBV values illustrating the heterogeneity of a high-grade glioma. To determine the level of interobserver reproducibility, the results from the independent observers were compared to the results from the cluster analysis using a Mann-Whitney test and a coefficient of variation test. All image analysis was performed using nICE^{TM} (NordicImagingLab, Norway).

Results: Of the thirty-five 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-one low-grade gliomas, three were pilocytic astrocytomas [grade I] and eighteen were astrocytomas, oligodendrogliomas or mixed oligoastrocytomas [grade II]. The peak nCBV distribution values of the oligodendrogliomas did not differ from the astrocytomas. All three observers obtained statistically significant higher histogram peak values for the low-grade gliomas compared to the high-grade gliomas (Mann-Whitney; p=0.002, p=0.004 and p=0.003). The cluster analysis method gave a more significant difference between the two cohorts (p=0.001). As shown in figure 2, the coefficient of variation was also lower for the cluster analysis method compared to the three observers (High-grade cohort: 0.34, 0.40, 0.37 for the observers and 0.30 for cluster analysis. Low-grade cohort: 0.38, 0.37, 0.44 for the observers and 0.32 for cluster analysis).

Discussion: We propose an alternative user independent method to improve delineation of *true* glioma volume. The method utilizes all available MR data generated in a standard CNS tumor protocol, thereby increasing the likelihood of correct tumor identification, which is a critical initial step in the glioma grading when using the histogram approach. Although the proposed method has so far been tested in a limited number of patients only, the preliminary results suggest that this method provides a more objective and robust approach compared manual identification of glioma volume.

Conclusion: With respect to glioma grading using the histogram method, the cluster analysis approach using multiple MR image types was shown to be equal or better than manual identification of glioma volume by three experienced neuroradiologists. The method therefore holds promise as a user independent approach to selecting the target region for glioma grading.

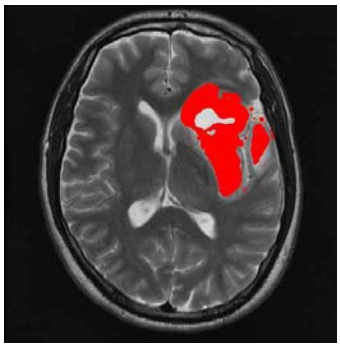

Figure 1: *Result of cluster analysis as overlay on a T2-w SE image. The patient was diagnosed with a low-grade astrocytoma. Note the exclusion of both the middle cerebral artery and the cystic components in the centre of the glioma.*

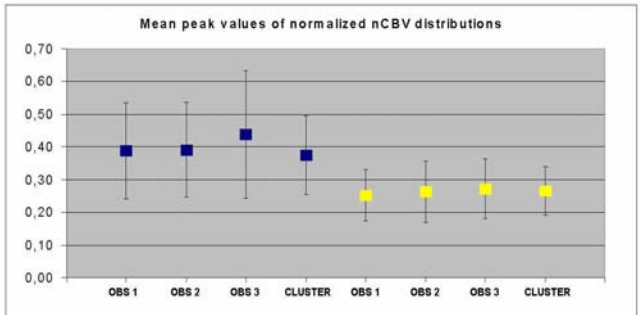

Figure 2: *Mean nCBV peak values with standard deviations for low-grade (blue) and high-grade (yellow) gliomas obtained by observers (OBS) and cluster analysis. Note the reduced relative standard deviation obtained by using cluster analysis compared to the manual selection of total glioma volume.*

References:

[1] Covarrubias DJ et al, The Oncologist, 2004;9:528-537
[2] Emblem KE et al, Proc ISMRM 2006; p 823
[3] Ostergaard L et al, Magn Reson Med, 1996;36:715-725
[4] Itskovich VV et al, Magn Reson Med, 2004;52:515-523