Serial Assessment of Therapy Response for Low-Grade Glioma Patients through MR Diffusion, Perfusion, Spectroscopic, and Anatomical Imaging

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Introduction: Prolonged survival of patients with Grade II gliomas has made it important to identify prognostic indicators that may be used to evaluate therapy response and manage patients on an individual basis [1]. Since a significant number of low-grade gliomas are non-enhancing, T2-hyperintensity is commonly used to judge the extent of tumor [2]. However, it is difficult to distinguish T2-hyperintensity due to tumor from that due to edema, and therefore other techniques should be evaluated. Diffusion, perfusion, and MR spectroscopic imaging (MRSI) have shown improvements over conventional MR in tracking patient response to therapy. Identifying MR parameters is valuable in assessing treatment response. Tailoring therapies for individual patients would spare the potentially toxic effects of agents. The purpose of this study was to investigate the serial changes in various MR parameters for a population of low-grade glioma patients undergoing treatment with chemotherapy.

Methods: A total of 27 MRSI examinations were performed on nine patients (6M/3F; 28-66 years; median 38 years) with histologically confirmed low-grade gliomas: 5 oligodendrogliomas, 3 astrocytomas, 1 oligoastrocytoma. Eight of the nine patients received gross total resections prior to their pre-therapy scan. All patients were treated with chemotherapy alone using temozolomide (no previous or adjunctive radiation or biological therapy). Temozolomide was delivered with a dose of 200mg/m^2/day for 5 days and then repeated every 28 days. Each patient received a series of MRI exams on a 1.5 Signa Echospeed scanner (GE Medical Systems, Milwaukee, WI) that were performed immediately before and at two month intervals after beginning chemotherapy. T2-FLAIR and T1-weighted SPGR images with and without Gd-contrast were acquired and used to exclude regions of T2 or T1-Gd abnormality. Diffusion weighted images were acquired using EPI-SE with 36x21 FOV, 256x128 matrix, 3mm thick, and b=1000s/mm^2. Perfusion images were obtained using a dynamic imaging sequence with an injection of a bolus of 0.1mmol/kg body weight of Gd-DTPA contrast agent at a rate of 5mL/s. MRSI data sets were acquired in 17 minutes at a nominal spatial resolution of 1.0cc, and TE of 144ms. Regions of T2-hyperintensity and T1-weighted contrast enhancement were manually contoured. 3D-MRSI peak parameters for choline and N-acetyl-aspartate were categorized using a choline/N-acetyl-aspartate index (CNI), a tool for quantitative assessment of tissue metabolite levels, with CNI2 being the lowest value corresponding to tumor [4]. CNI data were aligned to MRI and displayed as 3D contours used for volume analysis. The relative levels of CNI, the apparent diffusion coefficient (ADC), and the relative cerebral blood volume (rCBV) parameters were analyzed within the regions of T2 hyperintensity and CNI contours.

Results and Discussion: The pre-treatment T2-hyperintensity (T2h) volumes displayed a range of 4.4-104.8cc as shown in table 1. The volume of contrast enhancement found in T1-weighted images was negligible (maximum volume 1.2cc). The volumes of CNI2 lesions ranged from 1.3-38.7cc. In all but one case these were substantially smaller than the volume of the T2h (median 40%, range 7-227%). Median ADC values within the T2h region were in the range of 1002-1441x10^{-6} mm^2/s, and 25th percentile ADC values ranged from 854-1279x10^{-6}mm^2/s. ADC values for normal tissue had a significantly lower median value of 832x10^{-6}mm^2/s compared to ADC within regions of T2h ($p<0.05$). The ranges of rCBV values acquired within regions of T2h were close to those of normal tissue and did not appear to provide relevant information. The volumes of T2h were found to be significantly different at the second follow-up ($p<0.05$) compared to the pre-therapy exam (Wilcoxon Signed-Rank Test). Seven of the nine patients responded with a decrease in T2h, presenting a median decrease of 23.6%, with one patient remaining stable, and one patient showing progression. The ADC values within the regions of T2h as defined separately for each examination were stable as a function of time. The magnitudes of the volume changes in metabolic lesions were different from the changes in the T2h, providing contradictory results for 5/9 patients and indicating that there were six patients who responded, two who progressed and one who remained stable.

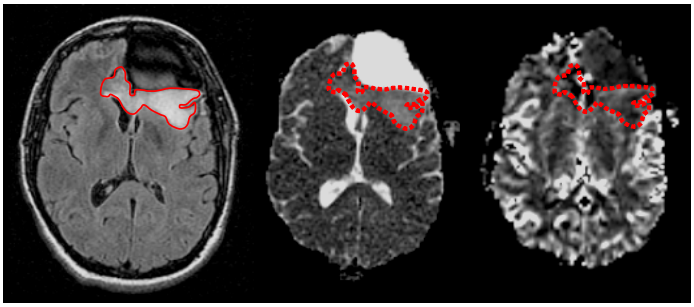

Figure 1. FLAIR, ADC map, and rCBV map with overlaid T2h region.

Low-Grade Gliomas	Median	Range
T2h volume (cc)	27.7	4.4-104.8
T2h change in responses (%)	23.6	23.6-72.9
CNI 2 volume at pre-therapy (cc)	16.6	1.3-38.7
ADC within T2h (10^{-6} mm^2/s)	1240	1002-1441
ADC within normal tissue (10^{-6} mm^2/s)	832	776-864
ADC within CNI (10^{-6} mm^2/s)	1206	969-1515

Table 1. T2 volumes, CNI volumes, and ADC values.

Conclusion: In our study we found that the volume of the metabolic lesion as defined by MRSI data was much less than the volume of the T2h for 8/9 patients with low grade gliomas. This has implications for the interpretation of response to therapy for such lesions and is consistent with the T2h corresponding to a mixture of tumor and edema. A significant change in T2-hyperintensity was found within the first four months of low-grade gliomas receiving chemotherapy; however, none of the other MR parameters indicated a positive response in the same time span. This may indicate that changes in the T2h reflect variations in the extent of edema in addition to the effects of chemotherapy and may be misleading in terms of patient response to treatment. Estimates of rCBV in the T2h were not significantly different from normal and the magnitudes of the ADC within the T2h regions were similar to pre-treatment values at both the 2 and 4 month follow-up examinations. Hence it seems unlikely that these parameters will provide additional information concerning response to therapy for this population of patients. Previous studies in our laboratory have suggested that metabolic lesions are a more reliable measure of tumor than morphological lesions. If the changes in the volume of the metabolic lesion are used to assess response to therapy rather than the volume of T2h, we would have made different conclusions for more than 50% of our patients. While further follow-up is required in order to determine whether these parameters are predictive of long term outcome, it seems likely the MRSI data contain information that will help in determining whether the observed changes are due to residual tumor or to changes in the spatial extent of edema.

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References

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