J Neurooncol (2008) 89:219–224
DOI 10.1007/s11060-008-9609-2

CLINICAL-PATIENT STUDIES

Relationship of glioblastoma multiforme to the lateral ventricles predicts survival following tumor resection

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Received: 9 December 2007 / Accepted: 22 April 2008 / Published online: 6 May 2008

Abstract *Objective* There has been an increased focus on the region adjacent to the lateral ventricles (LV) as a potential source of malignant tumors and/or more aggressive disease. We set out to determine if glioblastoma multiforme (GBM) bordering the LV was associated with decreased survival as compared to non-LV GBM. *Methods* We reviewed the clinical records of 69 consecutive patients undergoing craniotomy for GBM at a single academic institution. Twenty-six patients were identified with contrast-enhancing lesions (CEL) bordering the LV (LV CEL). These 26 patients were matched with 26 patients with CEL not bordering the LV (non-LV CEL). These cohorts were matched for factors consistently shown to be associated with survival, which were age, tumor size, Karnofsky performance score, extent of resection, Gliadel implantation, and Temodar chemotherapy. Overall survival was compared between the cohorts via Log-rank analysis. *Results* Despite similarities in pre-operative clinical status, tumor size, peri-operative outcome, and treatment regimens, the median survival for patients with LV CEL was significantly decreased as compared to patients with non-LV CEL (8 months vs. 11 months), $P = 0.02$. Additionally, survival analysis in patients stratified by primary and secondary resection also demonstrated a strong trend towards decreased survival after resection of LV CEL. After primary and secondary resection, patients with LV CEL versus non-LV CEL had a median survival of 11 months vs. 14 months ($P = 0.10$) and 7 months vs. 10 months ($P = 0.11$), respectively. *Conclusion* While the causal factors underlying this observation are not provided with this observational study, GBM bordering the LV may carry a prognostic significance.

Keywords Glioblastoma multiforme · Survival · Location · Lateral ventricles · Subventricular zone

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Introduction

Glioblastoma multiforme (GBM) are among the most common primary central nervous system tumors in adults [1]. Patients with these tumors only survive approximately 1 year despite advances in surgical technology, chemotherapy, and radiation therapy [2]. Although mean survival for patients with GBM remains short, individual patient survival is heterogeneous [3]. As a result, there is an emphasis on studying factors that are prognostic of improved survival for patients with GBM [4–7].

Tumors bordering the lateral ventricles (LV) may be associated with decreased survival. In clinical studies, GBM bordering the LV more commonly present with multi-focal disease, as well as recur in a non-contiguous pattern [8]. Furthermore, among patients with disseminated GBM lesions, patients with subependymal-spreading tumors had poorer survival as compared to patients without subependymal spread [9]. In basic science studies, the region located on the lateral wall of the LV is often referred to as the subventricular zone [10]. This unique brain region, which harbors neural stem cells [10], appears to be more susceptible, as compared to cortical regions, to tumorigenesis [11–13].

It remains unknown, however, if GBM tumors bordering the LV are associated with decreased survival. We therefore set out to determine if patients with GBM bordering the LV was associated with decreased survival as compared to GBM that occur elsewhere.

Methods

Patient population

We retrospectively reviewed 69 consecutive patients with available pre-operative and post-operative (<48 h post-operative) neuroimaging who underwent surgical resection of GBM and post-operative radiation therapy at a single academic institution between 1999 and 2004. We reviewed their clinical, operative, and hospital course records as well as their original pre-operative and post-operative magnetic resonance imaging (MRI). Pre-operative Karnofsky Performance Scores (KPS) [7] were assigned by the clinician at the time of evaluation and available in the chart for review in all patients. Outpatient clinic notes were available from both neurosurgical and neuro-oncology follow-up visits and reviewed in all cases. Demographics, co-morbidities, presenting symptoms and signs, degree of resection, peri-operative morbidity, adjuvant chemotherapy regimens, and date of death were recorded. Tumor grade was histologically confirmed in all cases by an expert neuro-pathologist. Patients with incomplete medical records lacking pre- and post-operative MRI imaging as well as long-term survival outcomes were excluded from the analysis. In addition, patients with multifocal, non-contiguous lesions at presentation were excluded.

Imaging characteristics and criteria

All patients underwent the same preoperative MRI protocol, which consisted of a three-plane localizer sequence (8.5/1.6 ms [TR/TE]), an axial fluid-attenuated inversion-recovery (FLAIR) sequence (10,000/148/2,200 [TR/TE/TI]), an axial fast spin-echo T2-weighted sequence (3,000/102, echo train length 16, matrix 256 3 196), axial diffusion-weighted imaging (10,000/99, b = 1,000 s/mm^2), and a post-contrast three-dimensional spoiled gradient-recalled acquisition in the steady state (SPGR; 34/8) T1-weighted sequence. For the purposes of this study, the pre-operative MRI was reviewed by a neurosurgeon blinded to all clinical and outcome data. As previously defined [8], the spatial relationship of the contrast-enhancing lesion (CEL) to the lateral ventricles (LV) was classified as: (1) CEL bordering the LV (LV CEL); and (2) CEL not bordering the LV (non-LV CEL), Fig. 1.

Degree of resection was retrospectively classified from MRIs obtained <48 h after surgical resection as gross-total resection (GTR) if no residual enhancement was noted on post-operative MRI or subtotal resection (STR) if any residual enhancement was noted on post-operative MRI. Peri-operative mortality was defined as death within 30 days of surgery. During the review period, all patients underwent post-operative radiotherapy (XRT) consisting of fractionated focal irradiation at a dose of 2 Gy per fraction given once daily 5 days per week over a period of 6 weeks, for a total dose of 60 Gy.

Statistical analysis

In order to compare the effects that location to the LV has on survival, a case–control study was performed [14]. Twenty-six of the 69 reviewed cases were defined as LV CEL. These 26 patients were matched with 26 patients with non-LV CEL. The groups were matched for factors consistently shown to be associated with survival [4–6]. These factors included age, KPS, tumor size, GTR, Gliadel wafer implantation, and post-operative Temodar chemotherapy [4–6].

Survival as a function of time after surgical resection was expressed as estimated Kaplan–Meier plots. Parametic data was expressed as mean ± standard deviation (SD). Non-parametric data was expressed as median (interquartile range (IQR)). Percentages were compared via χ^2 test. Continuous variables were compared via student *t*-test or Mann–Whitney U test where appropriate. Survival between patients with LV and non-LV CEL was compared via Log-rank analysis.

Results

Patient population

Twenty-six patients with LV CEL were matched with 26 patients with non-LV CEL, Table 1. These groups were matched for factors consistently shown to be associated with survival [4–6]. These factors included age, KPS, tumor size, GTR, Gliadel wafer implantation, and post-operative Temodar chemotherapy [4–6]. Baseline clinical and treatment variables were similar between patients with LV CEL and non-LV CEL, Table 1. For the entire group, the mean ± SD age was 51 ± 13 years and 35 (56%) were male. At presentation, median (IQR) KPS was 80 (80–90) and motor deficit was present in 14 (27%) patients, language deficit in 5 (10%), and visual deficit in 3 (6%). Craniotomy was performed for primary and secondary resection of GBM in 30 (58%) and 22 (42%) patients, respectively. Eighteen (35%) patients underwent GTR of their tumor. Gliadel wafer implantation and post-operative Temodar therapy (all after 2001) was utilized in 14 (27%) patients each. All patients had received post-operative radiotherapy for their GBM.

MRI characteristics and outcome

The incidence of peri-operative morbidity did not differ as a function of CEL location, Table 2. For the entire group,

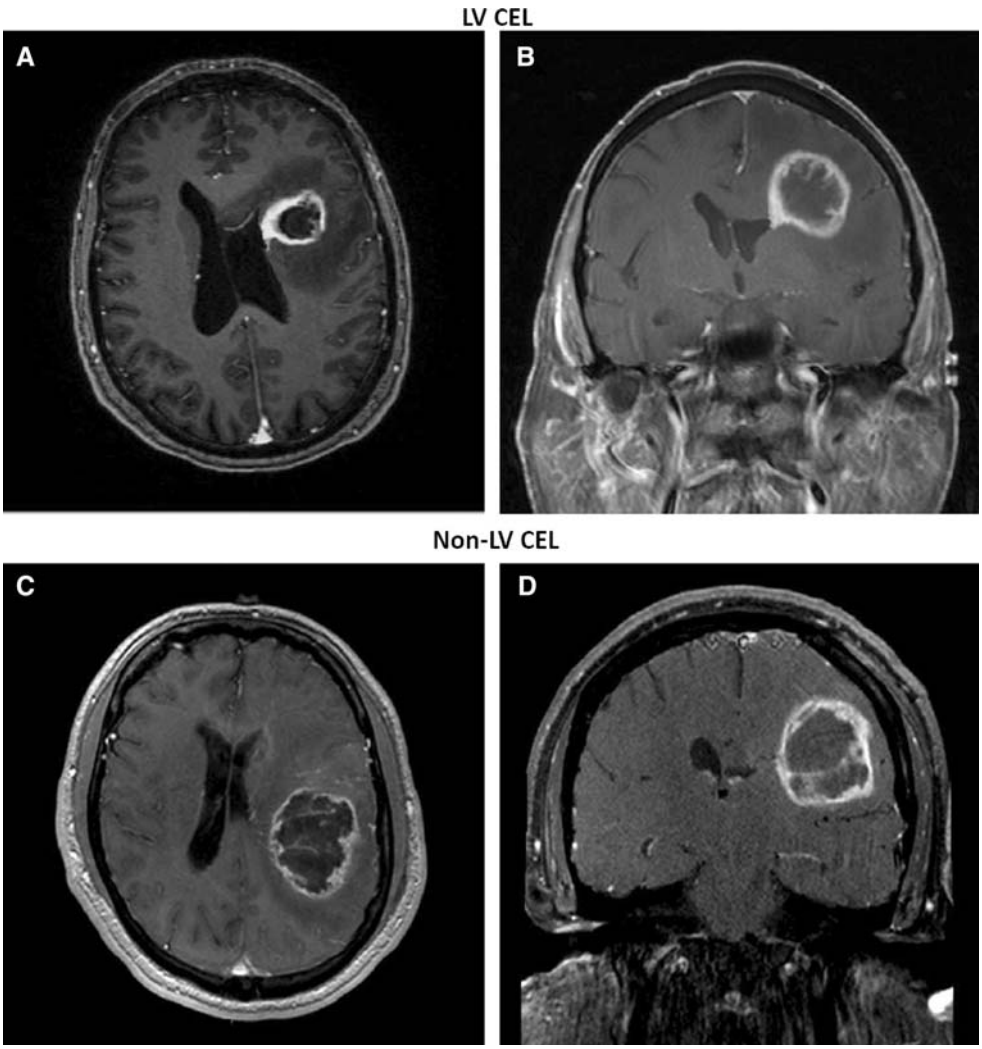

Fig. 1 Relationship of glioblastoma multiforme to the lateral ventricles (LV). Post-contrast T1-weighted magnetic resonance axial (**a**) and coronal (**b**) images demonstrating a contrast-enhancing lesion (CEL) bordering the lateral ventricles (LV). Post-contrast T1-weighted magnetic resonance axial (**c**) and coronal (**d**) images demonstrating a CEL not bordering the LV (non-LV CEL)

peri-operative mortality occurred in 0 patients, motor deficit in 7 (13%), language deficit in 3 (6%), deep vein thrombosis in 1 (2%), pulmonary embolism in 2 (4%), surgical site infection in 1 (2%), and meningitis in 2 (4%). The median (IQR) survival of the entire group was 10 (6–14) months.

Despite similarities in pre-operative clinical status and treatment regimens (Tables 1 and 2), patients with LV CEL demonstrated decreased survival as compared to patients with non-LV CEL, Fig. 2. Median survival for patients with LV CEL was 8 months as compared to 11 months for patients with non-LV CEL, $P = 0.02$. Additionally, survival analysis in patients stratified by primary or secondary resection also demonstrated a strong trend towards decreased survival after resection of LV CEL, Fig. 3. After primary resection, patients with LV CEL had a median survival of 11 months as compared to 14 months for patients with non-LV CEL, $P = 0.10$. For secondary resections, patients with LV CEL had a median survival of 7 months as compared to 10 months for patients with non-LV CEL, $P = 0.11$.

Discussion

In this case–control study, 26 patients with LV CEL were matched with 26 patients with non-LV CEL. Theses cohorts were matched for factors consistently shown to be associated with survival following GBM resection [4–6]. These factors were age, KPS, tumor size, GTR, Gliadel wafer implantation, and post-operative Temodar chemotherapy [4–6]. Despite similarities in pre-operative characteristics and treatment regimens, patients with LV CEL demonstrated decreased survival as compared to patients with non-LV CEL. In fact, the median survival for patients with LV CEL was 8 months vs. 11 months for patients with non-LV CEL. Additionally, the discrepancy in survival between patients with LV CEL and non-LV CEL also showed a strong trend

Table 1 Summary of clinical, radiological, and treatment characteristics of 52 patients with glioblastoma multiforme

Variable	LV CEL ($n = 26$)	Non-LV CEL ($n = 26$)	*P*-value
Clinical			
Age	51 ± 12	52 ± 14	0.87
KPS (IQR)	80 (80–90)	80 (80–90)	0.99
Motor deficit	6 (23%)	8 (31%)	0.53
Language deficit	2 (8%)	3 (12%)	0.61
Visual deficit	2 (8%)	1 (4%)	0.55
Primary resection	14 (54%)	16 (62%)	0.64
Gross total resection	9 (35%)	9 (35%)	0.99
Gliadel	7 (27%)	7 (27%)	0.99
Temodar	7 (27%)	7 (27%)	0.99
Pre-op MRI			
Tumor size (cc)	27 ± 16	28 ± 19	0.94

Twenty-six patients with contrast-enhancing lesions (CEL) bordering the lateral ventricles (LV) were matched with 26 patients with CEL not bordering the LV (non-LV CEL). The groups were matched for age, Karnofsky performance score (KPS), tumor size, gross total resection (GTR), Gliadel wafer implantation, and post-operative Temodar chemotherapy. Clinical and treatment variables were similar between patients with CEL bordering the LV (LV CEL) and patients with non-LV CEL

Table 2 Incidence of peri-operative morbidity and overall survival in 52 patients undergoing resection of glioblastoma multiforme

Variable	LV CEL ($n = 26$)	Non-LV CEL ($n = 26$)	*P*-value
Peri-op morbidity			
New motor deficit	3 (12%)	4 (15%)	0.68
New language deficit	1 (4%)	2 (8%)	0.55
Deep vein thrombus	1 (4%)	0 (0%)	0.31
Pulmonary embolus	1 (4%)	1 (4%)	0.99
Surgical site infection	0 (0%)	1 (3%)	0.31
Meningitis	1 (4%)	1 (4%)	0.99
Mortality	0 (0%)	0 (0%)	0.99
Median survival (months)			
All cases	8	11	0.02
Primary resection	11	14	0.10
Secondary resection	7	10	0.11

Twenty-six patients with contrast-enhancing lesions (CEL) bordering the lateral ventricles (LV) were matched with 26 patients with CEL not bordering the LV (non-LV CEL). The two patient cohorts were matched for age, Karnofsky performance score (KPS), tumor size, gross total resection (GTR), Gliadel wafer implantation, and post-operative Temodar chemotherapy. Incidence of perioperative morbidity did not differ between the two cohorts. However, patients with CEL bordering the LV (LV CEL) experienced decreased survival compared to patients with non-LV CEL

towards significance when stratifying by primary and secondary resections. CEL bordering the LV thus appears to carry a prognostic significance.

There is a great interest in ascertaining factors that are prognostic of survival for patients with GBM since survival for individual patients is heterogeneous [3]. Age and Karnofsky performance score (KPS) are currently the most significant prognostic factors of survival, where younger patients and higher KPS are associated with improved survival [5–7, 15]. Other factors that have been found to influence survival include degree of resection [5, 6, 15], adjuvant radiotherapy [16], Gliadel wafer implantation [4], and Temodar chemotherapy [2]. However, what remains less well known is whether tumor location and, more specially, adjacency to the LV are associated with poorer survival.

The region adjacent to the LV has been an area of increasing focus. In basic science studies, Sanai et al. demonstrated that cells obtained from the lateral wall of the lateral ventricles, which has been called the subventricular zone, harbors cells with stem cell-like features of self-renewal and multi-potentiality [10]. This area also has been

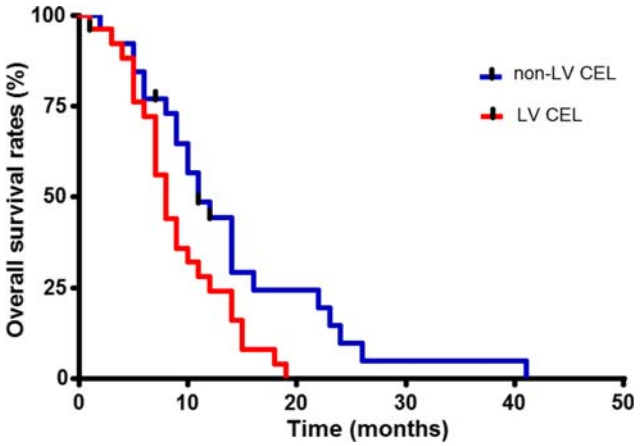

Fig. 2 Kaplan–Meier plots of survival in all patients undergoing resection of glioblastoma multiforme. Patients presenting with contrast enhancing lesions (CEL) bordering the lateral ventricles (LV) experienced decreased survival after surgery compared to patients with CEL not bordering the LV (non-LV CEL), $P = 0.02$. The median survival was 8 and 11 months for patients with CEL bordering the LV (LV CEL) and non-LV CEL, respectively

shown to have an increased propensity to form tumors in animal studies [11–13]. Interestingly, this region is also rich in extracellular matrix proteins, including basal laminin, tenascin-C, and chondroitin sulfate [17, 18], as well as microglia and endothelial cells [19], that potentiate tumor proliferation and migration. As a result, many speculate that tumors that arise in this region may behave differently than tumors that arise elsewhere [20, 21]. In fact, Lim et al. reported that 16 patients with GBM adjacent to the LV and had baseline invasion on MRI, more commonly presented with multi-focal disease and had non-contiguous recurrence [8]. Additionally, Parsa et al. reported that among patients with disseminated GBM disease, patients with subependymal spread had poorer prognosis [9]. However, it remains unknown whether single tumors that reside in this region are associated with poorer survival as compared to tumors that occur elsewhere.

This study is the first study to report that GBM tumors adjacent to the LV may be associated with poorer survival. The underlying causal factors of decreased survival in the LV CEL cohort in this observational study remain unknown, and are beyond the scope of the present study. However, several possible explanations can be theorized. Tumors associated with the LV may be in closer proximity to a higher density of subcortical fibers and/or more critical neurological tissue than tumors that occur more distally. Consequently, similar-size tumors that arise near the LV, as opposed to more peripherally, could cause more morbidity. Another interesting possibility is that GBM that arise from different anatomical regions (LV versus non-LV) may possess different cellular compositions. GBM arising near the LV may have a higher percentage of more potent cells, making them more invasive and infiltrative. Also, different anatomic regions (LV versus non-LV) may have different cellular environments more conducive for tumor proliferation and/or invasion. Therefore, tumors that arise in different anatomical regions may behave differently as a result of their cellular environment.

This study is inherently limited by its retrospective design, and, as a result, no direct causal relationships can be inferred from these observations. However, we tried to use strict inclusion criteria in order to provide more relevant information for patients with GBM. We only included patients with GBM who uniformly underwent post-operative radiation therapy and had immediate pre-operative and post-operative MRI imaging. Furthermore, we attempted to control factors associated with survival by matching patients with LV CEL and non-LV CEL for factors consistently shown to be associated with survival. Nonetheless,

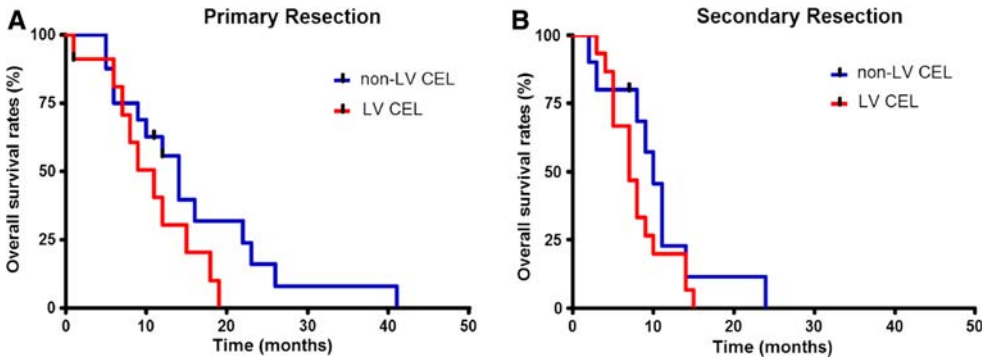

Fig. 3 Estimated Kaplan–Meier plots of survival in patients undergoing (**a**) primary resection and (**b**) secondary resection of glioblastoma multiforme. For both primary and secondary resections, patients with contrast enhancing lesions (CEL) bordering the lateral ventricles (LV) experienced a strong trend towards decreased survival versus patients with CEL not bordering the LV (non-LV CEL). For primary resections, patients with CEL bordering the LV (LV CEL) had a median survival of 11 months vs. 14 months for patients with non-LV CEL, $P = 0.10$. For secondary resections, patients with LV CEL had a median survival of 7 months vs. 10 months for patients with non-LV CEL, $P = 0.11$

larger, prospective studies capable of multivariate analysis, as well as basic science studies, may yield more pertinent information. However, given this relatively large patient series of LV CEL, statistical control, and a precise outcome measure, we believe our findings offer useful insights into the prognostic value of LV location for patients with GBM.

Conclusion

In our experience, patients with GBM bordering the lateral ventricles had decreased survival as compared to tumors not bordering the lateral ventricle. While the causal factors underlying this observation are not provided with this observational study, we feel the ominous outcomes associated with lateral ventricular location are valuable for prognosis, patient education, and appropriate stratification for future GBM research.

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