Longitudinal Analysis in Patients with Glioblastoma Multiforme Treated with External-beam Radiation Therapy: Changes of Choline to N-acetylaspartate Index

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Introduction: Proton MR spectroscopic imaging (^{1}H MRSI) enables the measurement and quantification of the spatial distribution of metabolite abnormalities. For patients with Glioblastoma Multiforme (GBM), it was shown that patients with remaining large metabolic lesions after surgery but prior to further therapy had significantly shorter survival [1]. In this study, changes in metabolic abnormalities were investigated for a cohort of patients after combined external-beam radiation therapy (XRT) and chemotherapy (CHT) and tested to assess predictive value of survival.

Methods: Twenty-eight newly diagnosed patients with GBM (mean age 50.3 years, range 14.6 – 79.6 years) were treated with XRT and CHT after surgery. MR data were acquired using a 1.5 GE Signa scanner equipped with a quadrature head coil prior to XRT (baseline), after XRT and at 8-week follow-up intervals. All subjects gave their written informed consent.

3D chemical shifting imaging (TR/TE = 1000/144 ms, 12×12×8 or 16×8×8 phase encoding matrix) with 1 cc nominal resolution was acquired with point resolved spectroscopic (PRESS) volume localization and very-selective saturation bands for outer voxel suppression using a post-gadolinium T1-weighted 3D spoiled gradient echo (SPGR) (TR/TE = 27/6 ms, 256×256×124 matrix, 240×240×186 mm^3 FOV, flip angle = 40º). A T2-weighted fluid attenuated inversion recovery (FLAIR) (TR/TE/TI = 10000/147/2200 ms, 192×256×48 matrix, 180×240×144 mm^3 FOV) image volume was also acquired. After each examination, images and raw spectra data were transferred to an offline workstation for post-processing. For each voxel in the 3D Proton Magnetic Resonance Spectroscopy Imaging (^{1}H MRSI) array, a choline to N-acetylaspartate index (CNI) image was calculated via an automated regression technique. The CNI images were resampled into high resolution 3D SPGR and contoured with a CNI value ≥ 2.0 (CNI2) representing metabolically active tumor [2]. Anatomic images and ^{1}H MRSI data for follow-up scans were aligned to the baseline data set. The CNI2 volumes within common PRESS regions for all examinations were calculated. Statistical analysis included a linear mixed model random effects [3] to estimate change of CNI2 volume, and Kaplan-Meier survival curves with an age adjusted log-rank test. The linear mixed model random effects estimated changes in CNI2 volumes relative to that of pre-XRT, $CNI2(t) = \alpha_i + \beta_i t$, where i stands for each patient and t is time in months, α_i is intercept (estimated volume of CNI2, representing metabolically active disease pre-XRT) and β_i is slope (change of CNI2 over time). In this study, $p < 0.05$ was regarded as significant.

Results: The median follow-up time was 5.2 months (range 1.1 – 16.6 months) for all patients. The volumes of CNI2 and contrast enhancement on T1w correlated significantly in all patients ($r = 0.44$, $p = 0.020$). The median CNI2 volumes pre-XRT were 15.7 ± 21.3 cc (median ± standard deviation). Figure 1 shows estimated CNI2 volume changes for all patients. Figure 2 summarizes the estimated parameters intercept (α_i) and slope (β_i) for all patients. It is interesting to note that the changes of metabolically active disease during follow-up were more pronounced for patients with initially rather large CNI2 volumes. It was observed that the CNI2 volume was reduced relative to that of pre-XRT in 17/28 patients who exhibited rather large CNI2 volumes pre-XRT (median value of -1.75 cc/month with range of -2.68 to -0.08). For nine patients among those 17, the CNI2 volume was reduced more than 25% relative to that of the initial CNI2 volume (nΔCNI2) by the end of observation. Interestingly, the CNI2 volume was found stable or slightly increased relative to that of pre-XRT (range 0.02 to 0.78 cc/month) in the remaining 11 patients who had small pre-XRT CNI2 volumes.

The median survival for all patients was 14.9 months (censored observations = 7 patients still alive at time of evaluation). A significantly shorter median survival (12.6 ± 1.7 months) was observed for patients with high intercept (> 20) and low slope (< -0.5) compared to the ones with low intercept and high slope (17.1 ± 1.5 months, $p = 0.001$). There was no significant difference in survival between patients with nΔCNI2 ≥ 25% and nΔCNI2 < 25% ($p = 0.839$).

Discussion and Conclusion: Post-XRT/-CHT follow-up evaluation of the CNI2 volumes revealed opposing effects that were dependent upon the pre-XRT CNI2 volume. The CNI2 volume was found to decrease in patients with an initially high CNI2 volume, suggesting that the XRT was having an effect upon the tumor. Despite this reduction, the remaining CNI2 volume was still relatively high and the patients had a significantly shorter median survival. This suggests that the absolute tumor burden as defined by CNI2 volume is a more important prognostic factor than the change in this parameter in large lesions. There was no significant change during the period of follow-up for patients in our study that had small pre-XRT CNI2 volumes. This may either have indicated that these lesions were not affected by the XRT/CHT or that the methods for estimating CNI2 were just not sensitive enough to detect small changes in volume.

References

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Acknowledgments: This study was supported by NIH grant R01 CA79719 and K01 CA76998.

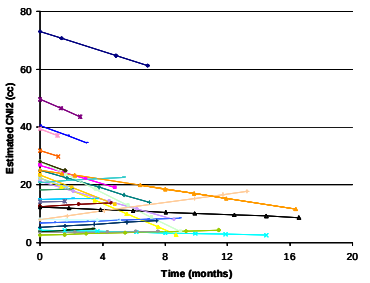

Figure 1. Estimated CNI2 volume changes for all patients.

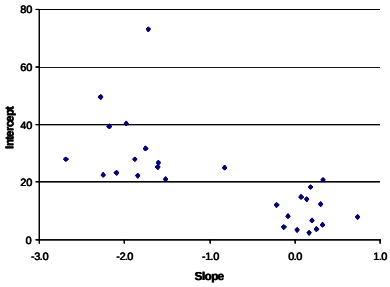

Figure 2. Mixed model outputs for all patients.