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Use of Gliadel (BCNU) Wafer in the Surgical Treatment of Malignant Glioma: A 10-Year Institutional Experience

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Background: Gliadel (polifeprosan 20 with carmustine [BCNU] implant) is commonly used for local delivery of BCNU to high-grade gliomas after resection and is associated with increased survival. Various complications of Gliadel wafers have been reported but not consistently reproduced. We set out to characterize Gliadel-associated morbidity in our 10-year experience with Gliadel wafers for treatment of malignant glioma.

Methods: We retrospectively reviewed records of 1013 patients undergoing craniotomy for resection of malignant brain astrocytoma (World Health Organization grade III/IV disease). Perioperative morbidity occurring within 3 months of surgery was assessed for patients and compared between patients receiving versus not receiving Gliadel wafer. Overall survival was assessed for all patients.

Results: A total of 1013 craniotomies were performed for malignant brain astrocytoma. A total of 288 (28%) received Gliadel wafer (250 glioblastoma multiforme (GBM), 38 anaplastic astrocytoma/anaplastic oligodendroglioma (AA/AO), 166 primary resection, 122 revision resection). Compared with the non-Gliadel cohort, patients receiving Gliadel were older (55 ± 14 vs. 50 ± 17, $P = .001$) and more frequently underwent gross total resection (75% vs 36%, $P < .01$) but otherwise similar. Patients in Gliadel versus non-Gliadel cohorts had similar incidences of perioperative surgical site infection (2.8% vs. 1.8%, $P = .33$), cerebrospinal fluid leak (2.8% vs. 1.8%, $P = .33$), meninigitis (.3% vs. .3%, $P = 1.00$), incisional wound healing difficulty (.7% vs. .4%, $P = .63$), symptomatic malignant edema (2.1% vs. 2.3%, $P = 1.00$), 3-month seizure incidence (14.6% vs. 15.7%, $P = .65$), deep-vein thrombosis (6.3% vs. 5.2%, $P = .53$), and pulmonary embolism (PE) (4.9% vs. 3.7%, $P = .41$). For patients receiving Gliadel for GBM, median survival was 13.5 months after primary resection (20% alive at 2 years) and 11.3 months after revision resection (13% alive at 2 years). For patients receiving Gliadel for AA/AO, median survival was 57 months after primary resection (66% alive at 2 years) and 23.6 months after revision resection (47% alive at 2 years).

Conclusion: In our experience, use of Gliadel wafer was not associated with an increase in perioperative morbidity after surgical treatment of malignant astrocytoma.

Key Words: Gliadel—Polymer delivery—Complications—Malignant astrocytoma.

Malignant gliomas are the most common form of primary brain tumor.[1,2] Glioblastoma multiforme, with an annual incidence of 10,000 cases in the United States and 74,000 cases worldwide, accounts for approximately 60% of primary brain tumors.[3] With a median survival of <2 years, the prognosis for

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patients with malignant gliomas remains relatively poor, despite the use of aggressive systemic chemotherapy and radiation.[4–14] Inevitably, malignant gliomas progress or recur, most often within 2 cm of the original site of resection.[15] The development of effective, systemic chemotherapy has been difficult due primarily to the presence of the blood-brain barrier.[16–18]

Carmustine, or BCNU (1,3-bis(2-chloroethyl)-1-nitrosourea), wafers (Gliadel, Guilford Pharmaceuticals, Baltimore, MD) represent an increasingly popular approach for delivery of chemotherapy, theoretically allowing concentration of chemotherapeutic doses locally while minimizing systemic adverse effects.[19–24] These biodegradable, BCNU-impregnated polymers are implanted in the tumor bed at the time of resection, providing a controlled-release form of local chemotherapy for approximately 3 weeks.[25]

Many studies on the use of Gliadel for the treatment of both primary and recurrent gliomas have shown improved survival with no marked increase in adverse effects.[26–38] However, concern about Gliadel-associated complications have arisen, both in published case reports and in a small case series.[39–42] These reported complications include malignant cerebral edema, resection cavity cyst formation, cerebrospinal fluid (CSF) leak, wound healing abnormalities, and increased perioperative seizure activity. However, in the largest Gliadel cohort to date ($n = 120$), there was no increased incidence of any of these complications.[31] In an attempt to accurately determine the incidence and characteristics of Gliadel-associated morbidity, we report our 10-year experience of 288 consecutive patients treated with Gliadel wafers for malignant astrocytoma.

METHODS

Patient Population

We retrospectively reviewed 1013 cases of craniotomy for resection of malignant brain astrocytoma (World Health Organization [WHO] grade 3 or 4) performed at a single institution from 1996 to 2006. Patients' presenting clinical, radiological, operative, and hospital course records were retrospectively reviewed. Outpatient clinic notes were available from both neurosurgical and neuro-oncology follow-up visits and reviewed in all cases. Pre- and postoperative magnetic resonance imaging (MRI) reports documented by an attending neuroradiologist were also reviewed. Demographics, presenting symptoms and signs, Karnofsky performance score, perioperative morbidity, intraoperative use of Gliadel, and date of death were recorded. Tumor grade was histologically confirmed in all cases. Patients whose death was not verified were recorded as lost to follow-up at the time of the last clinic visit.

MRI was performed <48 hours after surgery. Degree of resection was retrospectively classified from postoperative MRIs as gross total resection (no residual nodular enhancement on MRI) or as subtotal resection (residual nodular enhancement on MRI). Patients routinely underwent subsequent MRI at 3 and 6 months after surgery. If an increase in enhancement was noted on MRI, imaging was repeated monthly to help determine whether this radiographic change represented treatment effect versus recurrent tumor. The incidence of treatment-induced enhancement of the resection cavity was assessed on MRIs obtained within the first 6 months of treatment. An increase in enhancement that remained stable on subsequent imaging, that was not radiographically suggestive of progressive tumor, or that was pathologically confirmed as treatment effect was defined as a chemoradiation effect.

The incidence of perioperative morbidity was assessed during the first 3 months after surgery in all cases. Morbidities included perioperative surgical site infection, CSF leak, meninigitis, incisional wound healing difficulty, symptomatic malignant edema, 3-month seizure incidence, deep-vein thrombosis, and pulmonary embolism. Symptomatic malignant edema was defined as an acute increase in edema surrounding the resection cavity in the first 3 months that was not attributed to early tumor progression and that required hospital admission for corticosteroid therapy. Wound healing difficulty was defined as noninfectious dehiscence or wound breakdown occurring within the first 3 months after surgery. The incidence of 3-month seizure activity was defined by the presence of simple or generalized partial or complex seizure activity occurring within the first 3 months after surgery.

Treatment Algorithm

Gliadel wafers were not implanted in patients when tumors were multifocal, when they extended across the corpus callosum, when they required large opening of the ventricle, or when they were intraoperatively thought to be subtotally resected. This decision algorithm remained consistent by all operating surgeons during the reviewed time period.

TABLE 1. *Preoperative patient characteristics among patients receiving tumor resection for malignant glioma (World Health Organization grade III/IV)*[a]

Variable	All patients (n = 1013)	Gliadel (n = 288)	Non-Gliadel (n = 725)	P value
Age (y), mean ± SD	51 ± 17	55 ± 14	50 ± 17	.001
Male sex	598 (59%)	169 (59%)	429 (59%)	.886
Karnofsky performance status, median [IQR]	80 [80, 90]	80 [80, 90]	80 [80, 90]	.232
Preoperative seizures	157 (15%)	45 (16%)	112 (15%)	.944
Revision resection	405 (40%)	122 (42%)	283 (39%)	.330
Gross total resection	477 (47%)	215 (75%)	262 (36%)	<.001

[a] Gliadel patients were slightly older and received gross total resection more frequently.

TABLE 2. *Perioperative morbidity in patients receiving tumor resection for malignant glioma (World Health Organization grade III/IV)*[a]

Variable	All patients (n = 1013)	Gliadel (n = 288)	Non-Gliadel (n = 725)	P Value
Pulmonary embolism	41 (4.0%)	14 (4.9%)	27 (3.7%)	.408
Deep-vein thrombosis	56 (5.5%)	18 (6.3%)	38 (5.2%)	.526
Wound healing	5 (.5%)	2 (.7%)	3 (.4%)	.626
Primary resection (n = 613)	3 (.5%)	2/166 (1.2%)	1/447 (.2%)	.178
Revision resection (n = 400)	2 (.5%)	0/122 (0%)	2/278 (.7%)	1.00
Surgical site infection	21 (2.1%)	8 (2.8%)	13 (1.8%)	.333
Primary resection (n = 613)	5 (.8%)	2/166 (1.2%)	3/447 (.7%)	.617
Revision resection (n = 400)	16 (4.0%)	6/122 (4.9%)	10/278 (3.5%)	.582
Cerebrospinal fluid leak	21 (2.1%)	8 (2.8%)	13 (1.8%)	.333
Seizure	156 (15.4%)	42 (14.6%)	114 (15.7%)	.650
Symptomatic malignant edema[b]	23 (2.3%)	6 (2.1%)	17 (2.3%)	1.00
Meningitis	3 (.3%)	1 (.3%)	2 (.3%)	1.00

[a] There was no difference in the incidence of 3-month morbidity between patients receiving vs. those not receiving Gliadel wafers. Gliadel patients included 166 treated with primary tumor resection and 122 with revision resection. Non-Gliadel patients included 447 treated with primary tumor resection and 278 with revision resection.
[b] Cerebral edema requiring admission for corticosteroid treatment.

Statistical Analysis

Parametric data were expressed as mean ± standard deviation. Nonparametric data were expressed as median (interquartile range).

Count data (categorical variables) were compared between cohorts via χ^2 test in two-way tables. If any value was <10 in the two-way table, Fisher's exact test was used. Continuous variables were compared by the Student t-test. Estimated Kaplan-Meier plots were used to express survival as a function of time after surgical resection. Nonparametric data (Karnofsky performance score) was compared by Mann-Whitney U-test.

RESULTS

Patient Population

One thousand thirteen craniotomies from 1996 to 2006 were reviewed and included in our series. A total of 288 patients (28%) received Gliadel after tumor resection, while 725 (72%) did not.

In the Gliadel cohort, 169 patients (59%) were men and 119 (41%) were women. Surgery was for primary resection in 166 cases (58%) and revision resection in 122 cases (42%). Tissue pathology was consistent with WHO grade IV in 250 patients (87%) and WHO grade III in 38 patients (13%). Malignant astrocytoma was located in the temporal lobe in 66 patients (23%), in the parietal lobe in 64 (22%), in the occipital lobe in 21 (7%), and in the frontal lobe in 125 (43%). Seventy-three patients (25%) in this cohort received subtotal resection of tumor, and 215 (75%) received gross total resection.

Patients receiving Gliadel were older (55 ± 14 vs. 50 ± 17, P = .001) and more frequently underwent gross total resection (75% vs. 36%, $P < .01$) compared with the non-Gliadel cohort. Otherwise, baseline patient characteristics were similar (Table 1). Preoperative seizures were documented in 45 Gliadel patients (16%) and 112 non-Gliadel patients (15%) (P = .944).

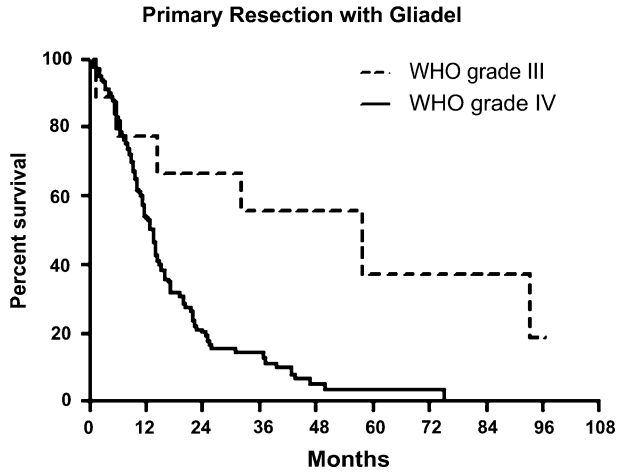

FIG. 1. Overall survival of patients receiving primary resection with implantation of Gliadel. Patients are broken down into those with grade III (anaplastic astrocytoma/anaplastic oligodendroglioma) and grade IV (glioblastoma multiforme) malignant gliomas. Median survival was 13.5 months with 20% survival at 2 years for grade IV gliomas, and 57 months with 66% survival at 2 years for grade III gliomas.

Perioperative Morbidity

Perioperative morbidities are summarized in Table 2. Among patients receiving Gliadel, 42 (15%) experienced postoperative seizures within the first 3 months of surgery. Surgical site infection was observed in eight patients (3%). Pulmonary embolism and deep-vein thrombosis was observed in 14 patients (5%) and 18 patients (6%), respectively. Symptomatic cerebral edema requiring admission for corticosteroid treatment occurred in six patients (2%). One patient demonstrated a symptomatic resection cavity cyst without evidence of tumor recurrence.

Comparison of morbidities between Gliadel versus non-Gliadel cohorts showed no statistically significant differences in the incidence of pulmonary embolism ($P = .41$), deep-vein thrombosis ($P = .53$), surgical site infection ($P = .33$), CSF leak ($P = .33$), wound healing problems ($P = .63$), seizure ($P = .65$), symptomatic malignant edema ($P = 1.00$), and meningitis ($P = 1.00$) (Table 2). Comparison of surgical site infection between Gliadel versus non-Gliadel cohorts among patients receiving primary (1.2% vs. .7%, $P = .62$) and revision resection (4.9% vs. 3.5%, $P = .58$) also showed no statistically significant differences. Similarly, comparison of wound healing problems between Gliadel and non-Gliadel cohorts among primary (1.2% vs. .2%, $P = .18$) and revision (0% vs. .7%, $P = 1.00$) resection showed no statistically significant differences (Table 2).

Among 223 patients of the Gliadel cohort with available 3-month follow-up by MRI, increased radiographic enhancement attributed to chemoradiation effect was seen in 76 patients (26%). In all 76 cases, this radiographic enhancement remained stable on subsequent 1- and 2-month MRIs.

Patient Survival

Patients receiving Gliadel during primary resection of grade IV glioma (GBM) experienced median survival of 13.5 months, with 20% survival at 2 years (Fig. 1). Patients receiving Gliadel during primary resection of grade III astrocytoma demonstrated median survival of 57 months, with 66% survival at 2 years (Fig. 1). Patients undergoing revision resection with implantation of Gliadel demonstrated a median survival of 11.3 for WHO grade IV and 23.6 months for WHO grade III (Fig. 2).

DISCUSSION

Among 288 patients undergoing Gliadel implantation during resection of malignant glioma, we characterized perioperative morbidity as well as survival. In our experience, Gliadel wafers were not associated with an increase in incidence of perioperative complications, including deep-vein thrombosis, CSF leak, wound healing complications, postoperative seizure, symptomatic malignant edema, tumor bed cysts, or meningitis. The morbidity rate between the Gliadel and non-Gliadel groups was similar despite patients being slightly older in the Gliadel group. The discrepancy in the extent of resection between Gliadel and non-Gliadel was a result of our implantation of Gliadel only if the surgeon thought he obtained a gross or near-total resection. Because of this treatment bias, a survival comparison is not the aim of this study.

The first documented benefit of Gliadel was in recurrent glioma. In the phase 3 study by Brem et al.,[27] Gliadel increased median survival after revision resection for recurrence glioma from 5.5 to 7.4 months. In our decade of experience, we have observed a much more favorable median survival of 11.3 months for Gliadel patients after revision resection.

Several studies subsequently demonstrated a survival benefit with Gliadel in primary malignant glioma. In a small, randomized, placebo-controlled study by Valtonen et al.[30] assessing the use of Gliadel versus placebo wafers in addition to primary resection and radiotherapy for malignant glioma, Gliadel increased median survival from 39.9 weeks (10.0 months) to 58.1 weeks (14.5 months). A study

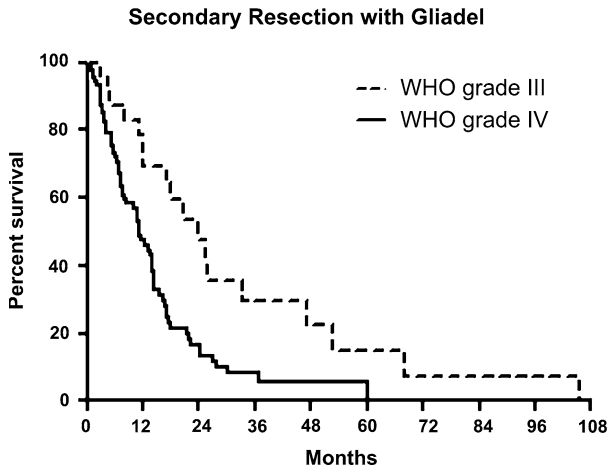

FIG. 2. Overall survival of patients receiving revision resection of recurrent malignant glioma with implantation of Gliadel. Patients are broken down into those with World Health Organization (WHO) grade III (anaplastic astrocytoma/anaplastic oligodendroglioma) and WHO grade IV (glioblastoma multiforme) malignant gliomas. Median survival was 11.3 months with 13% survival at 2 years in patients with WHO grade IV glioma and 23.6 months with 47% survival at 2 years in patients with WHO grade III gliomas. Survival was defined from time of revision resection to death.

by Westphal et al.,[31] similar in design to the Valtonen study but larger in scope, also demonstrated that Gliadel increased median survival from 11.6 months to 13.8 months. In our decade of experience, we have also observed a median survival of >13 months in primary malignant glioma patients when Gliadel is provided.

Use of temozolomomide (Temodar, Shering-Plough, Kenilworth, NJ), a systemic chemotherapeutic and standard radiotherapy in patients with glioblastoma multiforme has been reported by Stupp et al.[7] to increase median survival to 14.6 months after primary surgical resection. Although this treatment has become standard after tumor resection, this regimen does not deliver therapy to the resection region in the 3 weeks between surgery and radiotherapy. Use of Gliadel may provide treatment in this interval, bridging the gap between surgery and X-ray therapy/temozolomide. Recently, a phase 2 study of combined Gliadel with concomitant temozolomide was reported to be well tolerated with a median survival of 18.6 months.[43]

A major complication of concern among this patient population is postoperative seizure. In the Brem et al.[27] study, the incidence of postoperative seizure was observed to be 19% in both the Gliadel and non-Gliadel groups. In the Westphal et al.[31] study, there was similarly no statistically significant difference in the incidence of seizures (33% in the Gliadel group and 37.5% in the non-Gliadel group). However, Subach et al.[42] reported higher rates of postoperative seizure with Gliadel versus placebo (11.8% vs. 6.7%). This report did not account for the number of patients in each group with preexisting seizure disorders. Our results demonstrate a similar incidence of 3-month seizure activity with (15%) or without Gliadel (16%), and they support the findings of Brem et al. and Westphal et al., suggesting that Gliadel does not increase the risk of postoperative seizure activity.

Symptomatic malignant edema associated with Gliadel is another complication that has been reported.[41] Brem et al.[27] demonstrated a 4% incidence of symptomatic malignant edema with Gliadel treatment versus a 1% incidence with placebo in recurrent glioma. Subach et al.[42] demonstrated an increase in symptomatic malignant edema in the Gliadel group (5.9%) versus placebo (0%) in the treatment of recurrent glioma. Westphal et al.,[31] however, demonstrated a smaller incidence of symptomatic malignant edema in Gliadel (2.5%) patients compared with placebo (4.2%) in the treatment of primary malignant glioma. Our study similarly reports symptomatic malignant edema in 2.1% of Gliadel patients and 2.3% of non-Gliadel patients, suggesting that, in fact, Gliadel is not associated with symptomatic malignant edema requiring aggressive corticosteroid therapy.

Wound healing abnormalities have been reported in a series with Gliadel.[27] Brem et al.[27] showed that Gliadel versus placebo was associated with a far higher incidence of wound healing difficulty (14% vs. 5%). However, Westphal et al.[31] showed no difference between Gliadel (16%) and placebo (12%) groups. Our study similarly showed no difference in wound healing difficulty. Of note, our absolute proportion of wound healing difficulty was much lower in both Gliadel (.7%) and placebo (.4%) groups compared with our initial reported Gliadel experience,[27] perhaps reflecting our emphasis on the need for a meticulous watertight dural closure and slightly higher dexamethasone use perioperatively.

The effect that Gliadel may have on surgical site infection has been inconsistently reported in the literature. Among patients undergoing revision resection, Subach et al.[42] demonstrated surgical site infections in 23.5% of patients in their Gliadel group and 2.2% of patients in their comparison group. In contrast, our proportion of surgical site infections was only 2.8% in our Gliadel group and 1.8% in our non-Gliadel group. Brem et al.[27] reported infection

proportions of 3.6% among Gliadel patients and .89% in controls, and Westphal et al.[31] reported no statistically significant difference between groups. It is unclear why such a stark contrast exists between the proportions reported by Subach et al. versus those reported by Brem et al., Westphal et al., and us in our study. Multifactorial surgical factors and changing practicing patterns likely contributed to these differences.[33]

The incidence of meningitis has been reported to be very low with Gliadel and similar to patients in the control groups of the Westphal et al.[31] and Brem et al. trials.[27] The proportion of patients with meningitis was also low and similar between Gliadel and non-Gliadel cohorts in our retrospective study. However, CSF leak has been reported to be increased with Gliadel use. Westphal et al.[31] noted statistically significant differences between the proportion of CSF leak in Gliadel patients (11.8%) versus placebo (2.2%). Similar to previous trials,[27,31] the incidence of CSF leak observed in our experience was low and similar between Gliadel and non-Gliadel groups (2.8% and 1.8%).

The Subach et al.[42] study reported deep vein thrombosis in 5.9% of Gliadel patients and in 4.4% of non-Gliadel patients. In our study, the proportion of patients with deep vein thrombosis did not differ greatly between Gliadel (6.3%) and non-Gliadel (5.2%) groups. The proportion of patients with pulmonary embolism in our study similarly did not differ between Gliadel (4.9%) and non-Gliadel (3.7%) groups. Complications such as deep vein thrombosis and pulmonary embolism are generally not expected to be prominent clinical issues specific for Gliadel, given that the local use of this therapy theoretically minimizes systemic toxicity.

Although our study represents the largest series of Gliadel patients to date, it is subject to the weaknesses inherent to all retrospective studies. Strict criteria for postoperative symptomatology were used in an effort to minimize information bias. Also, because Gliadel wafers were not implanted in patients thought to have subtotal resection, it remains unknown how differences in the extent of resection may have affected perioperative morbidity. Despite inclusion of 1013 resections in our analysis, our series is not powered to prove the null hypothesis. Although there is no statistically significant difference between the groups, there is a small increased percentage of complications for Gliadel patients, and some may consider this clinically significant, particularly when summing all complications.

Nevertheless, our observational study demonstrates a more favorable survival with the use of Gliadel in recurrent glioma as compared with historical reports. Furthermore, and perhaps most importantly, this study demonstrates that the use of Gliadel is not associated with higher perioperative morbidity of any measure.

REFERENCES

1. Fisher PG, Buffler PA. Malignant gliomas in 2005: where to go from here? *JAMA* 2005; 293:615–7.
2. Jemal A, Siegel R, Ward E, et al. Cancer statistics, 2007. *CA Cancer J Clin* 2007; 57:43–66.
3. Reardon DA, Rich JN, Friedman HS, et al. Recent advances in the treatment of malignant astrocytoma. *J Clin Oncol* 2006; 24:1253–65.
4. Kornblith PL, Walker M. Chemotherapy for malignant gliomas. *J Neurosurg* 1988; 68:1–17.
5. Ohgaki H, Kleihues P. Genetic pathways to primary and secondary glioblastoma. *Am J Pathol* 2007; 170:1445–53.
6. Fine HA, Dear KB, Loeffler JS, et al. Meta-analysis of radiation therapy with and without adjuvant chemotherapy for malignant gliomas in adults. *Cancer* 1993; 71:2585–97.
7. Stupp R, Mason WP, Van den Bent MJ, et al. Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. *N Engl J Med* 2005; 352:987–96.
8. Stewart LA. Chemotherapy in adult high-grade glioma: a systematic review and meta-analysis of individual patient data from 12 randomised trials. *Lancet* 2002; 359:1011–8.
9. Mutter N, Stupp R. Temozolomide: a milestone in neuro-oncology and beyond? *Expert Rev Anticancer Ther* 2006; 6:1187–204.
10. Patchell RA, Regine WF, Loeffler JS, et al. Radiosurgery plus whole-brain radiation therapy for brain metastases. *JAMA* 2006; 296:2089–90.
11. Ewend MG, Brem S, Gilbert M, et al. Treatment of single brain metastasis with resection, intracavity carmustine polymer wafers, and radiation therapy is safe and provides excellent local control. *Clin Cancer Res* 2007; 13:3637–41.
12. Gururangan S, Cokgor L, Rich JN, et al. Phase I study of Gliadel wafers plus temozolomide in adults with recurrent supratentorial high-grade gliomas. *Neuro Oncol* 2001; 3:246–50.
13. Heery CR, Desjardins A, Quinn JA. Acute toxicity analysis of patients receiving surgery, Gliadel wafer implantation, and postoperative daily temozolomide with radiation therapy for primary high-grade glioma. *Proc Am Soc Clin Oncol* 2006; 24:11504.
14. La Rocca RV, Hodes J, Villanueva WG. A phase II study of radiation with concomitant and then sequential temozolomide (TMZ) in patients with newly diagnosed supratentorial high-grade malignant glioma who have undergone surgery with carmustine (BCNU) wafer insertion. *Neuro Oncol* 2006; 8:391–500.
15. Gaspar LE, Fisher BJ, Macdonald DR, et al. Supratentorial malignant glioma: patterns of recurrence and implications for external beam local treatment. *Int J Radiat Oncol Biol Phys* 1992; 24:55–7.
16. Guerin C, Laterra J, Hruban RH, et al. The glucose transporter and blood-brain barrier of human brain tumors. *Ann Neurol* 1990; 28:758–65.
17. Walker MD, Alexander E Jr, Hunt WE, et al. Evaluation of BCNU and/or radiotherapy in the treatment of anaplastic gliomas. A cooperative clinical trial. *J Neurosurg* 1978; 49:333–43.
18. Sandberg-Wollheim M, Malmstrom P, Stromblad LG, et al. A randomized study of chemotherapy with procarbazine, vin-

cristine, and lomustine with and without radiation therapy for astrocytoma grades 3 and/or 4. *Cancer* 1991; 68:22–9.
19. Fung LK, Ewend MG, Sills A, et al. Pharmacokinetics of interstitial delivery of carmustine, 4-hydroperoxycyclophosphamide, and paclitaxel from a biodegradable polymer implant in the monkey brain. *Cancer Res* 1998; 58:672–84.
20. Tamargo RJ, Epstein JI, Reinhard CS, et al. Brain biocompatibility of a biodegradable, controlled-release polymer in rats. *J Biomed Mater Res* 1989; 23:253–66.
21. Brem H, Tamargo RJ, Olivi A, et al. Biodegradable polymers for controlled delivery of chemotherapy with and without radiation therapy in the monkey brain. *J Neurosurg* 1994; 80:283–90.
22. Ewend MG, Williams JA, Tabassi K, et al. Local delivery of chemotherapy and concurrent external beam radiotherapy prolongs survival in metastatic brain tumor models. *Cancer Res* 1996; 56:5217–23.
23. Ewend MG, Sampath P, Williams JA, et al. Local delivery of chemotherapy prolongs survival in experimental brain metastases from breast carcinoma. *Neurosurgery* 1998; 43:1185–93.
24. Withrow SJ, Liptak JM, Straw RC, et al. Biodegradable cisplatin polymer in limb-sparing surgery for canine osteosarcoma. *Ann Surg Oncol* 2004; 11:705–13.
25. Brem H, Langer R. Polymer-based drug delivery to the brain. *Sci Med* 1996; 3:2–11.
26. Brem H, Mahaley MS Jr, Vick NA, et al. Interstitial chemotherapy with drug polymer implants for the treatment of recurrent gliomas. *J Neurosurg* 1991; 74:441–6.
27. Brem H, Piantadosi S, Burger PC, et al. Placebo-controlled trial of safety and efficacy of intraoperative controlled delivery by biodegradable polymers of chemotherapy for recurrent gliomas. The Polymer-brain Tumor Treatment Group. *Lancet* 1995; 345:1008–12.
28. Sipos EP, Tyler B, Piantadosi S, et al. Optimizing interstitial delivery of BCNU from controlled release polymers for the treatment of brain tumors. *Cancer Chemother Pharmacol* 1997; 39:383–9.
29. Olivi A, Grossman SA, Tatter S, et al. Dose escalation of carmustine in surgically implanted polymers in patients with recurrent malignant glioma: a New Approaches to Brain Tumor Therapy CNS Consortium trial. *J Clin Oncol* 2003; 21:1845–9.
30. Valtonen S, Timonen U, Toivanen P, et al. Interstitial chemotherapy with carmustine-loaded polymers for high-grade gliomas: a randomized double-blind study. *Neurosurgery* 1997; 41:44–8.
31. Westphal M, Hilt DC, Bortey E, et al. A phase 3 trial of local chemotherapy with biodegradable carmustine (BCNU) wafers (Gliadel wafers) in patients with primary malignant glioma. *Neuro Oncol* 2003; 5:79–88.
32. Whittle IR, Lyles S, Walker M. Gliadel therapy given for first resection of malignant glioma: a single centre study of the potential use of Gliadel. *Br J Neurosurg* 2003; 17:352–4.
33. Lawson HC, Sampath P, Bohan E, et al. Interstitial chemotherapy for malignant gliomas: the Johns Hopkins experience. *J Neurooncol* 2007; 83:61–70.
34. Limentani SA, Asher A, Heafner M, et al. A phase I trial of surgery, Gliadel wafer implantation, and immediate postoperative carboplatin in combination with radiation therapy for primary anaplastic astrocytoma or glioblastoma multiforme. *J Neurooncol* 2005; 72:241–4.
35. Kleinberg LR, Weingart J, Burger P, et al. Clinical course and pathologic findings after Gliadel and radiotherapy for newly diagnosed malignant glioma: implications for patient management. *Cancer Invest* 2004; 22:1–9.
36. Brem H, Ewend MG, Piantadosi S, et al. The safety of interstitial chemotherapy with BCNU-loaded polymer followed by radiation therapy in the treatment of newly diagnosed malignant gliomas: phase I trial. *J Neurooncol* 1995; 26:111–23.
37. Westphal M, Ram Z, Riddle V, et al. Gliadel wafer in initial surgery for malignant glioma: long-term follow-up of a multicenter controlled trial. *Acta Neurochir (Wien)* 2006; 148: 269–75.
38. Bohan E, Brem H. Treatment of brain tumors by local delivery of chemotherapy via biodegradable polymers. *Hosp Pharm Rep* 1997; 12–6.
39. Engelhard HH. Tumor bed cyst formation after BCNU wafer implantation: report of two cases. *Surg Neurol* 2000; 53:220–4.
40. McGirt MJ, Villavicencio AT, Bulsara KR, et al. Management of tumor bed cysts after chemotherapeutic wafer implantation. Report of four cases. *J Neurosurg* 2002; 96:941–5.
41. Weber EL, Goebel EA. Cerebral edema associated with Gliadel wafers: two case studies. *Neuro Oncol* 2005; 7:84–9.
42. Subach BR, Witham TF, Kondziolka D, et al. Morbidity and survival after 1,3-bis(2-chloroethyl)-1-nitrosourea wafer implantation for recurrent glioblastoma: a retrospective case-matched cohort series. *Neurosurgery* 1999; 45:17–22.
43. LaRocca R, Hodes J, Villanueva W, et al. A phase II study of radiation with concomitant and then sequential temozolomide (TMZ) in patients with newly diagnosed supratentorial high-grade malignant glioma who have undergone surgery with carmustine (BCNU) wafer insertion. Presented at the 11th Scientific Meeting of the Society for Neuro-Oncology, 2006.