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Gliadel (BCNU) wafer plus concomitant temozolomide therapy after primary resection of glioblastoma multiforme

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Abstract

Object—Gliadel (BCNU) wafer and concomitant temozolomide (TMZ) therapy, when used individually as adjuvant therapies, extend survival from that achieved by resection and radiation therapy (XRT) for glioblastoma multiforme (GBM). It remains unstudied whether combining Gliadel and TMZ therapy is safe or further improves survival in patients with newly diagnosed GBM. The authors reviewed their initial experience utilizing combined Gliadel, TMZ, and radiation therapy for the treatment of GBM.

Methods—All cases involving patients undergoing primary resection of GBM with or without Gliadel wafer (3.85% BCNU) implantation and adjuvant XRT over a 10-year period (1997–2006) were retrospectively reviewed. Beginning in 2004, concomitant TMZ became the standard of care at the authors' institution and all patients with Gliadel implantation also received concomitant TMZ (Stupp protocol). Overall survival and treatment-related morbidity were assessed for all patients treated with Gliadel plus concomitant TMZ (XRT + Gliadel + TMZ). Age-matched (70 years) comparison of survival and morbidity was performed between the XRT + Gliadel + TMZ (post-2003) and XRT + Gliadel (pre-2004) cohorts.

Results—Thirty-three patients were treated with XRT + Gliadel + TMZ. The median survival in this group was 20.7 months, with a 2-year survival rate of 36%. Six-month morbidity included surgical site infection in 1 case (3%), perioperative seizures in 2 cases (6%), deep-vein thrombus in 1 (3%), pulmonary embolism in 3 (9%), and cerebral edema requiring admission for intravenous dexamethasone in 1 case (3%). Myelosuppression required premature termination of TMZ in 7 patients (21%) (thrombocytopenia in 5, neutropenia in 2 cases). In patients 70 years of age, XRT + Gliadel + TMZ (30 patients, post-2003) was independently associated with improved median survival (21.3 vs 12.4 months, $p = 0.005$) versus XRT + Gliadel (78 patients, pre-2004),

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with 2-year survival of 39 versus 18%, respectively. In these patients, XRT + Gliadel + TMZ was not associated with an increase in perioperative morbidity in comparison with XRT + Gliadel.

Conclusions—In this experience, concomitant TMZ therapy in addition to Gliadel wafer implantation was associated with a median survival of nearly 21 months without increased perioperative morbidity. Temozolomide can be safely administered to patients receiving Gliadel wafers after resection of GBM.

Keywords

Gliadel wafer; glioblastoma multiforme; survival; temozolomide

GLIOBLASTOMA multiforme is the most common malignant primary brain tumor in adults. With an annual incidence rate of 4–5 cases per 100,000 persons, the number of new patients diagnosed with GBM every year is ~ 10,000 in North America and 3 million worldwide. Despite advances in the surgical and adjuvant treatment of malignant astrocytoma over the past few decades, median survival remains < 15 months.¹¹

Implantation of Gliadel wafers (MGI Pharma, Inc.), which provide local delivery of the chemotherapeutic polymer BCNU, has consistently been reported to extend median survival by 2–4 months for patients with newly diagnosed and recurrent malignant astrocytoma, resulting in a median survival of 13.9 months after initial tumor resection.^{2,3,16,19,20} More recently, adding the systemic chemotherapeutic agent TMZ (Temodar, Schering Corp.) to standard radiation therapy was reported to increase median survival by 2.5 months versus radiotherapy alone, further extending median survival to 14.6 months after primary resection.¹⁴ However, postoperative radiotherapy plus concomitant and adjuvant TMZ alone (Stupp protocol) does not deliver therapeutic agent to the debulked tumor during the 3-week period between surgery and radiotherapy.¹⁴ The Gliadel wafer offers a theoretical bridge of this nontherapeutic period, allowing continuous adjuvant therapy beginning immediately following tumor resection. It remains unknown whether this theoretical therapeutic advantage is associated with clinical benefit.

Although trials are underway, no other published studies to date have examined the effect of Gliadel wafer implantation plus concomitant and adjuvant TMZ for the initial treatment of GBM.⁸ In the setting of recurrent malignant astrocytoma, a single study of Gliadel wafer plus adjuvant TMZ has been reported;⁶ this study demonstrated minimal toxicity associated with the combination of these agents. We report our initial experience utilizing the combination of Gliadel wafer and concomitant TMZ therapy in 33 patients undergoing primary GBM resection and adjuvant radiotherapy.

Methods

Study Design

The records of all patients undergoing resection of malignant astrocytoma by 3 full-time faculty members at a single institution between 1997 and 2006 were identified and reviewed. Cases of stereotactic needle biopsy, open diagnostic biopsy, or cases involving surgery performed by part-time faculty members were excluded by the retrospective search criteria.

The medical records of all identified patients undergoing primary resection of new-onset GBM between 2004 and 2006 with or without Gliadel (3.85% BCNU) wafer implantation in addition to adjuvant XRT and concomitant TMZ therapy according to the Stupp protocol¹⁴ were then reviewed in detail. In 2004, concomitant daily TMZ therapy per the Stupp protocol was instituted as the standard of care at our institution. Therefore, all patients receiving Gliadel wafer implantation since 2004 have received Gliadel wafer, adjuvant XRT, and concomitant TMZ therapy (XRT + Gliadel + TMZ).

The primary aim of this study was the assessment of overall survival and treatment-related morbidity for the XRT + Gliadel + TMZ cohort (2004–2006). The overall survival of patients not receiving Gliadel (XRT + TMZ) during this period (TMZ era, 2004–2006) was also assessed.

The secondary aim of this study was to compare overall survival and treatment-related morbidity between age-matched (18–70 years of age) XRT + Gliadel + TMZ and XRT + Gliadel alone cohorts. Prior to 2004, patients receiving Gliadel wafer implantation and adjuvant XRT were not treated with additional adjuvant first-line chemotherapeutic agents. Therefore, all patients receiving Gliadel wafer implantation prior to 2004 received adjuvant XRT and Gliadel alone (XRT + Gliadel). Other than the introduction of concomitant TMZ therapy into practice during this 10-year period (1997–2006), the operating surgeons, surgical treatment strategies, adjuvant XRT, follow-up care, and all other practice patterns remained constant.

Data Collection

Presenting clinical, radiological, operative, hospital course, and outpatient neurosurgical and neurooncology follow-up records were available for all patients and retrospectively reviewed with appropriate institutional review board approval. Demographic data, presenting symptoms and signs, degree of resection, operative course, perioperative morbidity, adjuvant radiotherapy and chemotherapy regimens, and date of death were recorded. Degree of resection was retrospectively classified based on the neuroradiologist's interpretation of the postoperative MR images obtained < 48 hours after resection. Degree of resection was defined as gross-total if no residual nodular enhancement was noted on postoperative MR images and subtotal if residual nodular enhancement was noted on postoperative MR images. Tumor grade was histologically confirmed as WHO Grade IV (GBM) in all cases by a neuropathologist at our institution. It was recorded if patients underwent a secondary resection at time of subsequent tumor recurrence. Because all reviewed patients were followed up within our institution for at least 6 months, treatment-related morbidity occurring within 6 months after surgery was recorded. The incidence and cause of termination of TMZ prior to completion of 6 adjuvant TMZ cycles was also recorded. Incidence of death was confirmed by means of the US social security death database (Social Security Death Index Database). Living patients were recorded as lost to follow-up and "censored" in the Kaplan-Meier model at date of last contact with Johns Hopkins Hospital.

Treatment Protocols

During the reviewed time period, the decision algorithm for implantation of Gliadel wafers remained consistent for the 3 operating surgeons (H.B., A.O., and J.W.). Gliadel wafers were not implanted when tumors were multifocal, extended across the corpus callosum, required large opening of the ventricle, or were thought intraoperatively to be subtotally resected. The standard XRT regimen during the reviewed period consisted 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. The XRT was typically initiated 3 weeks after surgery. The concomitant TMZ regimen of Stupp et al.,¹⁴ instituted in 2004, consisted of administering 75 mg/m²/day, 7 days a week, from the first day of radiotherapy until the last day of radiotherapy. After a 4-week break, patients were then given TMZ at 150–200 mg/m² for 5 consecutive days every 28 days for up to 6 cycles.

Statistical Analysis

For assessment of the XRT + Gliadel + TMZ cohort (2004–2006), overall survival as a function of time after resection was expressed using the Kaplan-Meier method. Survival comparisons were made via the log-rank test. Parametric data were expressed as means $\pm$ SDs and compared using the Student t-test. Nonparametric data were expressed as medians (and IQRs) and compared using the Mann-Whitney U test. Percentages were compared using the chi-square test or Fisher exact test based on sample size.

For the survival comparison between the XRT + Gliadel + TMZ (post-2003) and XRT + Gliadel (pre-2004) cohorts, the independent effect of XRT + Gliadel + TMZ versus XRT + Gliadel alone on survival was assessed using multivariate proportional-hazards regression analysis (Cox model) adjusting for all other variables associated with survival in this series (age and subtotal resection).

Results

One thousand fifteen patients underwent resection of malignant astrocytoma during the reviewed period. The tumors were classified as WHO Grade IV in 829 (82%) cases, 480 (58%) of which were primary resections. Of the 480 primary GBM resections, Gliadel wafers were used in 145 (30%). One hundred twelve of these 145 patients were treated prior to the introduction of concomitant TMZ therapy (XRT + Gliadel, 1997–2004) and 33 were treated after introduction of concomitant TMZ (XRT + Gliadel + TMZ, 2004–2006). Forty-five patients underwent primary GBM resection without Gliadel after the introduction of concomitant TMZ (XRT + TMZ, 2004–2006).

Gliadel + TMZ Cohort: Patient Population and Survival

Thirty-three patients underwent primary resection, implantation of Gliadel wafers, adjuvant XRT, and concomitant TMZ for the treatment of new-onset GBM between 2004 and 2006. Their mean age was 60 $\pm$ 10 years and 19 (58%) were male. Three patients were older than 70 years of age (73, 78, and 81 years old). Median (IQR) preoperative Karnofsky Performance Scale score was 80 (80–90). Gross-total resection was achieved in 26 cases (79%). Subtotal resection was achieved in 7 cases (21%). Six-month morbidity included

surgical site infection requiring Gliadel removal 2 weeks after surgery in 1 patient (3%). Perioperative seizures occurred in 2 patients (6%), deep-vein thrombus in 1 (3%), and pulmonary embolism in 3 (9%). Postsurgical symptomatic cerebral edema of the surgical bed requiring admission for intravenous dexamethasone therapy occurred in 1 case (3%). Eighteen patients (55%) in the XRT + Gliadel + TMZ cohort died during the follow-up period. Mean $\pm$ SD follow-up for living patients in this cohort was 18 ± 10 months (range 6–32 months). Patients treated with XRT + Gliadel + TMZ had a median survival of 20.7 months, with a 2-year survival rate of 36% and a 6-month progression-free survival rate of 93%.

Toxicity of Gliadel + TMZ

Seven (21%) of these 33 patients experienced myelosuppression requiring premature termination of TMZ therapy; the myelosuppression was attributed to concurrent daily TMZ treatment in all of these cases. Of these 7 patients, 2 patients were unable to complete concomitant daily TMZ therapy due to thrombocytopenia $< 20,000$; 3 completed daily TMZ but received no adjuvant monthly TMZ due to thrombocytopenia $< 20,000$, 25,000, and 49,000; and 2 received only a single cycle of adjuvant monthly TMZ due to absolute neutrophil counts < 1500 . Two patients did not complete adjuvant monthly TMZ for other reasons: adjuvant monthly TMZ was withheld after completion of concomitant TMZ due to generalized weakness in an 81-year-old patient; in the other patient, TMZ treatment was terminated due to radiographic tumor progression after the first cycle of adjuvant monthly TMZ therapy.

Gliadel + TMZ Versus TMZ Alone

Forty-five patients underwent primary resection of GBM without Gliadel placement followed by XRT and concomitant TMZ between 2004 and 2006. In the majority of these cases, Gliadel was withheld due to an intra-operative presumption of subtotal resection, resulting in a higher incidence of subtotal resection in the XRT + TMZ cohort than in the XRT + Gliadel + TMZ cohort (60 vs 30%, $p < 0.05$). The XRT + TMZ cohort demonstrated a median survival of 14.7 months compared with 20.7 months in the XRT + Gliadel + TMZ cohort ($p < 0.01$). When gross-total resection was achieved, XRT + TMZ (18 cases) was associated with a median survival of 19.8 months, whereas XRT + Gliadel + TMZ (23 cases) was associated with a median survival of 21.5 months (not significant for this small sample size, $p = 0.30$).

Gliadel + TMZ Versus Gliadel Alone

Seventy-eight patients undergoing GBM resection with Gliadel and adjuvant XRT therapy alone between 1997 and 2004 (XRT + Gliadel) were between 18 and 70 years of age. Thirty patients receiving concomitant TMZ according to the Stupp protocol¹⁴ in addition to Gliadel wafer implantation (XRT + Gliadel + TMZ) between 2004 and 2006 were between 18 and 70 years of age. There were no significant differences in preoperative age, degree of disability, extent of resection, or incidence of subsequent adjuvant chemotherapy or revision resection between the XRT + Gliadel (1997–2004) and XRT + Gliadel + TMZ (2004–2006) cohorts (Table 1). Although the proportion of patients receiving adjuvant chemotherapy for tumor progression was similar in the 2 cohorts, the agents used prior to 2004 differed from

those used from 2004 through 2006 (Table 1). The incidence of surgical site infection, CSF leak, postoperative seizures, symptomatic cerebral edema requiring intravenous steroid therapy, perioperative deep vein thrombosis, or pulmonary embolism was not increased by adding concomitant TMZ to Gliadel therapy after 2003. The incidence of myelosuppression was increased in the XRT + Gliadel + TMZ in comparison with the XRT + Gliadel cohort (23 vs 0%, $p < 0.001$).

The XRT + Gliadel + TMZ cohort demonstrated an increase in median overall survival compared with the XRT + Gliadel cohort (21.3 vs 12.4 months, $p = 0.005$), with 2-year overall survival of 39 versus 18% (Fig. 1). Adjusting for factors associated with survival in this series (age [$p = 0.04$] and subtotal resection [$p = 0.04$]), XRT + Gliadel + TMZ remained independently associated with improved overall survival compared with XRT + Gliadel, (relative risk [95% CI]: 0.42 [0.24–0.73], $p = 0.002$). Furthermore, 6-month progression-free survival was significantly greater in the XRT + Gliadel + TMZ cohort than in the XRT + Gliadel cohort (90 vs 40%, $p < 0.05$).

This survival difference was observed after both gross-total resection and subtotal resection. For patients who underwent gross-total resection, median survival for XRT + Gliadel + TMZ versus XRT + Gliadel was 21.5 versus 14 months ($p < 0.01$). For those who underwent subtotal resection, median survival for XRT + Gliadel + TMZ versus XRT + Gliadel was 17.1 versus 9 months ($p < 0.05$).

Discussion

We report our initial experience with the combination of Gliadel (BCNU) wafers plus concomitant TMZ therapy using the Stupp protocol¹⁴ in patients undergoing primary resection and adjuvant radiotherapy for GBM. Since instituting this multimodal approach in 2004, we have observed a median survival of nearly 21 months without an increase in Gliadel-related morbidity. Premature termination of TMZ due to myelosuppression occurred in 21% of the cases in which patients were treated with TMZ and Gliadel. With respect to previous reports of XRT combined with TMZ for new-onset GBM, our incidence of myelosuppression was slightly higher than that reported by Stupp and colleagues¹⁴ but similar to the 19% incidence reported by Gerber and colleagues.⁵ The constant patient characteristics and practice patterns observed before and after 2004 in the XRT + Gliadel and XRT + Gliadel + TMZ cohorts suggest that adding concomitant TMZ to Gliadel wafer therapy may have contributed, in part, to the 8-month increase in median survival that we observed. In fact, an increased survival was observed in association with XRT + Gliadel + TMZ treatment versus XRT + Gliadel treatment in patients undergoing gross-total resection as well as those undergoing subtotal resection. Given the retrospective nature of this study, however, it remains unclear whether this multimodal therapy or other unmeasured factors such as differences in MGMT-promoter methylation contributed to this survival difference. Although it remains unclear whether this 8-month increase was a direct result of the combination of Gliadel plus TMZ, the 21-month median survival observed here is favorable for patients with GBM and suggests that TMZ and Gliadel can be used together without negative consequence.

Although a survival comparison between patients receiving and those not receiving Gliadel wafer implantation after 2004 was not the aim of this study, median survival for the XRT + Gliadel + TMZ cohort was 6 months greater than that for the XRT + TMZ cohort. This survival difference is most likely due to the large discrepancy in extent of resection between these cohorts. Interestingly, in patients undergoing gross-total resection, median survival for the XRT + Gliadel + TMZ cohort was 1.7 months greater than that of the XRT + TMZ cohort. Because this study was underpowered to compare these treatment cohorts, this difference did not achieve statistical significance. Hence, it cannot be determined whether the addition of Gliadel to concomitant TMZ therapy extends survival. However, our findings do suggest that, since adding concomitant TMZ to Gliadel therapy in 2004, we have experienced an increase in overall survival with a decrease in 6-month progression in our Gliadel-treated patients.

Temozolomide is an antineoplastic drug, the mechanism of action of which is a spontaneous, nonenzymatic conversion to the active alkylating metabolite (methyl-triazene-1-yl)-imidazole-4-carboxamide (MTIC). Efficacy has been demonstrated for TMZ in the treatment of both primary and recurrent malignant astrocytoma.^{9,12-15,21} Well-controlled studies of concomitant TMZ treatment, with radiotherapy, followed by delayed adjuvant TMZ treatment, have resulted in median survival times of 13–16 months in patients with newly diagnosed GBM.^{9,12,13} A randomized Phase II study comparing radiation plus TMZ with radiotherapy alone found median survival times of 13.4 and 7.7 months, respectively.¹ Stupp and colleagues¹⁴ also reported a 2.5-month increase in median survival with radiotherapy and concomitant TMZ compared with radiotherapy alone; this increase extended median survival to 14.6 months after primary resection. Many patients in the study of Stupp et al., however, underwent subtotal resection or biopsy, whereas all patients receiving Gliadel plus TMZ in our case series underwent more extensive resection. The definitive survival benefit of concomitant TMZ recently reported by Stupp and colleagues has resulted in the standardization of this protocol at many institutions. Therefore, determining the safety and efficacy of Gliadel wafer implantation in the TMZ era is critical.

Local delivery of BCNU via surgically implanted Gliadel wafers remains the only other adjuvant chemotherapy to consistently prolong survival in patients with primary malignant astrocytoma.^{2-4,10,16-20} A randomized double-blinded study demonstrated a 2.5-month median survival benefit associated with Gliadel wafer implantation in patients undergoing primary resection and adjuvant radiotherapy for malignant astrocytoma.¹⁶ A larger Phase III trial reported a 2.3-month increase in median survival in patients receiving Gliadel wafer compared with those receiving placebo after primary resection and adjuvant radiotherapy for malignant astrocytoma.¹⁹ This survival benefit, similar to that obtained with concomitant TMZ therapy, resulted in a median survival of 13.9 months.¹⁹

Combining immediately delivered local chemotherapy and more delayed systemic chemotherapy offers many theoretical advantages that may underlie the prolonged survival observed in our experience. First, systemic TMZ is most effective in regions of tumor that are most vascular, whereas local delivery of carmustine allows direct access of the chemotherapeutic agent independent of vasculature. In exposed resection cavities that are relatively avascular after surgical hemostasis, Gliadel allows treatment of residual tumor

cells that present a theoretical obstacle to systemic TMZ. Second, postoperative radiotherapy plus concomitant and adjuvant TMZ (Stupp protocol) does not deliver chemotherapeutic agent to the debulked tumor during the 3-week period between surgery and radiotherapy.¹⁴ Gliadel wafer delivery of local BCNU offers a theoretical bridge of this nontherapeutic period. Hence, the combination of Gliadel wafer implantation with concomitant and adjuvant TMZ treatment theoretically allows continuous adjuvant therapy for up to 9 months, beginning immediately following tumor resection.

The nearly 21-month median survival observed with Gliadel wafer plus concomitant TMZ therapy compares favorably to previously reported treatments and outcomes in surgical case series. The demographic and clinical characteristics of our patients who received this multimodal regimen are representative of most practices and are similar to those of many previously reported cohorts. Nearly 10% of our patients were > 70 years of age, and nearly a quarter underwent subtotal resection. This suggests that patient selection did not underlie the favorable survival observed in our practice, but factors other than the addition of TMZ to Gliadel might have contributed to this observed 8-month increase in survival. In particular, patients receiving postoperative concomitant TMZ alone have demonstrated equally favorable median survival (21.7 months) when MGMT-promoter methylation was present.⁷ Given that we did not account for this factor in our study, it remains possible, although unlikely, that a greater proportion of patients treated after 2004 were MGMT-promoter methylation positive, partially accounting for the improved survival noted with TMZ plus Gliadel. Furthermore, the adjuvant chemotherapeutic agents used at the time of tumor progression were different before and after 2004, potentially contributing to the survival difference observed. Recently, an interim analysis of a multicenter Phase II study reported an 18.6-month median survival with combined Gliadel and TMZ therapy.⁸ In this prospective study by La Rocca and colleagues,⁸ 35 patients (age range 18–71 years) with unilateral malignant glioma underwent resection, Gliadel wafer implantation, and concomitant TMZ therapy at 3 institutions. Median overall survival and progression-free survival were 18.6 and 6.9 months, respectively. Nevertheless, a prospective randomized trial is needed to determine whether combined Gliadel and concomitant TMZ therapy offers improved survival compared with either adjuvant therapy alone.

Conclusions

In our initial experience using Gliadel wafers plus concomitant TMZ in patients undergoing primary resection and adjuvant radiotherapy for GBM, we observed a median survival of nearly 21 months with an incidence of myelosuppression similar to that previously reported for TMZ treatment alone. Patients receiving Gliadel wafers should be considered for adjuvant TMZ therapy. Prospective trials are needed to confirm the potential survival benefit observed with this multimodal therapy.

Abbreviations used in this paper

BCNU	1,3-bis-(2-chloroethyl)-1-nitrosourea
GBM	glioblastoma multiforme

IQR	interquartile range
TMZ	temozolomide
XRT	radiation therapy.

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Fig. 1.

Kaplan-Meier plots of survival after primary resection of GBM and XRT in patients 70 years old. Patients receiving concomitant TMZ according to the Stupp protocol in addition to Gliadel wafer implantation (30 patients) demonstrated improved survival compared with patients receiving Gliadel wafers and XRT alone (78 patients); median survival, 21.3 versus 12.4 months, respectively ($p = 0.005$).

TABLE 1
Clinical, radiological, treatment, and perioperative outcome variables*

Variable	Gliadel + TMZ	Gliadel	p Value
no. of patients	30	78	—
yrs treated	2006–2004	2004–1997	
clinical presentation			
mean age in yrs	57 ± 8	56 ± 9	0.564
male	18 (60%)	47 (60%)	0.999
Caucasian	21 (70%)	61 (78%)	0.452
epilepsy	5 (17%)	13 (17%)	0.999
KPS score (IQR)	80 (80–90)	80 [80–90]	0.135
language deficit	4 (13%)	12 (15%)	0.999
radiological presentation			
frontal	8 (27%)	27 (35%)	0.497
temporal	11 (37%)	18 (23%)	0.133
parietal	6 (20%)	23 (29%)	0.356
occipital	5 (17%)	10 (13%)	0.548
mean tumor size in ml	44 ± 35	43 ± 30	0.486
treatment			
gross-total resection	23 (77%)	58 (74%)	0.999
subtotal resection	7 (23%)	20 (26%)	0.999
median no. Gliadel wafers (range)	8 (3–8)	8 (3–8)	0.542
TMZ stopped early	7 (23%)	—	—
subsequent resection	10 (33%)	27 (35%)	0.899
subsequent adjuvant chemo [†]	7 (23%)	15 (19%)	0.366
TMZ	0 (0%)	9 (12%)	
procarbazine	0 (0%)	6 (8%)	
BCNU	3 (10%)	0 (0%)	
CCNU	1 (3%)	0 (0%)	
BMS 247550	1 (3%)	0 (0%)	
sorafenib + erlotinib	1 (3%)	0 (0%)	
Gliadel at revision resection	1 (3%)	0 (0%)	
morbidity			
deep vein thrombosis	1 (3%)	4 (5%)	0.999
pulmonary embolus	3 (10%)	7 (9%)	0.999
surgical site infection	1 (3%)	1 (1%)	0.427
incisional CSF leak	0 (0%)	1 (1%)	0.354
perioperative seizures	2 (7%)	8 (10%)	0.278
marked cerebral edema [‡]	1 (3%)	2 (2.5%)	0.989
new postop motor deficit	2 (6%)	5 (6%)	0.999

Variable	Gliadel + TMZ	Gliadel	p Value
mean hospital stay in days	5 ± 2	5 ± 4	0.210
myelosuppression	7 (23%)	0 (0%)	0.001

Morbidity was assessed within the first 6 months after surgery. Abbreviations: CCNU = lomustine; chemo = chemotherapy; KPS = Karnofsky Performance Scale.

* Data are shown for patients 18–70 years of age who had GBM and underwent primary resection with Gliadel (BCNU) wafer implantation and adjuvant radiotherapy with or without concomitant TMZ therapy per the Stupp protocol. Values given represent numbers of patients, except as otherwise indicated. Means are given with standard deviations. Other than institution of concomitant TMZ therapy in 2004, the 2 patient populations remained similar.

† Systemic adjuvant chemotherapeutic agent administered at the time of tumor progression.

‡ Acute symptomatic cerebral edema at the resection cavity requiring intravenous dexamethasone therapy.