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Clinical, Radiographic, and Pathologic Findings in Patients Undergoing Reoperation Following Radiation Therapy and Temozolomide for Newly Diagnosed Glioblastoma

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Abstract

Purpose—Patients with glioblastoma (GBM) frequently deteriorate clinically and radiographically after chemoradiation and may require repeat surgical intervention. We attempted to correlate pathologic findings with preoperative clinical characteristics and survival in patients undergoing reoperation for GBM.

Materials and Methods—Patients eligible for this retrospective analysis had pathologically confirmed GBM diagnosed between 2005 and 2010, received standard radiation and temozolomide, and underwent repeat resection within 18 months of diagnosis.

Results—Thirty-eight patients were identified. Median age was 56 years (range, 30 to 80 y), 55% were male, and 66% had baseline performance status 90%. Median survival was 16.3 months (95% confidence interval [CI], 13.3–19.8) from initial surgery. At reoperation, 21% of patients had no pathologically evident tumor. Median time from initial diagnosis to second surgery was similar in patients with and without evident tumor (8.5 vs. 8.8 mo, respectively). Patients without evident tumor tended to have a worse performance status. Median overall survival from second surgery was 7 months (95% CI, 4.2–10.1) and 9.1 months (95% CI, 2.1–25.3) for patients with and without evident tumor, respectively. Multivariate proportional hazards analysis showed a hazard ratio for death of 0.61 (95% CI, 0.25–1.49) for patients without evident tumor after adjusting for Karnofsky performance status and second surgical procedure.

Conclusions—GBM patients with and without disease recurrence have similar clinical characteristics at the time of second surgical resection. Pathologic outcomes were not correlated with specific clinical or radiologic characteristics, including the time from diagnosis to reoperation. There was a trend toward improved overall survival among patients without evident tumor at reoperation.

Keywords

glioblastoma; recurrence; reoperation; pathology

Glioblastoma (GBM) is the most common malignant brain tumor diagnosed in the United States and accounts for approximately 65% of primary central nervous system malignancies.¹ Currently, no curative treatment for this disease is available. Standard treatment includes debulking surgery followed by radiation with concurrent temozolomide, followed by 6 months of temozolomide monotherapy. After concurrent chemoradiation, many patients with GBM develop new symptomatic lesions within the irradiated area that may represent either recurrent tumor or breakdown of the blood-brain barrier without pathologic evidence of recurrent disease. Current imaging technology is unable to discern whether or not tumor is present, and consequently patients often require a surgical intervention after adjuvant chemotherapy and radiation. This may provide symptomatic relief from mass effect as well as pathologic confirmation of disease status. However, outcomes following repeat resection among patients with GBM have not been well documented. In this paper, we report on a series of 38 patients who received standard radiation and temozolomide for GBM and required reoperation at a single high-volume academic institution.

MATERIALS AND METHODS

Patients

Approximately 450 patients underwent resection of newly diagnosed GBM at our institution between January 2005 and December 2009. Data from the institutional tumor registry and from the electronic medical record were reviewed to identify patients undergoing a second craniotomy for resection of suspected recurrent brain tumor. All patients included in this report completed a standard 6-week course of radiotherapy and concurrent temozolomide. Completing a full 6 months of adjuvant temozolomide monotherapy was not required for inclusion in the study. All patients underwent repeat surgical resection of an area within the irradiated field within 18 months of their original diagnosis. Thirty-eight patients met these criteria and are included in this report. This study was approved by the internal institutional review board.

Patients were considered for reoperation if their serial magnetic resonance imaging (MRI) scans revealed increasing contrast enhancement and the patients were experiencing significant corticosteroid-refractory symptoms related to edema and mass effect. Decisions relating to the need for repeat surgery are typically reviewed at the weekly meetings of a multidisciplinary brain tumor board. All surgical specimens were reviewed by a single senior neuropathologist at the institutional Department of Pathology. The formal pathology report was used to classify patients as having either “evident tumor,” or “no evident tumor.” Specimens classed as “evident tumor” were further characterized as “abundant active tumor” (> 50% of specimen consisting of proliferating tumor cells), “extensive active tumor” (10% to 50% of specimen consisting of proliferating tumor cells), “focal active tumor” (< 10% of specimen consisting of proliferating tumor cells), or “quiescent tumor” (specimen containing viable but nonproliferating tumor cells), and specimens classed as “no evident tumor” were further characterized as demonstrating “necrotic tumor” (recognizable but nonviable tumor cells), “treatment effect” (evidence of radiation effects with no recognizable tumor cells), or “gliosis” (scar tissue with no recognizable tumor cells).

Patient baseline characteristics were summarized using descriptive statistics. χ^2 test statistics were used for proportional comparison. Student *t* test was used for continuous data between group comparisons. Survival probability was estimated using the Kaplan-Meier method.² The confidence interval of median time survival was constructed by the method of Brookmeyer-Crowley.³ Univariate analysis was used to assess an association between the known prognostic factors of patients at baseline and overall survival (OS). A multivariate proportional hazards regression model was constructed through biological reasoning due to the small size of the data set. The proportional hazards regression model was used to estimate the hazard ratio (HR) for death attributable to prognostic factors. All *P* values are reported as 2-sided, and all analyses were conducted using the SAS software (version 9.1, SAS Institute).

RESULTS

Patients

The median age of the patients in this study was 56 years (range, 33 to 80 y) with 3 patients over the age of 70. Fifty-five percent of the patients were male, and 66% had a postoperative Karnofsky performance status (KPS) of 90 to 100. Fifty percent of patients had a gross total resection of their GBM at the time of initial surgery. One patient had only a tumor biopsy, and the remainder underwent subtotal resection (STR). Carmustine wafers (Gliadel) were placed in 7 patients (18%) at the time of initial surgery. Surgery was followed by conformal radiation therapy (60 Gy) administered with concurrent daily temozolomide (75 mg/m²/d). Ten patients (26%) received additional treatment with novel agents such as cilengitide and hydroxychloroquine on Cancer Therapy Evaluation Program-approved clinical trials. Patients were offered standard adjuvant temozolomide (150 to 200 mg/m²/d for 5 consecutive days each month for 6 mo) depending upon their clinical status. Sixty-five percent of the patients received at least 2 cycles of adjuvant temozolomide. The most common reason for stopping maintenance temozolomide was disease progression (51% of patients) or myelosuppression (19% of patients). After progression, patients were treated with a variety of salvage regimens; 10 patients (26%) received bevacizumab and 9 (24%) were enrolled in clinical trials. Further details regarding patient characteristics are provided in Table 1.

Reoperation

At the time of second surgery, 15 patients (40%) had a KPS of 90 to 100. Reoperation in all patients was performed between 5 and 15 months after initial surgical resection. Twelve patients (32%) had a gross total resection of the contrast enhancing abnormalities at the time of the second surgery. The remainder had STRs (defined as any surgical resection that was more extensive than a biopsy but did not remove all visible tumor). The formal pathology reports from the repeat resections documented that 30 patients (79%) had evident tumor, whereas 8 patients (21%) had no evident tumor. There was no statistically significant difference in median time to reoperation between patients with evident tumor (8.5 mo) and in patients without evident tumor (8.8 mo). Patients without evident tumor at the time of reoperation tended to have worse KPS than those with evident tumor (*P* = 0.08). The average number of maintenance temozolomide cycles received was not correlated with the

pathologic findings at the time of the second surgery. Patients with evident tumor received an average of 3.2 cycles of maintenance temozolomide, whereas patients without evident tumor received an average of 2.0 cycles.

Patterns of Failure Among Patients Without Evident Tumor at Reoperation

Eight patients had no evident tumor in tissue samples obtained at the time of second surgery. Data were collected on the clinical courses of these 8 patients to determine whether the ultimate site of failure was within the initially radiated field or out-of-field. Two patients did not have follow-up MRI available. Of the 6 patients who had follow-up radiographic data, 5 had tumor recurrence at the original treatment site, and 1 had simultaneous local and distant failure.

Survival

Thirty-seven patients have died and 1 patient remains alive with locally recurrent disease at the time of this analysis. The median survival for the entire cohort of 38 patients was 16.2 months (95% CI, 13.8–19.8 mo) from the time of initial surgery and 7.7 months (95% CI, 4.3–10.1 mo) from the time of second surgery. The median OS after second surgery was 7.0 months (95% CI, 4.3–10.1 mo) in patients with evident tumor and was 9.1 months (95% CI, 2.1–25.3 mo) in patients without evident tumor. Patient and disease characteristics were similar at the time of second surgery except with respect to performance status; patients without evident tumor had slightly worse performance status than those with tumor, as shown in Table 1. The unadjusted univariate HR for death attributable to the absence of tumor compared with the presence of tumor at the time of second surgery was 0.72 (95% CI, 0.3–1.7). A multivariable analysis accounting for performance status and the type of surgical procedure performed at the time of second surgery revealed a 39% (HR = 0.61; 95% CI, 0.25–1.49) decrease in the HR for death in patients who were without evident tumor at second surgery. Figure 1 shows the Kaplan-Meier survival curves for patients with and without evident tumor at the time of second surgery.

DISCUSSION

The addition of temozolomide to standard radiation has improved the prognosis for patients with GBM and remains the current standard of care. Interpreting patient response to combined modality therapy is complicated by the progressive changes in the integrity of the blood-brain and blood-tumor barriers that occur in up to 58% of patients and may or may not be associated with pathologically proven tumor recurrence.⁴ Radiographically, these changes resemble recurrent tumor, with peripheral contrast enhancement, central necrosis, edema, and mass effect which clinically result in neurological deficits and increasing glucocorticoid requirements. Mistaking this phenomenon for recurrent disease can lead to premature discontinuation of an effective therapy. Conversely, mistaking recurrent disease for treatment effect can delay the initiation of second-line chemotherapy or participation in clinical trials. Because there is no reliable clinical or radiologic means to distinguish patients who have true tumor progression from “pseudoprogression,” symptomatic patients often undergo surgical exploration.

Most prior publications on pseudoprogression lack pathologic confirmation of the diagnosis, which is often made only in retrospect after reviewing serial MRI studies. These publications have assumed that lesions which continue to grow represent recurrent disease and those that regress or remain stable represent treatment effect. In this report, we analyzed only patients with available pathology in an effort to objectively identify clinical characteristics that might distinguish patients with or without tumor recurrence.

The only molecular marker that has been prospectively validated as a predictor of OS in patients with GBM is methylation of the methylguanine methyltransferase (MGMT) promoter.⁵ Of note, MGMT-methylated patients appear to have a significantly higher incidence of pseudoprogression than patients with unmethylated tumors.⁶ However, these data need to be interpreted with care, as the investigators diagnosed pseudoprogression based on serial MRI changes rather than pathologic verification of disease status. Other studies have focused on identifying radiographic features to distinguish recurrent disease from pseudoprogression. For example, Traber et al⁷ reported on 44 malignant glioma patients who underwent serial MR spectroscopy studies during and immediately after treatment. Although increased choline signal appeared fairly sensitive (72%) in distinguishing patients with disease recurrence, the specificity was low, with 6 of 15 patients with normal choline signal experiencing disease recurrence within 3 months of completing treatment. Once again, serial radiologic assessments were used to make these judgments as pathologic correlations were not available.

Previous series that have attempted to correlate clinical and radiologic findings with tissue pathology are limited. Young and colleagues reported on 6 patients with pathologic confirmation of pseudoprogression and 22 patients with pathologically verified early progression. These investigators failed to identify any conventional MRI features that were reliably correlated with pseudoprogression.⁸ Kim et al⁹ retrospectively reviewed 20 patients who underwent resections of recurrent GBM in an attempt to identify pathologic characteristics that predicted for clinical outcomes. Specimens were graded in terms of the percent of active tumor (whether low or high grade) remaining in the specimen. Correlation with serial MRI scans was not performed. Their analysis revealed that patients with < 20% residual tumor in the resected surgical specimen had longer survival after surgery than patients with a greater burden of active disease. In this series, MIB-1 labeling index, IDH1 mutation status, and EGFR amplification status were not correlated with survival.

The selection criteria we used for the study reported in this manuscript are unique in several ways. First, we included only patients who had second surgery within 18 months of the initial diagnosis, at a time when questions about true progression versus pseudoprogression are most pressing. Second, all patients received the current standard treatment of radiation and temozolomide, which is known to be associated with pseudoprogression. Third, all patients had pathologic confirmation of the status of their tumor at a time when clinical uncertainty was an issue. All of the patients had an open resection performed, and 32% had a gross total resection of the contrast enhancing abnormality, ensuring that adequate tissue was available to the neuropathologist. Our findings suggest that patients with true progression had similar clinical characteristics to those with pseudoprogression. In addition, there was no difference in the time to second surgery between patients with true progression

and with pseudoprogression. Thus, the timing of the development of a symptomatic radiographic abnormality has no correlation with the nature of the abnormality. There were also no significant differences in the 2 groups of patients in terms of age, sex, or number of doses of administered adjuvant chemotherapy. Somewhat counterintuitively, patients with recurrence appeared to have a higher KPS at the time of second surgery than those without evident tumor. There was a trend toward shorter survival times in patients with recurrence at the time of reoperation compared with patients who had no pathologically evident tumor.

To our knowledge, this is the largest report correlating suspected radiographic progression with pathologic findings at second surgery. The results demonstrate a trend toward better OS in patients with pathologically confirmed pseudoprogression. This study has several unavoidable limitations. It is retrospective, and due to our restrictive eligibility criteria, the sample size is small. There are also inherent biases present in the selection of patients for a second surgery as patients must be symptomatic, the lesions must be localized and technically operable, and the patient must have a reasonable performance status for surgery to be considered. It is also possible that significant sampling errors could have occurred as 64% of the second surgeries were STRs. In addition, pathologic interpretation of the specimens is highly subjective and variable among different observers. Although the World Health Organization has a formal system for the grading of malignant gliomas at the time of initial surgery, no criteria have been developed for evaluating the extent of treatment effects. Finally, we were unable to obtain sufficient MGMT data on these samples to perform a formal correlation of MGMT status with pathologic disease status in these patients. This could be important given the reported relationship between MGMT status and the incidence of treatment-related radiographic pseudoprogression.

Despite these limitations, we have clearly shown that the pathologic outcome could not have been predicted by clinical or radiologic examinations or by the time from diagnosis to second surgery. Furthermore, the survival was somewhat better in patients with pseudoprogression than in those with tumor recurrence. Further research on this important topic is required, as pseudoprogression may increase in frequency as novel agents, particularly immunotherapeutics (which can cause brisk local inflammatory reactions), are added to radiation and temozolomide.¹⁰ Future studies should rely heavily on pathologic confirmation of the entity given the known unreliability of neuroimaging studies in this setting.

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FIGURE 1.

Kaplan-Meier survival curve depicting overall survival times among patients with and without evident tumor at the time of second surgery. The solid line represents patients without evident tumor and the dashed line represents patients with evident tumor.

TABLE 1

Patient Characteristics

	n (%)			P
	All Patients (n = 38)	Tumor Evident in Resected Tissue (n = 30)	No. Tumor Evident in Resected Tissue (n = 8)	
Age				
70	3 (8)	2 (7)	1 (13)	> 0.1
< 70	35 (92)	28 (93)	7 (87)	
Sex				
Male	21 (55)	16 (53)	5 (63)	> 0.1
Female	17 (45)	14 (47)	3 (37)	
Baseline KPS				
90–100	25 (66)	19 (63)	6 (75)	> 0.1
60–80	8 (21)	6 (20)	2 (25)	
Unknown	5 (13)	5 (17)	0 (0)	
Extent of initial surgery				
Gross total resection	19 (50)	14 (47)	5 (63)	> 0.1
STR	12 (32)	9 (30)	3 (37)	
Other	7 (19)	7 (23)	0 (0)	
Mean # cycles temozolomide received	2.9	3.2	2.0	> 0.1
KPS at second surgery				
90–100	15 (39)	14 (47)	1 (13)	0.08
60–80	23 (61)	16 (53)	7 (87)	
Extent of second surgery				
Gross total resection	12 (32)	11 (37)	1 (13)	> 0.1
STR	16 (68)	19 (63)	7 (87)	
Median time to second surgery (mo)	8.8	8.5	8.8	> 0.1

KPS indicates Karnofsky performance status; STR, subtotal resection.