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Citation

Sastry, Rahul. 2017. The Impact of Surgery on Survival After Progression of Glioblastoma: A Retrospective Cohort Analysis of a Contemporary Patient Population. Doctoral dissertation, Harvard Medical School.

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The impact of surgery on survival after progression of glioblastoma: a retrospective cohort analysis of a contemporary patient population

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Acknowledgements: The authors would like to thank Alona Muzikansky, MS, for biostatistical review of the manuscript.

Funding: Departmental

Conflict of Interest: None

Unpublished Papers Cited: None

Presentations: E-poster, AANS Annual Meeting, April 22-26, 2017, Los Angeles, CA

Total Word Count: 2550

Abstract

Background: Despite updated management of glioblastoma (GB), progression is virtually inevitable. Previous data suggest a survival benefit from resection at progression; however, relatively few studies have evaluated the role of surgery in the context of contemporary GB treatment and widespread bevacizumab use.

Objective: The purpose of this study is to evaluate outcomes following surgical resection in patients with progressive GB since 2008.

Methods: The records of all patients who underwent biopsy or resection of GB between January 1, 2008, and December 31, 2015, were retrospectively identified and reviewed to identify 368 patients with progressive GB. Median survival and 95% confidence intervals were generated with the Kaplan-Meier method. Multivariate analysis, which controlled for age, Karnofsky Performance Status (KPS), extent of resection, adjuvant chemotherapy and radiation, tumor location, and tumor multifocality, of post-progression survival was carried out using a Cox proportional hazards model.

Results: Of 368 patients with progressive disease, 77 (20.9%) underwent resection at first documented progression. The median post-progression survivals for patients who did and did not undergo resection at this time were 12.8 and 7.0 months, respectively. In multivariate analysis, $KPS \geq 70$ at progression (HR 0.438), receipt of bevacizumab at first progression (HR 0.756), and receipt of chemotherapy at first progression (HR 0.644) were associated with increased post-progression survival.

Conclusions: Surgery for progressive GB may not improve post-progression survival in the context of contemporary maximal non-surgical therapy. Further investigation is necessary to elucidate what role, if any, bevacizumab has in prolonging post-progression survival in patients with progressive GB.

Running Title: Surgery for progressive glioblastoma

Keywords: glioblastoma; neurosurgery; neuro-oncology; bevacizumab; progressive glioblastoma

Importance

Despite advancements, the prognosis for patients with glioblastoma remains poor. Progression is nearly inevitable. Although previous studies have suggested a benefit of surgery for patients with progressive disease, relatively few have re-assessed this benefit in the context of modern treatment regimens and, specifically, widespread use of bevacizumab at progression. We conducted a large retrospective single-institution analysis in a contemporary series of patients, many of whom received bevacizumab for progressive disease. Our multivariate analysis suggests that undergoing craniotomy for resection of progressive glioblastoma is not associated with increased post-progression survival. Maximal non-surgical treatment may be a more reasonable choice than surgery for prolongation of life in patients with progressive GB.

Introduction

Glioblastoma (GB) is the most common primary malignancy of the central nervous system¹. Standard therapy for newly diagnosed GB consists of surgical resection followed by concurrent involved field radiotherapy and temozolomide and subsequent adjuvant temozolomide^{2, 3}. The prognosis for patients with GB remains poor, with median overall survival of 14-17 months from time of diagnosis³⁻⁵. Options for nearly inevitable disease progression include resection, systemic chemotherapy, radiation therapy, or clinical trial enrollment. Among these options, two interventions are currently approved by the Food and Drug Administration (FDA) for progressive GB: bevacizumab, which is now commonly used in the United States in this population, and delivery of low energy alternating electric fields via the Tumor Treating Fields (Optune, Novocure Ltd, St. Helier, Jersey) device.

As quality of life for patients with newly diagnosed or progressive GB has improved over the last two decades, resection at progression has become an increasingly frequent choice and is performed on 20-30% of patients with progressive disease^{6, 7}. Surgery at progression may extend life, obtain tissue for diagnostic confirmation, allow entrance into a clinical trial, or improve symptoms by relieving mass effect. There is also a risk, however, of incurring new post-operative deficits, which may reduce quality of life, diminish survival, or delay subsequent treatment options. The majority of data suggest that there is a survival benefit associated with resection at progression⁸⁻¹⁰, with increasing benefit associated with greater extent of resection (EOR)^{9, 11-16}. However, many of the patients included in these series were diagnosed and initiated treatment prior to the currently accepted standards of treatment at diagnosis and prior to the current widespread availability of bevacizumab for progression¹⁷. In fact, recent studies have suggested that when the initial disease is managed according to current standards of treatment, resection at progression does not offer a survival benefit over non-surgical therapy¹⁸⁻²⁰. To date, only three studies have evaluated resection at progression in the context of bevacizumab use at progression^{12, 18, 21}. By reviewing a large contemporary series of GB patients treated at a single institution, we sought to update our understanding of which patients with progressive disease benefit from resection.

Materials and Methods

Population

This study was approved by the Institutional Review Board of Massachusetts General Hospital (MGH). We retrospectively identified all patients who received care at the MGH Pappas Center for Neuro-Oncology and who underwent craniotomy for biopsy or resection of newly diagnosed GB between January 1, 2008 and December 31, 2015. GB pathology was confirmed in each case by neuropathologists in accordance with the 2007 World Health Organization (WHO) classification system. Patients with the pathologic diagnosis of gliosarcoma were included. Patients with both primary and secondary GBs were included in this study. Patients who underwent surgery or received treatment at other medical centers were included as long as adequate documentation (patient notes, pathologic specimens, peri-operative imaging) was available for review. In total, 563 patients met these criteria (**Supplemental Figure 1**).

Data Collection

All relevant data available in the health record system were reviewed in June 2016. Data collection included patient age at diagnosis, patient gender, date of initial pathologic diagnosis of GB, date of initial surgery, EOR at initial surgery, peri-operative KPS (recorded as ≥ 70 or < 70)^{3, 22}, adjuvant radio- and chemo-therapy, and clinical trial enrollment. We also recorded the dates at which patient tumors were observed to progress, whether the tumor was multifocal or in an eloquent location at progression, date(s) and type of surgery at the time of observed progression, EOR for each craniotomy after initial progression, post-progression treatments, and date of death or last follow-up.

Date of initial diagnosis was defined as the first surgery at which the diagnosis of WHO Grade IV was established regardless of prior surgery for low-grade glioma. EOR was assessed via retrospective review of radiology, neuro-oncology, radiation oncology, and brain tumor board assessments of peri-operative imaging. Gross total resection (GTR) was defined as complete removal of contrast-enhancing disease on gadolinium-enhanced T1-weighted magnetic resonance imaging (MRI). Any non-biopsy resection not considered to be a GTR was considered to be a sub-total resection (STR). Eloquent location at progression was defined by assessment of location of contrast-enhancing tumor in eloquent cortex (motor/supplementary motor cortex, primary somatosensory cortex, Broca's and Wernicke's area, and primary visual cortex) with intraoperative language-/motor-mapping or with pre-operative imaging and concurrent symptoms at presentation; in the brainstem; adjacent to or infiltrating the ventricles; or adherent

to major blood vessels²³. Multifocality was defined as multiple foci of contrast-enhancement on MRI. Peri-operative KPS was assessed by neuro-oncologists or radiation oncologists at peri-operative consultations. If KPS was not formally recorded, a score was retrospectively assessed based on chart review. Date of progression was retrospectively identified as the imaging date at which the patient's neuro-oncologist, neuro-radiologist, or the institutional brain tumor board felt the evidence supported progression. For cases in which radiographic diagnosis of progressive disease was equivocal, the date of diagnostic biopsy or surgery was recorded as the date of progression. An operation was only considered to be a resection at progression if the patient underwent a craniotomy for non-biopsy resection with confirmed post-operative pathologic diagnosis of progressive GB. As such, patients who underwent either stereotactic biopsy or craniotomy for debulking of subsequently confirmed pathologic diagnosis of pseudoprogression were considered to have not undergone resection for progression. In total, 368 patients had documented progression per these criteria and were included in all subsequent analyses **(Supplementary Figure 1)**. Resection, radiotherapy, cytotoxic chemotherapy, and bevacizumab for progression were recorded as binary variables after initial surgery and at first progression²⁴. Deaths were recorded regardless of cause.

Statistical Analysis

Statistical analysis was conducted with MATLAB (MathWorks, Natick, MA). Fisher's exact test was used to compare binary variables, the Chi-square test was used to compare categorical variables, and the two-sample t-test was used to compare continuous variables. In order to accurately model the effects of post-progression treatment decisions and to address the inherent time bias that arises from prolonged pre-progression survival in patients who may also be better re-resection candidates²⁵, we used post-progression survival, instead of overall survival, as our primary outcome measure. Median survival and 95% confidence intervals were generated with the Kaplan-Meier method. Multivariate analysis was carried out using a Cox proportional hazards method for post-progression survival. Standard censoring was utilized for patients who were lost to follow up. Only variables that satisfied the proportional hazards assumption, as determined by examination of scaled Schoenfeld residuals, were included in the model; as such, clinical trial status and radiation at first progression were excluded²⁶. Thirteen variables were included in the model: age at diagnosis, KPS at diagnosis, extent of resection at initial resection,

post-operative radiation, post-operative temozolomide, time to first progression, eloquence at first progression, multifocal disease at first progression, KPS at first progression, number of resections at first progression, extent of resection at first progression, bevacizumab at first progression, and other chemotherapy at first progression. EOR at initial diagnosis (GTR, STR, biopsy), EOR at first progression (GTR, STR, no resection), and number of resections at progression (2+ re-resections, 1 re-resection, no re-resection) were treated as categorical variables with more than 2 levels. In order to avoid over-estimation of significance and other sources of bias, variable selection methods were not used²⁷. As there are more than 10 patients per included variable, the model is not at risk of being overfit²⁷⁻²⁹. Hazard ratios and 95% confidence intervals were generated for each variable in the model. All statistical tests used a significance level of $p \leq 0.05$. Results are reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines³⁰.

Results

The characteristics of the overall patient population are summarized in **Table 1**. Two hundred and seventy-three patients (74.2%) of patients died within the study period. The median follow-up period was 16.7 months. Of the 368 patients with documented progression, 118 (32.1%) underwent GTR at initial surgery, 182 (49.5%) underwent STR at initial surgery, and 68 (18.5%) underwent biopsy at initial surgery. Three hundred and fifty-two (95.7%) patients underwent subsequent treatment radiotherapy and temozolomide. One hundred and eighty-five (50.3%) of patients were enrolled in a clinical trial at some point during their disease course. The median overall survival for the entire patient cohort was 19.5 months (95% CI: 17.6-21.2 months, **Figure 1A**). The median post-progression survival for the entire patient cohort was 8.1 months (95% CI: 7.16-8.74 months, **Figure 1B**).

We collected demographic data to better understand the baseline differences between patients who underwent resection at first progression (n=77 patients, 20.9%) and those who did not (n=291, 79.1%) (**Table 2**). Patients who underwent resection for progression were significantly younger at initial presentation (56.4 years vs. 61.4 years, $p = 0.002$) and underwent a greater proportion of GTRs (41.6% vs. 29.6%, $p = 0.01$) at initial resection. Patients who underwent resection for progression experienced progression 2.7 months later than those who did not (13.7 months vs 11.0 months, $p = 0.03$). Patients who underwent resection for progression

presented with higher KPS at progression (94.8% KPS $\geq$ 70 vs. 79.7%, $p = 0.001$) and were less likely to have either a multifocal (22.1% vs. 51.6%, $p < 0.001$) or eloquently situated tumor (66.2% vs 83.1%, $p = 0.002$) at progression. A substantially smaller proportion of patients who underwent resection at first progression received bevacizumab at first progression (39.0% vs. 60.1%, $p = 0.001$), though there was no difference in the proportion of patients who received bevacizumab at any time for first or subsequent progressions (71.4% vs. 77.3%, $p = 0.30$). Rates of radiotherapy at first progression (9.1% vs. 6.2%, $p = 0.44$) and chemotherapy at first progression (74.0% vs. 62.9%, $p = 0.08$) did not differ significantly between these groups, however. Among the 77 patients who underwent resection of progressive GB, 12 (13.6%) had further resections. At the time of resection for first progression, GTR was achieved in 26 (33.8%) and STR was achieved in 51 (66.2%) patients. Notably, 11 patients (3.8%) who did not undergo resection at first progression eventually underwent resection for a subsequent progression. None of these 11 patients underwent multiple reoperations for progression. Patients who underwent craniotomy for resection for first progression of GB had increased median post-progression survival (12.8 months vs. 7.0 months) and median follow-up (21.6 vs. 16.0 months) when compared to patients who did not.

Multivariate Analysis

We performed a multivariate analysis to identify those that were significantly associated with increased post-progression survival. Three variables were identified: KPS $\geq$ 70 at progression (HR 0.438, 95% CI 0.307-0.624, $p < 0.001$), bevacizumab at first progression (HR 0.756, 95% CI: 0.579-0.987, $p = 0.04$), and cytotoxic chemotherapy at first progression (HR 0.644, 95% CI 0.485-0.855, $p = 0.002$). Notably, in this multivariate analysis, extent of resection achieved at initial operation, whether a patient underwent resection at the time of progression, extent of resection at time of surgery for progression, and the number of post-progression resections were not significantly associated with increased post-progression survival, although extent of resection at time of resection did trend toward significance. Results from select variables of interest are briefly summarized in **Table 3**. Kaplan-Meier curves of selected variables are presented in **Figure 2**.

Discussion

Key Results

We sought to reassess the survival benefit of resection for progressive GB in a patient population in which the use of adjuvant chemoradiation following initial resection was high (95.7%) and in which the use of bevacizumab at progression was more widespread (76.1% of all identified) than has been reported in any previous study of this topic^{12, 18, 21}. The results of this study suggest that, when controlling for several potentially confounding factors, resection of progressive GB is not significantly associated with prolonged post-progression survival even if a GTR is achieved. In addition, our analysis identified KPS $\geq$ 70 at first progression, use of bevacizumab at first progression, and use of chemotherapy at first progression as being significantly associated with improved post-progression survival.

Interpretation

The finding of our study that resection of progressive GB does not significantly prolong post-progression survival is at odds with some previous analyses. Notably, although Chaichana et al previously concluded that resection for progressive GB and the number of resections were both associated with improved overall survival in a case-control analysis⁹, the low overall survival of single-resection patients (6.8 months) and low proportion of patients receiving both radiation (65%) and temozolomide (27%) following initial surgery limit the relevance of results to the current era of GB treatment. More recent studies have suggested that resection at progression is valuable if a GTR is achieved or if post-progression EOR exceeds initial EOR^{8, 11-13, 16}. Our results are concordant with the conclusions reached by Ortega, et al. who determined that repeat resection was not significantly associated with increased overall survival in a contemporary patient population that was commonly treated with bevacizumab for progression¹⁸. Our findings expand on these data by including a larger and more heterogeneous population, considering more variables in our model, and examining post-progression survival instead of overall survival.

Taken together, these results suggest that resection for progression may have offered a clearer survival benefit before the widespread adoption of aggressive initial resection followed by concurrent chemoradiation. Despite the fact that resection for progressive GB may not be life-extending, there are still indications for resection at progression, such as to debulk tumor mass to

palliate symptoms, to minimize steroid dependence, to acquire tissue for molecular analysis, and to allow enrollment in clinical trials.

Interestingly, our model identifies post-progression bevacizumab and cytotoxic chemotherapy as being significantly associated with improved post-progression survival. The significant survival benefit attributed to bevacizumab is at odds with findings from recent data from the yet unpublished EORTC 26101 study which suggest that use of bevacizumab in combination with lomustine, despite initial promise in early trials, improves only progression-free survival and not overall survival³¹⁻³⁴. This discordance may be a result of divergent treatment combinations, dosages, or durations utilized at our practice as compared to the EORTC 26101 protocol. Of course, with any retrospective analysis, there may be an unidentified source of confounding that has contributed to this result. Further study of the role of bevacizumab for progressive GBM will likely be necessary to determine which, if any, subsets of patients with progressive GB benefit from bevacizumab.

Limitations and Generalizability

As with any retrospective analysis, this study has limitations. A number of patients were lost to follow-up. Furthermore, we did not consider patients who underwent biopsy or resection of pseudoprogression as having undergone resection of progressive disease; however, these procedures undoubtedly carry their own benefits and risks of morbidity and mortality. Molecular characteristics of the tumor, notably including *IDH1* mutation status and *MGMT* methylation status, were not included in our analysis as testing results were not routinely available for every patient throughout the study time period. While we have identified three variables as being independently associated with post-progression survival, it is possible that these are surrogate markers for other, as yet unidentified, features of these tumors or their hosts. Finally, the generalizability of our results may be limited by its retrospective nature and by variations in management of GB at other centers, and constantly evolving treatment options for GB.

Conclusions

Despite maximal treatment, progression of GB is a near inevitability. A variety of treatment options, including surgery, chemotherapy, radiation, and clinical trial enrollment, are available to patients at progression. In the context of contemporary treatment approaches and

recent widespread adoption of bevacizumab for progressive GB, we sought to reevaluate the role of resection for progressive GB. Our multivariate analysis suggests that undergoing resection of progressive GB is not associated with post-progression survival. Our findings also support the idea that maximal medical therapy may be a more reasonable choice than surgery for managing GB progression.

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Figures

Figure 1 – Overall and Post-Progression Survival for entire patient cohort. (A) Kaplan-Meier curve demonstrating overall survival for total cohort of 368 patients. The median overall survival for the entire patient cohort was 19.5 months (95% CI: 17.6-21.2 months). (B) Kaplan-Meier curve demonstrating post-progression survival for total cohort of 368 patients. The median post-progression survival for the entire patient cohort was 8.1 months (95% CI: 7.16-8.74 months).

Figure 2 – Kaplan-Meier curves demonstrating post-progression survival stratified by selected variables. (A) Kaplan-Meier curve demonstrating post-progression survival for patient cohort stratified by KPS (KPS $\geq$ 70, KPS < 70) at first recurrence. Median survivals were 8.6 months (7.9-9.4 months) and 4.4 months (3.1-5.8 months). (B) Kaplan-Meier curve demonstrating post-progression survival for patient cohort stratified by post-progression bevacizumab use. Median survival was 8.15 months (6.94-9.10) for those who received bevacizumab and 5.19 months (4.27-6.01 months) for those who did not. (C) Kaplan-Meier curve demonstrating post-progression survival for patient cohort stratified by re-operation status. Median survival was 12.8 months (9.3-14.0 months) for those who underwent resection at first progression and 7.0 months (6.25-8.15 months) for those who did not. (D) Kaplan-Meier curve demonstrating post-progression survival for patient cohort stratified by maximum extent of resection achieved at resection at progression. Median survival was 14.4 months (12.8-26.3 months) for those who achieved GTR, 9.4 months (7.16-12.2 months) for those who achieved STR, and 7.0 months (6.25-8.15 months) for those who did not undergo re-operation.

At Risk

No Reoperation:	291	143	54	24	10	5	4	3
Reoperation:	77	59	31	12	7	3	0	0

At Risk

No Reop:	291	143	54	24	10	5	4	3
Reop GTR:	26	23	15	5	4	2	0	0
Reop STR:	51	36	16	7	3	1	0	0

Supplementary Figure 1 – Schematic of patient selection

Tables

Table 1 – *Characteristics of 368 patients with documented progression of GB.*

	Documented Recurrence (n = 368)
Mean Age at Diagnosis (years)	60.3 years (Range: 18.5-90.1)
KPS at Diagnosis	
≥70	339 (92.1%)
< 70	29 (7.9%)
EOR	
GTR	118 (32.1%)
STR	182 (49.5%)
Biopsy	68 (18.5%)
Post-operative TMZ/Radiation	352 (95.7%)
Clinical Trial Enrollment	185 (50.3%)
Death Within Study Period	273 (74.2%)
Median Follow-Up (months)	16.7 (IQR: 12.0-25.2)
Median Overall Survival (months)	19.5 (95% CI: 17.6-21.2)
Median Post-Progression Survival	8.1 (95% CI: 7.16-8.74)

Table 2 – *Descriptive statistics for patient cohort stratified by re-operation status.* Tests of statistical significance are carried out with Fisher’s exact test unless otherwise specified.

	No Resection at First Progression (n = 291)	Resection at First Progression (n = 77)	P-value
Mean Age at Diagnosis (years)	61.4	56.4	0.002 (t-test)
KPS at Diagnosis			
≥ 70	264 (90.7%)	75 (97.4%)	0.058
< 70	27 (9.3%)	2 (2.6%)	
EOR at initial surgery			0.012 (χ^2)
GTR	86 (29.6%)	32 (41.6%)	
STR	143 (49.1%)	39 (50.6%)	
Biopsy	62 (21.3%)	6 (7.8%)	
Post-operative TMZ/Radiation	275 (94.5%)	77 (100%)	0.029
Clinical Trial Status	132 (45.4%)	53 (68.8%)	< 0.001
Mean Time to Progression (months)	11.0	13.7	0.028 (t-test)
KPS at Progression			0.001
≥70	232 (79.7%)	73 (94.8%)	
< 70	59 (21.3%)	4 (5.2%)	
Multifocal at Progression	150 (51.6%)	17 (22.1%)	< 0.001
Eloquent Location at Progression	242 (83.1%)	51 (66.2%)	0.002
Reoperation at Subsequent Progression	11 (3.8%)	12 (13.6%)	
EOR at Resection for First Progression			
GTR		26 (33.8%)	
STR		51 (66.2%)	
Radiation at First Progression	18 (6.2%)	7 (9.1%)	0.443
Chemotherapy at First Progression	183 (62.9%)	57 (74.0%)	0.081
Bevacizumab at First Progression	175 (60.1%)	30 (39.0%)	0.001
Bevacizumab at Any Progression	225 (77.3%)	55 (71.4%)	0.295
Median Follow-Up (months)	16.0 (IQR: 11.3-24.5)	21.6 (IQR: 14.9-31.3)	
Median Post-Progression Survival (months) [95% CI]	7.0 (6.25-8.15)	12.8 (9.3-14.0)	

Table 3 – *Results of Cox proportional hazards multivariate analysis.* All variables were included in the multivariate model.

Variable	Hazard Ratio	Confidence Interval (95%)	P Value
Age at diagnosis	1.005	[0.994-1.016]	0.341
GTR at initial resection	1.028	[0.701-1.507]	0.889
STR at initial resection	1.042	[0.745-1.456]	0.811
KPS $\geq$ 70 at Diagnosis	1.372	[0.829-2.272]	0.219
Post-operative radiation	0.452	[0.192-1.062]	0.068
Post-operative temozolomide	1.087	[0.490-2.413]	0.837
Time to first documented progression	0.991	[0.978-1.003]	0.156
Eloquence at first progression	1.030	[0.742-1.429]	0.860
Multifocal disease at first progression	1.232	[0.957-1.585]	0.106
KPS $\geq$ 70 at first progression	0.438	[0.307-0.624]	< 0.001
Resection at first progression	0.975	[0.672-1.414]	0.895
Multiple resections for progression	0.707	[0.334-1.496]	0.364
GTR at resection for first progression	0.583	[0.317-1.070]	0.082
Bevacizumab for first progression	0.756	[0.579-0.987]	0.040
Chemotherapy for first progression	0.644	[0.485-0.855]	0.002