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Histopathological correlates with survival in reoperated glioblastomas

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Abstract

The addition of concomitant and adjuvant chemotherapy to radiation therapy after surgical resection has increased significantly the survival of patients with glioblastoma (GB). In conjunction, there has been an increasing fraction of patients who present with new enlarged areas of contrast enhancement and edema on post-treatment imaging that improve without further treatment. It remains to be established how this phenomenon, commonly termed pseudoprogression, can be distinguished from true tumor recurrence defined as the histological presence of active high-grade tumor, as well as its prognostic significance. Data for over 500 patients undergoing surgery for recurrent GB were reviewed. Pathological specimens were categorized as those that contained active high-grade glioma in any amount, and those that did not. Patient survival was compared between these two groups, and independent associations were assessed using Cox proportionate hazards regression analysis. 59 patients met the study criteria including complete pathological and follow-up data. Mean age was 53 ± 11 years. Median survival from suspected recurrence and initial diagnosis were 8 [5–14] and 20 [12–30] months. Seventeen patients (29 %) had no evidence of active high-grade tumor and 42 (71 %) had at least focal active high-grade glioma. Pathologic pseudoprogression at re-operation ($p = 0.03$) and gross

total resection ($p = 0.01$) were independently associated with survival. The histopathological features defined here and used to assess the tumor at reoperation were independently associated with survival. These findings may be important in designing treatment strategies and clinical trial endpoints for patients with GB.

Keywords

Glioblastoma; Pathology; Recurrence; Treatment effect; Pseudoprogression

Introduction

With the addition of concomitant and adjuvant chemotherapy to radiation therapy after surgical resection, survival of patients with glioblastoma (GB) has increased significantly in recent years [1]. In conjunction, there have been an increasing number of patients that present with new or enlarged areas of contrast enhancement and edema, typically within 3–6 months of completing therapy, that subsequently improve without further treatment.

Termed “pseudoprogression” since it mimics true tumor recurrence, this phenomenon typically evolves along a different clinical course than that of true recurrent, “active” tumor. Tumors in patients with the former phenomenon often comprise paucicellular tissue with areas of gliosis and hyalinized vessels. The mitotic index is low [2, 3]. Treatment of such lesions is varied but often includes observation or continuation of prior treatment until there is strong evidence of true tumor progression [4, 5]. In contrast, patients with active recurrent GB are generally treated with aggressive salvage treatment regimens and/or offered experimental therapies. A major limitation to current clinical practice is the lack of histopathological criteria for pseudoprogression, as opposed to true tumor progression.

The majority of clinical studies have used radiologic criteria to differentiate tumor from treatment effect [6–10]. However, no specific imaging pattern has emerged to differentiate these two processes conclusively. Clinical trials based on assessments of radiologic progression-free survival or those enrolling patients with radiologic recurrence may include patients with pseudoprogression. The study outcome can be thus inadvertently affected. Histopathological analysis remains the diagnostic standard for guiding clinical decision-making and further treatments. The few studies that have included histopathological analysis have not clearly defined the pathologic criteria for distinguishing treatment effects from active neoplasm and, as a result, observed a broad range (6–19 %) of lesions diagnosed as pseudoprogression at the time of re-operation [3, 11, 12]. Currently, the advantage of pathologic diagnosis of the latter is debated, and histopathological requirements for active tumor versus treatment effect are undefined.

We conducted a retrospective study using series of patients with recurrent GB to define the pathologic features that distinguish pseudoprogression and active tumor, as well as to evaluate potential association of these two pathologically defined groups with survival outcome using a Cox proportional hazards regression model.

Methods

Study design and patient population

Approval for review of patient medical records was obtained from the Johns Hopkins University (JHU) Institutional Review Board. Clinical information for patients treated for GB at JHU between 1996 and 2009 were collected. Inclusion criteria were: initial surgery and pathological diagnosis of GB at JHU, second surgical resection or biopsy and pathological assessment at JHU, and availability of demographic, operative, radiologic, and follow-up data. Exclusion criteria included: initial pathological diagnoses of World Health Organization grade II or III or oligodendroglial tumors and initial surgical biopsy only or incomplete pathological specimen for histopathological study. Cases were reviewed individually in the multi-disciplinary brain tumor conference for a combined treatment recommendation from neuro-oncologists, neurosurgeons, neuroradiologists, neuropathologists, and radiation oncologists. Pathological assessments were done initially or reviewed by a single neuropathologist (PCB) who categorized the lesions as either containing or not containing active high-grade tumor by criteria detailed below.

Demographic, clinical, operative, radiological, pathological, treatment, and follow-up data were collected and reviewed for each patient. Diabetes mellitus and hypertension categorizations were made based on pre-operative classification and ongoing medical management of these conditions. Patients being actively treated with oral hyperglycemic medication and/or insulin were considered 'DM'. In cases where the death date was unavailable from local sources, this information was obtained through the public United States Social Security Death Index database (<http://ssdi.rootsweb.ancestry.com/>).

Pathological analysis

Specimens at recurrence were classified as either containing "active" or "no active" high-grade tumor. Active tumors were defined as those with any area of highly cellular tumor similar to GB prior to treatment (Fig. 1), although neither necrosis nor vascular proliferation was required in the recurrent lesions. Mitoses were usually present, but were not required in a small specimen wherein cellularity was high in an obviously anaplastic recurrent tumor. Coexisting tissue patterns that we associate with prior treatment such as coagulation necrosis in paucicellular areas, gliosis, pleomorphic sometimes multi-nucleated cells in low density, vascular changes such as fibrinoid necrosis, telangiectases, and hyalinization (Fig. 2), were often present, and did not detract from the designation "active tumor present" if the aforementioned cellular areas were present as well. If not, then the lesion was considered not to have "active tumor". The relative proportions of active tumor and treatment effects varied considerably, being low in some and high in others. These were not quantified. The presence of only low grade astrocytoma was not considered evidence of "active tumor". While Mib-1 preparations were available in some cases, and useful in confirming suspicions about a high-grade process, these were not part of the criteria used.

Statistical analysis

Patient characteristics at time of reoperation and prior treatment were summarized using descriptive statistics. The proportion of patients with "no active high-grade tumor" was

estimated along with 95 % CI assuming a binomial distribution. Cohort summary data were given as mean $\pm$ standard deviation for parametric data, median [interquartile range (IQR)] for non-parametric data, and number (percentage) for proportional data. The primary outcome of survival was defined from the date of reoperation to death due to all causes. Survival probability was estimated using the Kaplan–Meier method [13, 14]. Univariate associations were assessed using log-rank analysis. Important patient characteristics associated with survival were identified in the univariate analysis using a $p = 0.05$. Given the relatively small cohort size, a stepwise Cox proportional-hazards regression model was applied to assess independent associations with survival over time; a p value ≤ 0.15 was required to enter and a p value >0.05 was the cut off to exit the analysis. The only exception to this was the inclusion of patient age in the model which is a well-known prognostic factor for this study patient population. A Kaplan–Meier curve was constructed to visually represent the survival distribution of the two histopathological groups. All p values are reported as 2 sided and all analyses were performed using JMP 8 (SAS Institute, Carey, NC, USA).

Results

Patient population

The medical records and pathology database reviews yielded over 500 patients with recurrent GB during the study period. After applying the inclusion and exclusion criteria, 59 patients were included in the statistical analysis (Tables 1, 2). Mean age was 53 ± 11 , 38 (64 %) were female. Fifty-six (95 %) of patients had died at time of the data analysis. The surgery for suspected recurrence occurred at a median of 9.3 months after the initial diagnosis. The median survival from surgery for suspected recurrence and from initial diagnosis was 8 [5–14] and 20 [12–30] months, respectively. Following pathological review, 17 patients (29, 95 % CI 18–42 %) had a diagnosis of “no active high-grade tumor”. Forty-two (71, 95 % CI 58–82 %) had diagnosis of “active GB”. Data for each pathological group are compared in Tables 1 and 2. Mean age for each group, co-morbidities, pre-operative Karnofsky performance scores (KPS), presenting symptoms, imaging characteristics and locations, surgical variables and degrees of resection, post-operative findings and treatments are given for each group. Notably, the median time between the first and second surgeries was similar between each pathological group, suggesting that differences in time between surgeries did not contribute to survival differences between the two groups. Median survival from reoperation was longer in the no active tumor group compared to the group with active GB. These variables were analyzed individually in relation to the survival outcome using log-rank analysis.

The most common treatment algorithm followed for patients in this study included maximal resection [15, 16] followed by standard fractionated radiation therapy and concurrent chemotherapy (Stupp Protocol [1]). In some cases, patients were enrolled in an experimental treatment protocol in conjunction with or following standard therapies or received carmustine-impregnated wafers (6, 7), Table 2. Any therapy that caused intolerable or dangerous side effects, including, but not limited to, severe fatigue, nausea, or cytopenia, was stopped. Following completion or termination of initial treatments, patients were

followed closely for signs of neurological or radiologic changes every 2–3 months. When clinical symptoms worsened in the setting of new imaging findings, patients were presented at the multi-disciplinary neuro-oncology review conference. Additional surgery was offered if the group felt that the patient would benefit from either a tissue diagnosis and/or debulking in the case of significant mass effect. Following this second surgery and pathology analysis, patients were offered further treatment if active high-grade tumor was diagnosed. If not, patients were continued on their pre-operative treatment or observed without additional tumor therapy. Patients confirmed to have active high-grade tumor were treated with standard chemotherapy, clinical trials, or repeat radiation therapy, Table 2. In rare cases, patients with significant radiologic and clinical worsening after initial chemoradiation were not surgical candidates and were treated on clinicians' best estimates of active tumor or pseudoprogression. These patients are excluded from analysis as no tumor tissue was available.

Treatment regimen differences

We also compared the relative percentage of patients with pseudoprogression and their survival based on the treatment regimen. Carmustine-impregnated wafer and temozolimide-based regimens had similar patient percentages with non-active tumor at the time of repeat surgery, Table 3. Based on our data, there were no significant survival differences among the treatment regimens. Patients receiving chemoradiation or radiation alone had statistically similar survival from recurrence and overall survival in this study, although the groups were too small to detect survival differences at the published level.

Associations with survival from recurrence

Univariate, non-adjusted associations with survival following the second surgery are detailed in Table 4. These variables were entered into the stepwise multivariate analysis given the relatively small cohort size. The results of this model are given in Fig. 3. Older age (>65 years) did not maintain statistical significance in the adjusted model [HR 1.11 95 %CI (0.72–1.85), $p = 0.63$]. The factors significantly associated with poor survival after re-operation included co-morbidities (diabetes mellitus [HR 2.36 95 %CI (1.18–4.25), $p = 0.02$] and hypertension [HR 2.15 95 %CI (1.09–3.82), $p = 0.03$]), and new post-operative motor deficits [HR 3.70 95 %CI (2.56–7.41), $p = 0.01$]. Independent associations with decreased hazard of death included high pre-operative performance status (KPS ≥ 70) [HR 0.32 95 %CI (0.15–0.85), $p = 0.03$], initial gross total resection [HR 0.60 95 %CI (0.42–0.86), $p = 0.01$], and pseudoprogression [HR 0.61 95 %CI (0.36–0.96), $p = 0.03$]. Patients with histopathologically documented absence of active high-grade tumor lived nearly two times longer from re-operation compared to those with active tumor recurrence. None of the radiologic characteristics of the recurrent lesion on standard MRI sequences showed strong correlations with survival outcome or differentiated these two pathological groups, including enhancing pattern ($p = 0.94$), associated edema ($p = 0.27$) or hemorrhage ($p = 0.23$) (Table 4). The survival distributions for each pathological group are given as a Kaplan–Meier plot in Fig. 4, ($p = 0.03$).

Discussion

In this study, patients with the diagnosis of GB who underwent a second open surgery for suspected recurrence due to worsening clinical symptoms and/or mass effect were studied. The pathological presence of active high-grade tumor compared to the absence of tumor (pseudo-progression) was found to be independently associated with survival. Of note, the time between the first and second surgery for each of these histopathological groups was similar, and longer than what is commonly quoted. While repeat surgery has risk, the morbidity was low in this series and offered either clinical benefit from reduction of mass effect, tissue diagnosis for optimizing treatment planning, or both. Yet, a limitation of this approach and subsequent analysis is the bias when surgery is favored in higher functioning patients and/or in patients who have experienced a precipitous decline in function. Importantly, the data indicate that there were no standard radiologic or clinical findings that predicted the histopathologic features at recurrence. In most cases, the pathology diagnosis directly influenced treatment decisions allowing patients without active tumor to avoid the potential side effects of further treatments and patients with active high-grade tumor to initiate new therapies.

The reported incidence of pseudoprogression in patients with GB/high-grade glioma ranges from 2 to 50 % depending in part on the diagnostic modalities employed [5, 17–21]. We found pseudoprogression present in 29 % of our re-operated patient cohort. This percentage is dependent on the accuracy of the test used, including the representative portion of the tissue being analyzed, and the inclusion/exclusion criteria for the patient cohort being studied. Each of these studies may over- or under-estimate the incidence of pseudoprogression based on these factors.

Previously noted associations with pseudoprogression have included chemo-radiation treatments, type of chemotherapy, histopathological findings, and MGMT promoter methylation status [22–25]. Brandes et al. suggested that MGMT status predicts the incidence of and outcome following radiologic pseudoprogression, but did not correlate promoter methylation with histopathological features. While our analysis did not include MGMT promoter methylation status, this represents an interesting area for future study.

The majority of previous studies exploring this topic have used clinical and radiologic rather than pathological endpoints to determine the nature of progression [5, 24, 26]. In one study, progression, according to RECIST criteria within 8 weeks of RT/TMZ treatment were divided into those who progressed further within 6 months of completing RT/TMZ and those who did not. Median survival was significantly longer for the pseudoprogression group [19]. Thus, there is a difference in outcome between true progression and pseudoprogression, but the difficulty has been to define these prospectively. Unfortunately, standard imaging modalities have not been sufficiently sensitive or specific in differentiating between the two [4, 27–31].

Our analysis also did not show a significant correlation between specific radiologic findings and histopathological features at recurrence or on patient survival. While careful analysis of the radiologic characteristics of equivocal lesions can aid in establishing a follow-up plan,

many require more concrete evidence before proceeding with repeat radiation or chemotherapy [4]. It is likely that more advanced imaging modalities will aid in this distinction with possibilities being: amide proton transfer [32–34] and dynamic susceptibility-weighted [30, 35] magnetic resonance imaging, as well as parametric response maps using changes in cerebral blood flow and volume [36]. Regardless of the diagnostic modality, the prognosis and treatment implications associated with specific recurrence patterns remain central questions in the clinical decision making in patients with recurrent GB.

A strength of this study is a histopathological definition of active versus inactive tumor at the time of recurrence. In a 1995 study, Forsyth et al. reviewed stereotactic biopsy results of 51 patients with mixed low-grade gliomas treated with external beam radiation. They found that the amount of viable tumor could be used to correlate necrosis and survival [11]. These results are not directly applicable to GBs in the post-chemoradiation era, but they are in keeping with the results of the present study.

Tihan et al. addressed the issue of pathologic diagnosis of tumor versus treatment effect in a manner very similar to the present study by categorizing cases as recurrent tumor or treatment effect, except that they added a third category for ‘indeterminate’ lesions consisting of mixtures of treatment effects and active tumor recurrence. They noted no difference in clinical behavior between patients with recurrent tumor or treatment effect [37]. More recently, Topkan et al., reviewed their series of patients with early (<6 mo.) tumor progression that had received standard chemo-radiation therapy, who were re-operated for histopathological confirmation. They found that 19 % of these patients had pseudoprogression and that this pathologic diagnosis corresponded with improved survival using non-controlled, log-rank analysis [12]. The authors mention morphologic characterization, however they did not offer clear histopathological criteria for the diagnosis of pseudoprogression. Supportive findings with Mib-1 (Ki-67) staining was mandatory. Finally, Kim et al. [38] studied 20 GBs in specimens of both initial and recurrent tumors, finding that the amount of total tumor, whether high-grade, low grade, or a combination thereof, was predictive of overall survival from the time of clinical recurrence. The extent of high-grade tumor alone, or of therapy-related necrosis, was not prognostic.

Our study suggests that prognostically significant categorization can be accomplished by dichotomous assignment based on the histopathological criteria suggested. We recognize this is a subjective distinction that may be difficult to standardize across diverse institutions. Tissue sampling is a difficult issue and as much tissue as possible should be submitted for pathological study, recognizing that, even then, surgical methods such as sonification or coagulation can alter the architecture. Based on the results of this and other studies described above, re-operated GB patients without active tumor are likely to live longer and can delay additional treatments, with their possible side effects. For these, watchful waiting until there is confirmation of active high-grade tumor before changing or adding new treatments is appropriate. Accounting for the retrospective nature of this study and the strict inclusion and exclusion criteria designed to reduce sampling error, our findings offer useful insights into the definition of post-treatment tumor recurrence as well as the management of patients with recurrent GB.

Conclusion

The histopathological features defined here and used to assess the tumor at reoperation were independently associated with survival. Wider application of strictly defined pathological criteria for active GB versus pseudoprogression may be important in designing treatment strategies and clinical trial endpoints for patients with presumed recurrent GB.

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Fig. 1.

Histological features of active high grade tumor—true tumor recurrence. **a** Highly cellular tumor, in this case around an area of necrosis, establishes the presence of “active” high grade tumor. While common in pretreatment specimens, perinecrotic pseudopalisading was, as here, usually absent. **b** Microvascular proliferation and highly cellular tumor tissue establish the presence of active recurrent glioblastoma. **c** While cytologically bland, small tumor cells in this density were considered evidence of active recurrent tumor. Mitoses were typically present (*arrow*) but were sparse or even absent in small specimens.

Hypertrophic endothelial cells are consistent with, but not diagnostic of, active high grade tumor

Fig. 2.

Histological features of treatment effect—pseudoprogression. **a**. Necrosis, *left*, hyalinized vessels, and pleomorphic tumor cells in low density are considered evidence of treatment effect, not expressions of recurrent or residual active high grade tumor. **b**

Areas of brightly eosinophilic coagulation necrosis are common effects of treatment. Telangiectatic vessels (*arrows*) are additional, but less specific, features. **c** Necrosis in this treated lesion is associated with fibrillary and gemistocytic astrocytes in low density. It can be difficult in cases such as this to determine whether these cells are reactive or neoplastic. Even if the latter, we did consider them evidence of tumor recurrence. **d** Well differentiated neoplastic astrocytes in low numbers were not interpreted as evidence of recurrent active, high grade glioma. Coagulation necrosis in a paucicellular lesion such as this is typical of treatment effect. **e** Widely scattered pleomorphic astrocytes consistent with irradiated tumor cells were not taken as evidence of active high grade astrocytoma. **f** Fibrinoid necrosis of vessels is a common feature of treatment effect

Fig. 3.

Stepwise multivariate Cox proportionate hazards regression analysis with Forest plot demonstrating independent association with survival from re-operation. (<0.15 to enter, 0.05 to exit)

Fig. 4.

Kaplan–Meier survival plot by recurrence pathology from (A) time of suspected recurrence (Log rank $p = 0.03$) (*solid line* pseudoprogression, *dotted line* active GB recurrence). Patients without active tumor at the time of suspected recurrence went on to live significantly longer than those patients with active high grade tumor recurrence ($p = 0.03$). This was the case even without additional treatments until the time of active tumor recurrence

Table 1

Demographic, clinical, and follow-up data for 59 patients who underwent repeat surgery for suspected recurrent glioblastoma (GB)

Variable	Pseudoprogression (n = 17)	Active GB (n = 42)	p value
<i>Demographics</i>			
Age (years)	57 ± 7	54 ± 10	0.26
Female	14 (82 %)	24 (57 %)	0.07
Caucasian	14 (82 %)	33 (79 %)	0.74
Diabetes mellitus	1 (6.0 %)	5 (12 %)	0.53
Coronary artery disease	1 (6.0 %)	1 (2.4 %)	0.71
Hypertension	1 (6.0 %)	4 (10 %)	0.66
<i>Presenting symptoms</i>			
KPS	80 ± 10	80 ± 10	0.85
Headache	2 (12 %)	13 (31 %)	0.07
Seizures	6 (37 %)	7 (16 %)	0.08
Motor deficit	0 (0 %)	9 (21 %)	0.19
Sensory change	0 (0 %)	2 (4.8 %)	0.50
Language deficit	2 (12 %)	5 (12 %)	0.95
Visual change	4 (22 %)	2 (5 %)	0.08
<i>Imaging findings at recurrence</i>			
Tumor size (cm) largest diameter	4.8 ± 1.3	4.1 ± 1.6	0.16
Eloquent location	8 (47 %)	17 (41 %)	0.64
Hemorrhage	0 (0 %)	7 (16 %)	0.23
Mass effect	14 (85 %)	40 (94 %)	0.27
Ribbon enhancing pattern	5 (27 %)	11 (26 %)	0.94
Nodular enhancing pattern	2 (12 %)	1 (2.4 %)	0.22

Table 2

Treatment and outcome data for 59 patients who underwent repeat surgery for suspected recurrent glioblastoma (GB)

Variable	Pseudoprogression (n = 17)	Active GB (n = 42)	p value
<i>Repeat surgery variables</i>			
Biopsy	0 (0 %)	2 (5 %)	0.63
STR (< 95 %)	2 (12 %)	6 (15 %)	0.89
NTR (95–99 %)	5 (29 %)	17 (40 %)	0.41
GTR (> 99 %)	10 (59 %)	17 (40 %)	0.41
Surgical site infection	2 (12 %)	1 (2.4 %)	0.14
Meningitis	0 (0 %)	0 (0 %)	–
<i>Post-operative findings</i>			
Hospital stay (days)	3.7 ± 1.9	4.8 ± 2.9	0.17
KPS	60 [50–80]	70 [60–80]	0.80
Hydrocephalus	0 (0 %)	0 (0 %)	–
Pulmonary embolus	2 (12 %)	1 (2.4 %)	0.14
Myocardial infarction	0 (0 %)	0 (0 %)	–
<i>Post-operative treatments</i>			
Repeat Gliadel	0 (0 %)	7 (29 %)	0.11
Repeat Temodar	0 (0 %)	5 (12 %)	0.14
Repeat radiation	0 (0 %)	2 (4.8 %)	0.36
Other adjuvant therapies	0 (0 %)	5 (12 %)	0.14
Additional surgery	7 (41 %)	14 (33 %)	0.57
<i>Time-related variables</i>			
Time 1st–2nd surgery (mo.)	9.0 [6.0–11.0]	9.5 [6.8–13.3]	0.42
Survival from 2st surgery (mo.)	12.5 [4.7–27.6]	8.1 [5.2–13.6]	0.03
Survival from 1nd surgery (mo.)	21.2 [11.1–40.1]	20.1 [13.6–30.8]	0.08

Data given at mean ± standard deviation, median [interquartile range], or number (percentage)

KPS Karnofsky performance score, STR sub-total resection, NTR near total resection, GTR gross total resection

Table 3

Comparison of the relative percentage of patients with pseudopogression and survival by each chemo-radiation therapy regimen

Treatment regimen	% Pseudopogression	Time 1st–2nd surgery	Survival from 2st surgery	Survival from 1nd surgery
Radiation + Temodar (n = 29)	8 (27 %)	9.0 [7.5–13.5]	8.4 [6.0–14.5]	20.6 [15.1–34.2]
Radiation + Gliadel (n = 24)	9 (38 %)	8.5 [6.0–11.0]	8.1 [5.0–14.6]	20.2 [10.8–34.6]
Radiation + BCNU (n = 6)	0 (0 %)	11.0 [6.5–16.8]	12.0 [4.6–24.1]	23.1 [13.3–45.5]

None of the patients in this series received combination chemotherapy. Gliadel and Temodar-based regimens had similar percentages without active tumor at the time of repeat surgery, but both had more the intravenous BCNU-based regimens

Table 4

Univariate associations with worse survival following surgery for suspected glioblastoma recurrence

Variable	Hazard ratio (95 % CI)	p value
<i>Demographics</i>		
Age > 65 years	1.46 (1.00–2.03)	0.05
Female	1.00 (0.76–1.31)	0.99
Caucasian	0.97 (0.69–1.32)	0.85
Diabetes mellitus	1.98 (1.20–3.00)	< 0.01
Coronary artery disease	7.03 (0.38–39.5)	0.15
Hypertension	2.09 (1.19–3.34)	0.01
Obesity	1.88 (0.75–3.51)	0.15
<i>Presenting symptoms</i>		
KPS > 70	0.50 (0.26–1.04)	0.11
Headache	0.93 (0.65–1.38)	0.68
Seizures	0.97 (0.70–1.39)	0.86
Motor deficit	1.34 (0.85–1.97)	0.19
Sensory change	1.60 (0.64–2.96)	0.26
Language deficit	1.93 (1.17–2.94)	0.01
Visual change	1.03 (0.56–1.63)	0.92
<i>Imaging findings</i>		
Tumor size (cm) largest diameter	1.23 (1.01–1.50)	0.04
Eloquent location	1.22 (0.93–1.60)	0.16
Hemorrhage	1.18 (0.72–1.75)	0.48
Mass effect	1.35 (0.80–2.77)	0.29
Ribbon enhancing pattern	0.47 (0.11–1.04)	0.07
Nodular enhancing pattern	0.66 (0.46–0.92)	0.02
<i>Repeat surgery variables</i>		
Pseudoprogression	0.72 (0.51–0.97)	0.03
Biopsy	1.00 (0.24–2.17)	0.99
STR (< 95 %)	1.31 (0.83–1.93)	0.23
NTR (95–99 %)	1.20 (0.89–1.60)	0.22
GTR (> 99 %)	0.74 (0.55–1.00)	0.05
Time 1st–2nd surgery	1.01 (0.98–1.05)	0.48
<i>Post-operative findings</i>		
Hospital stay (days)	1.04 (0.94–1.14)	0.42
KPS > 70	0.84 (0.62–1.13)	0.25
New motor deficit	7.04 (1.40–35.36)	0.02
New language deficit	1.21 (0.49–2.19)	0.62
Surgical site infection	0.80 (0.32–1.45)	0.52
Pulmonary embolus	1.65 (0.90–4.13)	0.11
<i>Post-operative treatments</i>		
Repeat Gliadel	1.02 (0.72–1.39)	0.90

Variable	Hazard ratio (95 % CI)	<i>p</i> value
Repeat Temodar	2.45 (0.86–5.03)	0.22
Repeat radiation	1.28 (0.51–2.34)	0.52
Other adjuvant therapy	0.88 (0.47–1.40)	0.61

p <0.15 considered significant (italicized) and used as the threshold for inclusion in the stepwise, multivariate analysis

KPS Karnofsky performance score, *STR* sub-total resection, *NTR* near total resection, *GTR* gross total resection