Serial Analysis of imaging parameters in patients with newly diagnosed Glioblastoma Multiforme

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Introduction

Gliomas account for the majority of primary brain tumors and vary from benign to malignant. Glioblastoma Multiforme (GBM) is the most common and the most malignant type of glioma, with a median survival of one year. The purpose of this study was to test the predictive value of MR parameters in relation to survival and time-to-progression (TTP) for patients with newly diagnosed GBM, to exam differences in parameter values between stable and progressed patients and to evaluate the importance of such parameters in scans obtained prior to progression.

Methods

A total of thirty patients (10 females and 20 males, median age = 53 years) with newly-diagnosed GBM were studied after surgical resection or biopsy (17 gross-total resection (GTR), 12 subtotal resection (STR) and 1 biopsy (Bx)) but prior to RT and chemotherapy (pre-RT), immediately after RT (post-RT) and every 2 months thereafter until presumed tumor progression up to a maximum of 1 year. Chemotherapy was given concurrently as temozolomide alone (16 patients), temozolomide with Tarceva (6 patients), Poly ICLC (6 patients) or R115777 (2 patients). The MR data were acquired from either 1.5 T or 3 T GE scanners (GE Healthcare Technologies, Waukesha, WI). Anatomic MR images included a T1-weighted sagittal scout, axial fluid attenuated inversion recovery (FLAIR), pre- and post-Gadolinium T1-weighted spoiled gradient echo (SPGR), diffusion (DWI) and perfusion weighted (PWI) images. The apparent diffusion coefficient (ADC) and relative cerebral blood volume (rCBV) were calculated using software developed in our group (1). Regions of Interest (ROIs) included the normal-appearing white matter (NAWM), the contrast-enhancing lesion (CEL), T2 hyperintense region (T2ALL) and non-enhancing lesion (NEL), which was defined as the T2ALL lesion subtracted by the CEL lesion and necrosis. The statistical analysis was performed using the SPSS software package (Chicago, IL, USA). A P-value of <0.05 was regarded as significant. The survival and TTP were determined from the date of the pre-RT MR examination. Kaplan-Meier survival curves, Cox proportional hazards models and log-rank tests were applied to evaluate the influence of the parameters on survival and TTP. A Wilcoxon signed-rank test was used to test the difference in values between time-points (+/- 10 days) for nADC values, but not for the nCBV values because there was a smaller number of patients who had complete coverage of the lesion at all time points.

Results

The median survival time was 649 days (95% CI 529-769 days) with 7 patients censored. Age and gender were not significantly correlated with survival. Patients with a GTR had median survival of 1116 days, while those who received a STR had median survival of 481 days. The log rank test between these two groups gave a P value of 0.016. Response to treatment was used to divide the patients into two groups based upon whether they had stable disease or showed progression. 73% of the patients (22/30) progressed within a year as confirmed by follow-up imaging criteria (12/22) or by a second surgery (10/22). In patients who were stable, the median survival was 1833 days, compared with 527 days in patients who progressed (P=0.002). The median TTP was 174 days with 8 patients censored. Patients with larger CEL volume (median CEL = 3.5 cc, P = 0.004), lower median nADC in the CEL (median nADC = 1.40, P = 0.05) and higher median nCBV in the CEL (median nCBV = 1.05, P = 0.05) and NEL (median nCBV = 0.85, P=0.048) at pre-RT had shorter TTP. The changes in volume of the CEL, T2ALL and NEL for individual patients are shown in Figure 1. Median nADC values were compared between the two groups at different time-points (+1, 30, 60, 90, 120, 150, 180, 210, 240, 270, 300, 350 days). The median nADC in the CEL and T2ALL at the pre-RT scan for patients in the stable group were significantly higher than those who progressed (Table 1). There was no significance for the parameters (volumes, nADC) between the pre-RT and any other time-point for the patients in the stable group. Six patients progressed at the post-RT time point with a median TTP of 64 days (early progression), while the other 16 patients had a median TTP of 162 days (late progression). The median ratio of the 75th percentile of the nADC in the T2ALL lesion at the pre-progression exam (-60, 60 days before progression) to that at the time of progression (-1) was 0.82 in the patients with early progression (N = 6), and 0.93 in the patients who progressed later (N = 9). Differences in parameters for the patients who progressed are shown in Table 2.
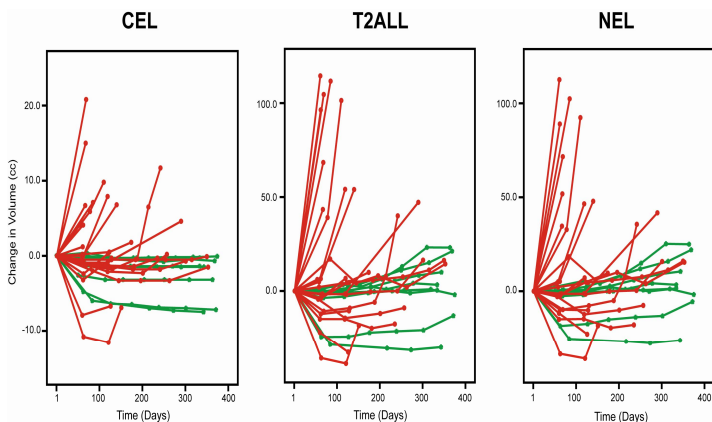

Figure 1: Change in volume for patients with progression (red) and stable disease (green). Note that some patients who progress show an initial reduction in lesion volume.

	CEL	T2ALL	NEL
Stable (N=7)	1.74±0.60	1.54±0.31	1.57±0.33
Progression (N=21)	1.37±0.20	1.28±0.22	1.30±0.24
P-value	**0.03**	**0.03**	0.06

Table 1: Median nADC at the pre-RT examination.

	Time	CEL	T2LL	NEL
Volume	-60/-1 (N=15)	0.47±0.23	0.46±0.36	0.45±0.40
	P-value	**0.0001**	**0.0012**	**0.0015**
Volume	+60/-1 (N=8)	0.46±0.28	0.32±0.54	0.34±0.58
	P-Value	**0.016**	**0.039**	**0.039**
Median nADC	+1 (N=20)	1.40±0.20	1.21±0.26	1.22±0.27
	-1 (N=20)	1.64±0.18	1.46±0.24	1.46±0.25
	P-value	**0.026**	**0.0215**	**0.0215**
Median nADC	-60 (N=15)	1.47±0.35	1.32±0.15	1.32±0.16
	-1 (N=15)	1.61±0.16	1.51±0.16	1.50±0.17
	P-value	0.22	**0.0151**	**0.0215**

Table 2: Parameters in the patients who progressed.

Discussion

Neurosurgery, RT and chemotherapy are standard treatments for patients with GBM. The extent of resection and response to therapy were significantly associated with survival. Patients having relatively large regions with breakdown of the blood brain barrier (BBB), lower median diffusion or large CBV at the pre-RT time point had relatively shorter TTP. The increase in the volume and nADC within the anatomic lesions between time points were associated with infiltrative tumor progression. The relative large increase in the nADC in the T2ALL lesions from 60 days prior to progression relative to the values at progression were observed in these patients who progressed early compared with later. This suggested that there were significant treatment effects which included the formation of necrosis, edema or gliosis. In conclusion, our studies have highlighted MR parameters that provide useful information for predicting outcome in the patients with GBM, which may be valuable to clinicians for patient management.

Reference 1. Lee, MC. et al. J. Magn. Reson. Imaging 21. 683-93.