Evaluation of MR markers that predict survival of pre-treatment GBM patients

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Introduction: GBM is the most common and lethal primary brain tumor in adults. It is nearly uniformly fatal, with a median survival that has been reported as approximately 1 year, despite multimodality treatment approaches. Prediction of survival for newly diagnosed GBM patients could assist oncologists in evaluation of the effectiveness of new therapies in clinical trials by providing an improved baseline estimate of survival. We hypothesize that perfusion weighted MRI, diffusion weighted MRI and ^{1}H MRSI are more likely to identify the true spatial extent and malignancy of tumor than conventional MRI and are useful to predict survival for patients with GBM. The goal of this study was to test the predictive value of these techniques in relation to the survival of patients with newly diagnosed GBM who were scanned prior to receiving adjuvant radiation and chemotherapy.

Methods: The study population comprised 71 patients who had surgical resection and were scanned prior to being treated with fractionated external beam radiation therapy (XRT) and chemotherapy. The patient age ranged from 27 to 78, with a median of 53 years. Out of 71 patients 27 had gross total Resection (GTR), 33 had sub-total resection (STR) and 11 had biopsy. Subjects were imaged one day prior to resection using a pre-surgery protocol that included post-gadolinium (Gd) T1-weighted image, axial T2-weighted images, 3D MRSI using PRESS volume localization (VSS outer volume suppression bands; TR/TE = 1100/144ms; nominal voxel size of 1cc), and three directional axial diffusion imaging (TR/TE = 1000/110-86ms), voxel size = 1.4x1.4x5mm, b=1000. Diffusion images were quantified using in-house software to calculate ADC. The spectroscopic data were quantified using in-house software [1, 2] to yield metabolite peak height maps for Choline, Creatine, N-acetylaspartate (NAA), lactate, lipid, Choline to NAA index (CNI), and creatine-to-NAA index (CrNI) maps. Perfusion datasets were processed to yield relative cerebral blood volume (CBV), percent ΔR2* recovery, and ΔR2* peak height maps using in-house software [3]. The contrast enhancement (CE) region was segmented from the post-Gd SPGR using in-house semi-automated segmentation software. The T2 hyperintense region (T2ALL) was segmented likewise from FLAIR images. The diffusion, perfusion and spectroscopic parameter values were analyzed within each of these regions. To facilitate comparison of parameter values between patients, choline, creatine, NAA, CBV, ΔR2* peak height, and ADC maps were normalized to the median value within normal appearing white matter (NAWM). Lactate and lipid maps were normalized to the median value of NAA within NAWM because median value of these metabolites in normal brain should be close to zero. ΔR2* percent recovery, CNI, CrNI were not normalized. Median parameter values within every region were adjusted for age and subjected to proportional hazards analysis.

Results: The median overall survival time as determined from the Kaplan-Meier survival curve (Fig.1) was 609 days. The median survival time for patients received GTR was 733 days and for the patients who received a STR or biopsy was 513 days. The median volume of CEL was 2.93 cc with a range of 0 to 43.8cc and the median volume of T2ALL was 23.3cc with a range of 0.92 to 354cc. The patients with larger contrast enhancement and larger overall regions of T2 hyperintensity tended to have a higher risk for poor outcome (HR = 0.046, p = 0.011; HR = 0.009, p = 0.027), which suggests that the residual tumor burden is an important factor in determining outcome. The volume of CNI2 (Number of pixels with CNI > 2) and CNI3 (Number of pixels with CNI > 3) are found to be strongly associated with decreased survival (HR = 0.063, p = 0.001; HR = 0.069, p = 0.006). Low ADC values in the T2 region were also observed to be associated with poor survival (HR = 0.040, p = 0.002). High Lactate values in contrast enhancement and T2 hyperintense regions also relate to poor patient survival (HR = 2.66, p = 0.004; H = 2.68, p = 0.004) and low lactate/lipid were predictive of good survival (HR = -1.19, p = 0.026; H = -1.422, p = 0.009). High CBV values were also found to be correlated with poor survival (HR = 0.123, p = 0.000).

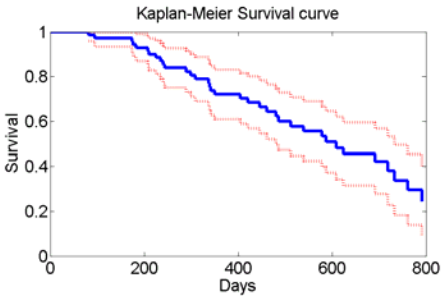

Fig1: Kaplan-Meier survival curve (blue) with 5% and 95% confidence intervals (dotted red) for 71 patients, 37 of whom were censored.

Discussion: Our studies showed that parameters significantly predictive of survival based upon a proportional hazards analysis were volume of CEL, volume of NEC, volume of T2ALL, volume of CNI2, volume of CNI3, high lactate, total lactate/lipid combined, low ADC and high CBV in lesion regions. The high CNI value observed in tumors reflects both loss of NAA due to the absence of functioning neurons and increased choline due to increased cell density and/or more extensive proliferation/higher cell density [4]. As the latter characteristics are both associated with malignancy, it is not surprising that a high CNI volume was correlated with shorter survival. Increased lactate may occur when the anaerobic glycolic pathway exceeds the capacity of the lactate catabolizing respiratory pathways or when the cellular capacity for exporting lactate to the blood stream is impaired [5,6]. This would indicate tumor metabolism, infiltration and growth. Low ADC is thought to be indicative of higher cellularity and hence larger tumor burden [7, 8]. High CBV indicates that the lesion is more vascular than normal tissue and is a characteristic used to define malignant glioma.

Conclusions: The survival for patients with glioma can depend on both the malignancy of the tumor and its response to treatment. Since both tumor progression and response to radiation or cytoxic drugs are intrinsic properties of tumor cells, the goal of the present study was to examine if there is a relationship between the pre treatment MR parameters and survival. Our study shows that several of the pre-treatment MR parameters are predictive of survival. This information may be important for assigning patients to specific treatment protocols and in planning focal therapy.

References:

1. Nelson SJ. et al. “Volume MRI and MRSI techniques for the quantitation of treatment response in brain tumors: presentation of a detailed case study”, J Magn Reson Imaging 1997; 7:1146–1152.
2. Nelson SJ. “Analysis of volume MRI and MR spectroscopic imaging data for the evaluation of patients with brain tumors”. Magn Reson Med 2001;46:228–239.
3. Henry RG.et al. “Comparison of relative cerebral blood volume and proton spectroscopy in patients with treated gliomas”, AJNR Am J Neuroradiol 2000;21:357–366.
4. Pirzkall A. et al, “MR-spectroscopy guided target delineation for high-grade gliomas”, Int. J. Radiat. Oncol. Biol. Phys. 2001; 50: 915–928.
5. Warburg O. “The Metabolism of Tumors”, Constable: New York, 1930.
6. Prichard JW. “What the clinician can learn from MRS lactate measurement”, NMR Biomed 1991; 4: 99–102.
7. Sugahara T. et al, “Usefulness of diffusion weighted MRI with echo-planar technique in the evaluation of cellularity in gliomas”, J Magn Reson Imaging 1999;9:53–60.
8. Tien RD. et al, “MR imaging of high-grade cerebral gliomas: value of diffusion-weighted echo planar pulse sequences”, AJR Am J Roentgenol 1994;162:671–677.

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