Multiparametric analysis of advanced MR imaging changes following concurrent Radiation Chemotherapy

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Introduction:

Glioblastoma multiforme (GBM) is the most malignant type of brain tumor in adults. It is characterized by poor outcome even following multimodality therapy that consists of concurrent radiation/chemotherapy following surgical resection. In light of the increasing availability of newer, targeted agents, the early assessment of therapy response is critical but often hindered by questionable changes in morphological appearance. Advanced MRI techniques, such as 3D ^{1}H Magnetic Resonance Spectroscopy Imaging (MRSI), Diffusion Weighted Imaging (DWI) and Perfusion Weighted Imaging (PWI) have proved valuable for assessing the metabolic and physiologic aspects of normal and brain tumor tissue[1,2]. In this study, we have evaluated these MR imaging modalities in a population of postsurgical patients with newly diagnosed GBM prior to and immediately after conclusion of radiation therapy (RT) in order to assess changes that occur between these two time points.

Materials And Methods:

Forty five patients with newly diagnosed GBM were scanned within 1 week prior to initiation of concurrent RT/CHT (pre-RT) and within 1-2 weeks after completion of RT (post-RT). Chemotherapeutic agents included Temozolomide alone (19) or in combination with Tarceva (17), and Poly ICLC (9). Six patients received biopsy only, 14 were assessed as having undergone a gross total resection and 25 a subtotal resection. Postsurgical diffusion weighted abnormalities were subtracted from possible contrast enhancement at pre-RT[3]. Twenty six patients were examined on a 1.5T GE Signa Echospeed scanner and 19 on a 3T Excite MR scanner (GE Healthcare Systems, Milwaukee, WI). The imaging protocol consisted of axial post-Gad-DTPA T1-weighted, axial T2-weighted images, 3D PRESS ^{1}H MRSI (TR/TE=1000/144 ms, 1 cc nominal spatial resolution), axial DWI (TR/TE=5000/105 ms, and b-value=1000s/mm2) and axial PWI (injection of a bolus of 0.1mmol/kg with T2* -weighted gradient-echo, echo-planar images [TR/TE=1250/54ms, 35° flip angle, FOV 26*26 cm^2, 120x128 matrix, 3-6mm slice thickness]). All imaging data were rigidly aligned and resampled to the resolution of the pre-RT post Gadolinium T1-weighted image. Peak heights of choline (Cho), creatine (Cr), N-acetyl-aspartate (NAA), indices of Cho-to-NAA (CNI), Cho-to-Cr (CCrI) and excess choline (ExCho, [Cho/normal Cho]-[NAA/normal NAA]) were calculated[4]. For the 21 cases where lactate editing was applied at 1.5T separate estimates of lactate (Lac) and lipid (Lip) peak heights were obtained and for the other cases the highest peak in magnitude spectrum from the combined Lactate/Lipid (LL) region was considered. The PWI data (cerebral blood volume [CBV], peak height [PH] and % recovery [RECOV]) were calculated and normalized to the peak of a model curve function derived from normal appearing brain[1]. The DWI data were assessed via apparent diffusion coefficient (ADC) maps. MRI morphologic abnormalities were manually contoured as mutually exclusive regions of interest (ROIs) and included the regions of contrast-enhancement (CEL), non-enhancing T2-hyperintense lesion (NEL), resection-cavity, necrosis (Nec) and a reference ROI for normal appearing white matter (NAWM). All ROIs and analysis of imaging data were restricted to the extent of the PRESS box. The difference between pre- and post-RT imaging parameters was calculated for mean, median, maximum, and percentile (25th, 75th, 90th) values for all patients using a Wilcoxon sign rank test to determine statistically significant changes in the morphologic, metabolic and physiologic parameters. A p value of <0.05 was considered significant.

Results:

There were statistically significant changes in volumetric measures during RT which included an increase in the median volumes of CEL, NEL, CEL+Nec, and CEL+NEL and a decrease in the volumes of CBV>3, max Recov, and the SumLL (which is the sum of LL values within NEL). Morphologically, the increase of CEL for the overall patient population can be mainly attributed to patients who showed a >25% increase (16) or new CEL (1). The overall increase in the NEL could be attributed in part to the relative decrease of the CEL in 8 patients. The CEL volume remained stable in 20 patients. Table 1 summarizes statistically significant changes in metabolic/physiologic imaging parameters observed between pre- and post-RT. It is interesting to note that the changes in perfusion parameters dominate within the CEL, whereas changes in spectroscopic parameters are most dominant within the NEL. Within the CEL, observed significant decreases in perfusion parameters CBV and PH signify that the RT is reducing the microvascular components of the lesion. The reduction in 25th percentile of Recov suggests that the CEL tends to be leakier following RT. Decreases in ExCho, Cho, CNI, CCrI and CrNI indicate a decrease of the most proliferative component of the tumor which presumably also contributes to an increase in the extracellular space (increased ADC). Within the NEL, the decrease in measures of Lac indicates a relatively less hypoxic environment which could be explained by the phenomenon of reoxygenation which is known to occur during fractionated RT. The decrease in CCrI in the NEL may reflect both the decrease in Cho and relative increase in Cr due to reoxygenation. A decrease in the 25th percentile of Lip and LL suggests response to RT for the majority of patients, while the increase in maximum LL may either be due to patients failing therapy or, less likely, due to the formation of RT induced necrosis.

		ADC	CBV	PH	Recov	CNI	CrNI	CCrI	Lac	Lip	LL	Cho	ExCho
CEL	mean	*10.5*	-28.0	-26.1			-29.4						
	median	*12.0*	-29.8	-30.9									
	25th percentile	*9.7*	-24.9	-16.5	-14.9				-39.8				
	75th percentile	*19.2*	-29.6	-28.3		-26.0	-25.5						
	90th percentile		-34.7	-27.9		-33.9	-28.7	-43.3					
	max		-37.0	-29.0	-28.7	-39.0	-22.4	-35.3					
NEL	mean							-27.9	-16.1			-16.1	-21.4
	median	*6.7*						-36.4	-9.1			-16.7	-22.0
	25th percentile							-85.5	-32.0	-122.8	-81.7	-18.9	-46.4
	75th percentile	*3.2*						-22.1	-22.4			-13.0	-21.4
	90th percentile							-16.7	-16.4			-8.2	-16.8
	max							-27.1			*29.5*		-22.3

Table 1: Percent changes in values of imaging parameters that proved statistically different between pre- and post-RT. Highlighted, italic entries signify relative increase, others indicate relative decrease.

Discussion:

We have demonstrated the feasibility of performing a multiparametric analysis of short-term temporal changes between pre- and post-RT in a large uniform patient population utilizing morphologic, metabolic and physiologic MR imaging information. Despite the fact that CEL and NEL increase overall, the metabolic/physiologic imaging suggests that the changes are dominated by treatment effects rather than by tumor progression. While further patient follow-up is required to relate these changes to survival (38% of our patients are currently still alive, and so a survival analysis would be premature), it is clear that the integration of these metabolic and physiologic parameters into the evaluation of response to therapy could make a major impact upon the management of patients with gliomas.

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