Pre-surgery Lactate, Lipid, and ADC Predict Survival for Patients with Glioblastoma Multiforme

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Introduction: Patients diagnosed with glioblastoma multiforme (GBM) generally have a very poor prognosis, but it is difficult to predict survival for individual patients prior to initial resection. Accurate 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. In a retrospective analysis, pre-surgery high-grade gliomas, age, KPS, tumor location, volume of lactate and lipid, contrast enhancement (CE) volume, choline, and creatine were shown to be predictive of survival (1,2). In resected glioma patients prior to radiation therapy and chemotherapy, volume of abnormal relative cerebral blood volume (rCBV), volume of Choline-to-NAA index (CNI) greater than 2, and mean apparent diffusion coefficient (ADC) within the T2 region were all found to be predictive of survival (3). We sought to prospectively determine whether MR spectroscopic imaging or diffusion-weighted MRI markers would predict survival immediately prior to surgery for patients with GBM.

Methods: We studied 54 patients (39 men and 15 women) with GBM who had undergone no prior resection or treatment. Mean age was 59 ± 13.4 and ranged from 29 to 84 at the time of the pre-surgery exam. Every subject received either a total or subtotal resection and was subsequently treated with radiation therapy and chemotherapy. 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 with (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 to yield metabolite peak height maps for Choline, Creatine, N-acetylaspartate (NAA), lactate, lipid, CNI, and creatine-to-NAA index (CrNI) maps. Diffusion data were processed to yield ADC maps. The CE and necrotic (Nec) regions were segmented from the post-Gd SPGR using in-house semi-automated segmentation software. The T2 hyperintense region was segmented likewise from FLAIR or FSE images. An example of the segmentation for a typical patient is shown in Figure 1a. The diffusion and spectroscopic parameter values were analyzed within each of these regions. Values for the ADC, Choline, Creatine, and NAA were normalized to the median value in normal-appearing white matter (NAWM). Lactate and lipid values were normalized to the median NAA value in NAWM. CNI and CrNI maps were not normalized. Parameter values within every region were adjusted for age and subjected to proportional hazards analysis.

Results: The median survival after surgery, from the Kaplan-Meier curve shown in Figure 1b, was 541 days (n = 54, 24 censored). The normalized histogram peak values of lactate and lipid within the T2 region were found to be associated with decreased survival (hazard ratio HR = 0.584, p = 0.031; HR = 0.428, p = 0.006, respectively). The median normalized ADC values within both the CE and Nec areas were associated with increased survival (HR = -1.693, p = 0.034; HR = -0.642, p = 0.062, respectively). The total volume of CE was associated with decreased survival (HR = 0.021, p = 0.055). Peak values of lactate and lipid within T2 region, controlled for volume of tissue with CNI greater than 2 (vCNI2), CE, and T2 lesion volume were also significantly correlated with survival. The mean volume of CE was 17.8cc ± 14.4 and ranged from 0cc to 62.6cc. The mean volume of T2 hyperintensity was 70.2cc ± 42.5 and ranged from 12.1cc to 182.2cc. The mean volume of necrosis was 7.0cc ± 8.7 and ranged from 0cc to 32.2cc.

Discussion: The results of our study suggest that normalized values of lactate and lipid measured within the T2 hyperintense region, and ADC measured within the CE and Nec regions may be predictive of survival. The presence of lipid within the non-enhancing region is likely due to cell death resulting in micro-necrosis. Lactate is a byproduct of anaerobic glycolysis, and hence could indicate hypoxic tumor metabolism, tumor infiltration and growth. Additionally, the correlation between ADC values within the CE and Nec regions and better survival could indicate that such areas have more extensive edema rather than infiltrative tumor. Larger volumes of CE and T2 hyperintensity were associated with worse survival and could indicate that patients with larger tumors prior to surgery have a worse prognosis. In the multivariate analyses, the influence of lactate and lipid levels on worse survival was increased by inclusion of volumetric estimates of tumor size such as vCNI2, vCE, and vT2L, possibly indicating that both metabolic and anatomical information are of use in predicting survival before surgery. Identification of factors other than age and KPS that predict survival could help clinicians in the design of new clinical trials and selection of treatments by helping to stratify patients into groups with different outcomes or which would benefit from specific therapies. Future research using follow-up scans will allow multivariate modeling and partitioning of groups with differing outcomes. Pre-surgery ADC within the CE and Nec regions, and lactate and lipid within the T2 region may provide valuable information regarding prognosis and pre-surgery tumor burden that may affect prognosis of patients with GBM.

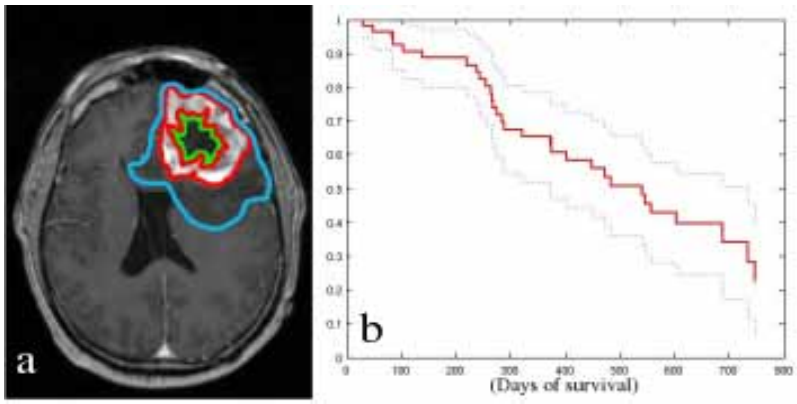

Figure 1: a) Segmented T2 hyperintense (blue), CE (red), and Nec (green) regions for a typical patient. Normalized spectroscopic and diffusion parameters within these regions were analyzed for correlation with survival. b) Kaplan-Meier survival curve (red) with 5% and 95% confidence intervals (dotted blue) for n = 54 patients, 24 of whom were censored.

References

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