Prediction of clinical outcome in glioma patients using a combination of epidermal growth factor receptor (EGFR) and relative cerebral blood volume (rCBV) measured by dynamic susceptibility-weighted contrast-enhanced magnetic resonance imaging

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Background and purpose: Dynamic susceptibility-weighted contrast-enhanced magnetic resonance (DSC-MR) imaging has been shown to be useful in predicting clinical outcome of gliomas. Primary glioblastomas are associated with amplification of epidermal growth factor receptor gene (EGFR), a molecular genetic marker, that has been implied with poor prognosis. To our knowledge no study has shown a correlation between EGFR, relative cerebral blood volume (rCBV) and clinical outcome. The purpose of our study was to examine potential correlation between rCBV and EGFR and to evaluate whether the combination of rCBV measurements and EGFR expressions can be used to predict clinical outcome in glioma patients.

Materials and Methods: We retrospectively analyzed 44 consecutive patients (27 male; median age, 58 years; range, 21 - 79 years) with pathologically proven gliomas (1 subependymal giant cell astrocytoma, 5 low-grade astrocytomas, 2 low-grade oligoastrocytomas, 1 anaplastic astrocytoma, 5 anaplastic oligodendrogliomas, 30 glioblastomas) for which DSC-MR imaging was available. DSC-MR images were acquired on a 3T system (MAGNETOM Trio; Siemens, Erlangen, Germany) with a gradient-echo echo-planar imaging sequence during first pass of a (0.1 mmol/kg) bolus of gadoterate meglumine (Dotarem), at a rate of 2.5 mL/s. Imaging parameters were as follows: TR/TE 1670/45; FOV 230x230 mm; section thickness 5 mm; matrix 128x128; voxel size 1.8x1.8x5.0mm³; intersection gap 30%; flip angle 90⁰; signal bandwidth 1346 Hz/Px. Fifteen axial sections were obtained through the brain.

Calculation of rCBV from the DSC-MR data was performed with a program developed by G. Johnson (NYU Langone Medical Center, New York). Measurements were performed in an ROI of 20 pixels in the tumor regions with the highest perfusion seen on CBV color overlay maps.

EGFR copy number was established using Multiplex Ligation-dependent Probe Amplification (MLPA) analysis. Using MLPA analysis distinction can be made between normal EGRFR copy number (group 1), a low-level gain (group 2) and (high copy number) amplifications (group 3) of EGFR.

Receiver operating characteristic (ROC) analyses were performed to determine the optimum threshold for an adverse event (death). Spearman’s rho test was used to determine correlation between rCBV and EGFR copy number. Log-rank tests were used to evaluate the association between rCBV, the combination of rCBV and EGFR copy number and overall survival by using Kaplan-Meier survival curves.

Results: At an optimum threshold value of 5.45 for rCBV the ROC analysis found a sensitivity of 71% and a specificity of 69% (AUC = 0.712, p = 0.028). Kaplan-Meier estimates of overall survival (in days) in the group of 44 patients indicated that patients with a rCBV < 5.45 had a median overall survival of 568 days, whereas patients with a rCBV > 5.45 had an overall survival of 343 days (p = 0.044). MLPA analysis was performed on 18 tumor samples revealing a normal EGFR, a low-level gain and a high copy amplifications in 8, 4 and 6 samples respectively. Spearman’s rho test showed a significant relationship between rCBV and EGFR (R² = 0.732, p = 0.001). Patients with rCBV < 5.45 and EGFR group 1 (n = 6) had a significantly longer survival than patients with rCBV > 5.45 and EGFR group 2 or 3 (n = 9) (p = 0.036).

Discussion and Conclusion: Our study showed a correlation between rCBV and EGFR status. rCBV is a good prognostic factor to predict overall survival in glioma patients. EGFR in combination with rCBV did improve the prediction of the overall survival.