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ORIGINAL ARTICLE

Clinical Course and Pathologic Findings After Gliadel® and Radiotherapy for Newly Diagnosed Malignant Glioma: Implications for Patient Management

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ABSTRACT

Randomized trials have demonstrated Gliadel® improves survival for appropriately selected patients with newly diagnosed malignant glioma. As only limited information is available to guide the management of patients who have Gliadel® controlled-release BCNU wafers implanted in the cranial resection cavity prior to radiotherapy (RT), this retrospective review was conducted to describe clinical course, toxicity, and pathologic findings after this therapy for newly diagnosed malignant glioma. Forty-six consecutive patients receiving Gliadel® (3.8% BCNU impregnated wafers) followed by radiotherapy for newly diagnosed malignant glioma at Johns Hopkins Hospital from 1990 to August 1999 were identified, although one was lost to follow up and is excluded. Patients were evaluated for postoperative infection, pathology at reoperation, and survival. Twenty-eight patients received radiotherapy at Johns Hopkins and these patients are also evaluable for toxicity experienced during and one month after completion of RT. The median age of all patients is 57 years. Eighty-nine percent had glioblastoma, and median follow-up of surviving glioblastoma patients is 16.8 (12–20) months. Postoperative infection or need for reoperation within 30 days was uncommon after Gliadel® placement. Full-dose radiotherapy was tolerable after Gliadel® implantation. Five patients (19%) developed neurologic symptoms during

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#Dr. Brem is a consultant to Guilford Pharmaceuticals, Inc. The Johns Hopkins University and Dr. Brem own Guilford Stock, the sale of which is subject to certain restrictions under University Policy. The terms of this arrangement are being managed by the University in accordance with its conflict of interest policy.

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radiotherapy responding to increased steroids and/or anticonvulsants, whereas an additional 8 of 27 (30%) developed neurologic symptoms during dexamethasone taper that responded to increases in dexamethasone dose. At one month after RT, 58% of patients were still on dexamethasone despite attempted taper. Fifteen of 45 patients, 33% underwent reoperation or biopsy for a new local contrast-enhancing lesion. In five of 15 (33%) the reoperation revealed necrosis or treatment effect without active tumor. Two of five patients with treatment/effect necrosis had a third surgery 2.9 and 3.2 months after the initial reoperation, and treatment effect/necrosis without tumor was demonstrated in both cases. The Kaplan–Meier median survival for all the glioblastoma patients is 12.8 (95% CI 9.6, 15.9) months. For glioblastoma patients under 55 years old, median survival is 15.9 (95% CI 13.5, too few events) months whereas for older patients it is 9.6 (7.7, 14.4) months. We conclude that Gliadel® followed by full-dose standard radiotherapy is acutely well tolerated, although, close supervision should be emphasized during dexamethasone taper. Median survival in excess of one year suggests that there are not complications that result in overall premature death. The finding of necrosis/treatment effect was noted in five of 45 (11%) of all patients and five of 15 (33%) of those undergoing reoperation. Therefore, the possibility of necrosis/treatment effect should be considered for each patient with radiographic findings suspicious for local recurrence.

Key Words: Gliadel; BCNU; Radiotherapy; Glioblastoma.

INTRODUCTION

Gliadel® wafers are biodegradable polymers developed for the therapy of malignant glioma, which are implanted into the cranial resection cavity resulting in controlled release of BCNU directly into the tumor bed.[1,2] This therapeutic approach was developed as a means to provide high local concentrations of chemotherapy without systemic toxicities. A 222 patient randomized trial of Gliadel® wafers implanted directly into the brain in patients with recurrent GBM demonstrated median survival improved from 23 weeks to 31 weeks and six month survival improved from 44% to 64%.[3] These patients received radiotherapy (RT) at the time of initial diagnosis, but not after Gliadel® placement. Gliadel® is also used with increasing frequency in newly diagnosed patients prior to radiotherapy, when both the potential to impact on disease course and the potential for toxicity (from interactions with radiotherapy) may also be greater. Therefore, this analysis was undertaken to investigate toxicity and clinical course for a large group of patients treated with Gliadel® followed by radiotherapy.

There is evidence that Gliadel®, prior to radiotherapy, may be safe and also efficacious. A 22-patient phase I trial conducted in the United States demonstrated that this approach to the therapy of glioblastoma is generally safe but did not specifically address the issue of radiotherapy related toxicities.[4] A randomized trial conducted in Europe with a total sample size of 32 patients, did demonstrate a significant survival benefit but toxicities resulting from radiotherapy were not reported.[5] The initial report of survival outcome from the 240 patient European randomized trial of gliadel prior to radiotherapy for malignant glioma demonstrates that this treatment is efficacious but toxicity data is not yet available.[6] Therefore, there continues to be a need for more information about safety and outcome with this therapy.

We have analyzed the toxicity and results of this treatment approach in 46 newly diagnosed patients treated with Gliadel® and radiotherapy. This is the largest series of such patients reported to date. The endpoints of this analysis include severe acute toxicity during radiotherapy, pathologic findings at reoperation, and survival. We examined histopathological findings at reoperation, as it was our clinical impression that a significant proportion of patients with radiographic findings suspicious for local tumor recurrence actually had necrosis/treatment effect without viable tumor. This analysis indicates that full dose radiotherapy is tolerated after Gliadel®, that there are not toxicities adversely affecting overall survival, and that there is a significant incidence of necrosis/treatment effect as a pathologic finding at reoperation for presumed local recurrence.

MATERIALS AND METHODS

Patients

Forty-six patients received Gliadel® (3.85% BCNU) followed by radiotherapy for newly diagnosed brain malignancy between 1990 and August 1999. Ten

of these patients were enrolled at Johns Hopkins Medical Institution in a multi-institutional phase I trial testing Gliadel® prior to RT that was conducted in 1990 and 1991. These patients provided informed consent for experimental protocol therapy. The remainder of the patients were treated after Gliadel® was approved by the U.S. Food and Drug Administration for use in recurrent malignant glioma in 1996. For these patients, informed consent was obtained prior to surgery including discussion of the possible diagnosis of malignant brain tumors and existence of other treatment options. All patients were evaluable for survival, perioperative morbidity, and histopathology at reoperation. Twenty-eight of these patients received their radiotherapy treatment at Johns Hopkins Hospital, and only these patients were evaluable for analysis of acute toxicity during radiotherapy. Outcome was assessed as of June 15, 2000.

Gliadel®

Gliadel® polymer with 3.85% loading of BCNU was used. Gliadel® is a copolymer of poly-carboxyphenoxypropane and sebacic acid prepared in a 20/80 ratio. The discs, which are 1.4 cm in diameter and 1.0 mm thick, are loaded with 50 μg BCNU per mm^3 of polymer. Up to eight discs were placed as needed to cover the surface of the resection cavity.

Selection of Patients for Initial Therapy with Gliadel®

Patients who had surgically resectable lesions, which were thought likely to be primary malignant glioma, were considered to be candidates for treatment with Gliadel® at the time of initial operation. Patients were required to have a unilateral enhancing mass lesion with no evidence of systemic disease. Informed consent was obtained from the patient and their families for possible intraoperative use of chemotherapy waters. Patients and their families were informed that by placing the chemotherapy wafers they would be excluded from participating in phase I and II studies evaluating newly diagnosed tumors at our institution. Prior to placement of the wafers, a frozen section pathologic diagnosis of malignant glioma was required in all patients.

Radiotherapy

Radiotherapy dose details were available for 40 patients. Six patients received 51 Gy in 17 fractions, the standard regimen at Johns Hopkins during the period including 1990–1991. One patient received 66.6 Gy in 37 fractions and 1 patient 55.8 Gy in 31 fractions. The remaining 33 patients received standard radiotherapy, 59.5–60 Gy at 1.8–2.0 Gy per day.

Twenty-two of 28 patients irradiated at Johns Hopkins received 59.4–60 Gy. The edema containing regions, as determined by T2 weighted images on MRI scan, were generally treated with a 2–3 cm margin until 45–46 Gy and then the contrast enhancing lesion or tumor bed was treated with a 2–3 cm margin to the final dose of 60 Gy. For one patient the planned total dose was 54.8 Gy. Five patients irradiated at Johns Hopkins during 1990 and 1991 received an alternative regimen of 30 Gy at 3.0 Gy per day to the initial volume. After a two week break, an additional 21 Gy at 3.0 Gy per day was administered to the reduced volume.

Surgical Outcome

Perioperative death, infection, length of hospital stay, hospital readmission within 30 days, and need for reoperation within 30 days, were assessed for all patients to evaluate serious surgical complications potentially related to Gliadel® placement.

Toxicity Assessment

Toxicity and dexamethasone dosing were assessed for 28 patients receiving radiotherapy at Johns Hopkins only, as adequate records were not uniformly available for patients irradiated elsewhere. Toxicity consisted of any new or worsening neurologic symptom developing during or within 30 days after treatment that required at least an alteration in medication. Precise grading of severity of the toxicities was not possible in this retrospective analysis. The expected toxicities of skin erythema, mild fatigue, and hair loss were not uniformly recorded in the record and were not assessed during this analysis.

Survival

Survival was measured from the date of histologic diagnosis.

Pathology

The histopathologic findings at reoperation were assessed by review of the histological sections. In one case, the reoperation occurred at another hospital, and the specimen demonstrating tumor recurrence was not independently reviewed at Johns Hopkins. Two cases of reoperation for perioperative complications [after initial resection (1) and after a second resection (1)] were excluded from this analysis as was an instance of surgery for a lesion distant from the site of Gliadel® implantation.

Histopathologically, the lesions were divided into three categories: 1) Total necrosis. These lesions were void of viable tumor tissue. Necrotic foci were coagulative in nature, and often had sharp borders. 2) Treatment effect indicating treated ''quiescent'' neoplasms. These were paucicellular lesions in which scattered pleomorphic nuclei were present, but which lacked the dense cellularity and mitotic activity of ''active'' tumor as described below. Vascular hyalinization was usually prominent. Multiple foci of discrete coagulative necrosis consistent with prior therapy were common. Dystrophic calcification was seen in some cases. 3) Active tumor. This category was defined by the presence of densely cellular neoplasms similar to those expected in the pretreatment lesions. Necrosis with pseudopalisading was present in some cases. Changes similar to those described in category 2, i.e., treatment effect, were seen along with active tumor in some cases within category 3. Any foci of active tumor were sufficient for inclusion in category 3, even if the bulk of the specimen demonstrated treatment effect.

RESULTS

Forty-six patients were identified as having received Gliadel® followed by radiotherapy for newly diagnosed malignant glioma from 1990–1999. One patient was lost to follow-up shortly after surgery and is excluded. Patient characteristics are described in Table 1.

Surgical Outcome

Only one of 45 (2%) patients underwent reoperation within 30 days of the initial surgery. In this patient, reoperation occurred on postoperative day 2 for lethargy and increased mass effect. Hematoma and wafers were removed, and recovery was uneventful. One (2%) patient developed a superficial wound infection, which was incised and drained. There were no instances of bone, dural, subdural, or brain parenchymal infection. Two additional patients were readmitted to an acute care unit within 30 days: one for deep venous thrombosis and one for right lower lobe pneumonia. The mean length of stay following craniotomy was 5.61 (SD 3.69) days (range 4–21) for the whole group, and was 4.63 (SD 2.28) days (range 4–14) when the patients operated in 1990 and 1991 are excluded.

Table 1. Patient characteristics.

Patient characteristics	
Age	
Median	57
Range	34–77
Preoperative Karnofsky performance status	
<70	9/45 (20%)
≥ 70	36/45 (80%)
Histology	
Glioblastoma	39/45 (87%)
Anaplastic astrocytoma	4/45 (9%)
Anaplastic oligodendroglioma	1/45 (2%)
Malignant xanthroastrocytoma	1/45 (2%)

Toxicity During and After Radiotherapy

During and within 30 days following radiotherapy, four of 28 patients required acute hospital admission. Two patients developed pneumonia (one fatal), one person was admitted with lethargy during dexamethasone taper after RT, and one patient was admitted for management of severe phenytoin reaction. Five of 28 (18%) patients developed increased neurologic symptoms during RT that responded to dexamethasone and/or anticonvulsants. An additional eight (30%) developed neurologic symptoms during dexamethasone taper that responded to increases in dexamethasone dose.

Dexamethasone Dosing

Twenty-three of 28 (82%) patients irradiated at Johns Hopkins (who were therefore evaluable for radiation-related toxicity) were on dexamethasone at the start of radiotherapy, and two additional patients began dexamethasone during the radiotherapy. Overall, eight of 28 (29%) patients required an increase in steroids during therapy. In five cases, the symptoms were likely the result of radiotherapy-induced edema, and in two patients dexamethasone dose was increased for neurologic symptoms developing in the setting of the physiologic stress of pneumonia. In the additional patient, the steroid dose was increased to treat a severe phenytoin rash. In 13 of the 24 (54%) patients where a dexamethasone taper was attempted during radiotherapy, dexamethasone dose needed to be increased again because of the development of neurologic symptoms. Finally, at 30 days after radiotherapy, 16 of 27 (59%) surviving patients were still on dexamethasone.

Survival

The Kaplan–Meier median survival for the glioblastoma patients treated with Gliadel® and radiation

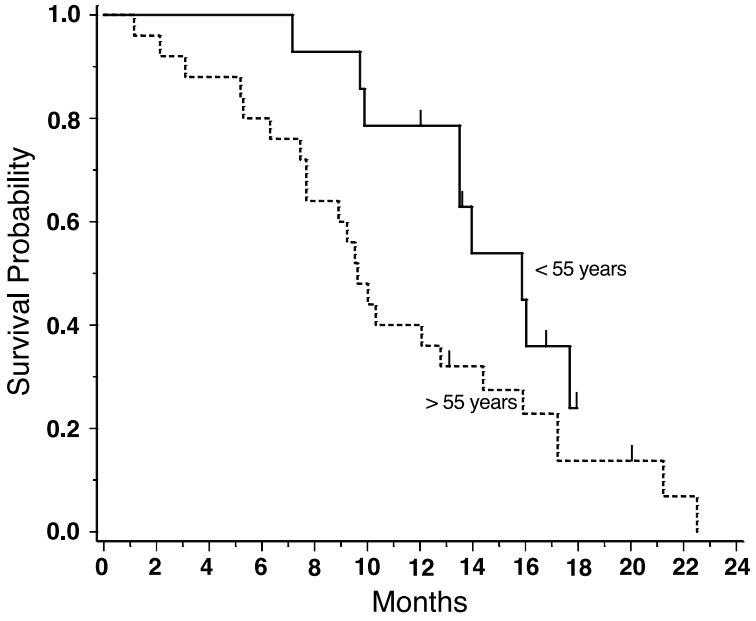

Figure 1. Kaplan–Meir survival with Gliadel® followed by radiotherapy for newly diagnosed glioblastoma, by age greater than or less than 55 years old.

therapy was 12.8 months (95% CI 9.6, 15.9). For patients less than 55 years old the median survival was 15.9 months (95% CI 13.5, too few events) whereas for older patients it was 9.6 months (95% CI 7.7, 14.4). There was no difference based upon preoperative performance status less then 70 or greater than/equal to 70. For the patients with other neoplasms, the survival times were: anaplastic astrocytoma (4 patients): 11.1+, 25.4+, 41.3+, and 102.9 months; malignant oligodendroglioma (1 patient), 26.5+ months, and for malignant xanthroastrocytoma (1 patient), 32.4+ months (Figure 1).

Reoperation Histopathology

Fifteen patients underwent reoperation or biopsy for localized contrast enhancing lesions. Representative pathology specimens are shown in Figure 2. The median time to reoperation was 7.4 months (2.8–79.5) Additionally, four patients underwent a second reoperation for suspected recurrence. Eight of 19 specimens, including those from four repeat reoperations, were necrosis/treatment effect alone. An additional two specimens had only a foci of active tumor. There was no evidence of significant inflammatory response to Gliadel®.

In five of 15 (33%) patients the initial reoperation revealed total necrosis (2) or treatment effect with quiescent tumor only (3). These five patients all had glioblastoma multiforme (GBM). The median time to reoperation for these five patients was 6.8 months (2.8–8.8). In the remaining ten of 15 patients, there was recurrence with a median time to reoperation of 8.5 months (3.6–79.5). However, in two of these ten patients there was only a foci of active tumor at first reoperation.

Four patients had a third resection. Two patients had a third surgery after initial reoperations with histologic confirmation of treatment effect or necrosis. In both cases, which occurred 2.9 and 3.2 months after the initial reoperation, histopathology was again treatment effect or necrosis. Intervening treatments were not given. A patient with an initial reoperation histopathology of treatment effect with a foci of viable tumor had a third operation 8.7 months later revealing treatment effect only. The fourth patient had an initial reoperation confirming recurrence and nine months later had an additional reoperation also revealing frank recurrence.

For five GBM patients with a pathologic finding of primarily necrosis/treatment effect, the median survival from the time of initial diagnosis was 15.6 months (7.0–20.8) and for those with frank recurrence it was 12.1 (8.7–17.4) months. Statistical comparison was not performed as the number of patients was too small for reliable comparison, and there was no apparent difference for those with treatment effect (quiescent tumor) and those with total necrosis.

Treatment effect/necrosis was found in one of three reoperations in patients who received 51 Gy at

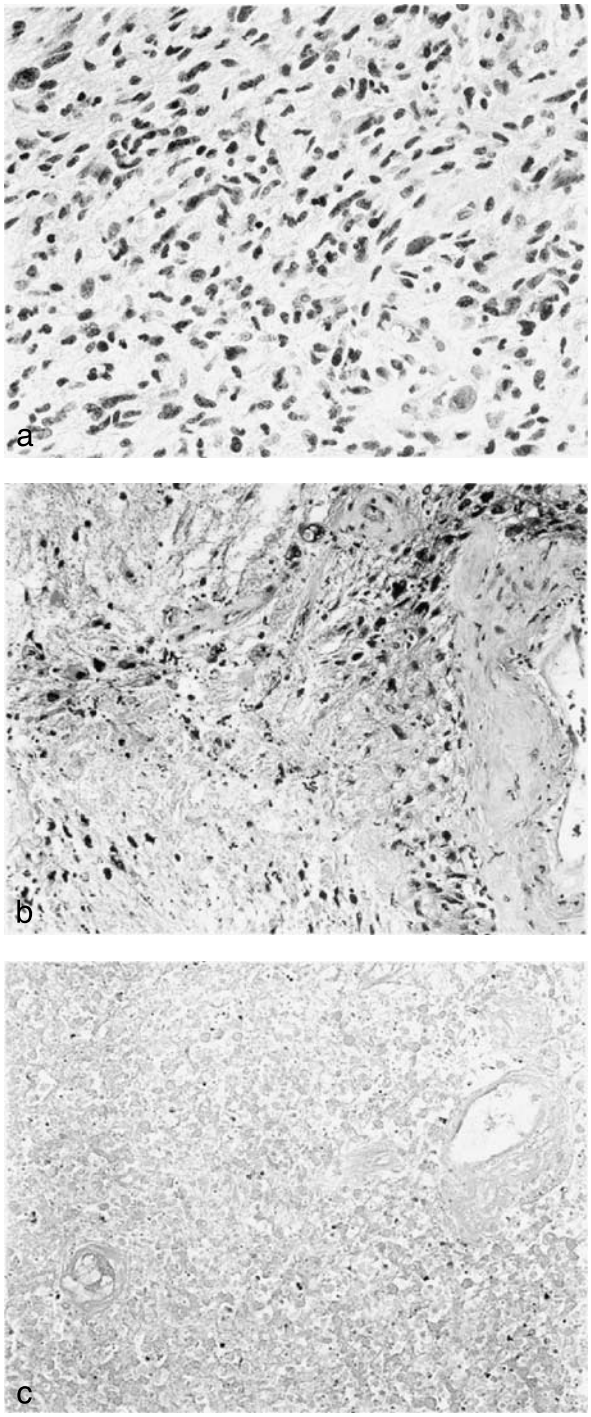

Figure 2. (a) Tumor recurrence was defined as the presence of a cellular, small cell neoplasm. (b) Glioblastomas that were considered persistent, rather than recurrent, had widely separated, large dark nuclei, hyalinized blood vessels, and multiple foci of necrosis without peripheral pseudopalisading. (c) There was no visible tumor in some specimens, only necrosis.

3 Gy per day and in three of 11 reoperations in patients known to have received standard radiotherapy.

DISCUSSION

As randomized trials have demonstrated that Gliadel® wafers improve survival outcome for properly selected patients with newly diagnosed malignant glioma, this therapy is being used with increasing frequency prior to the administration of radiotherapy. Although there is data that Gliadel® is safe and efficacious in this situation, more information is clearly needed. The purpose of this analysis is to provide information about toxicity and pathologic findings in a group of patients at a single institution after therapy with Gliadel® followed by radiotherapy. Previous published reports examining these issues included 22 patients treated in a prospective phase I trial and 16 patients treated in a randomized trial. Our results confirm that Gliadel® followed by full-dose radiotherapy is well tolerated, but that there may be a substantial incidence of necrosis/treatment effect in specimens removed at reoperation for suspected recurrence. These findings may have implications for the management of patients with Gliadel® placed prior to radiotherapy.

The use of Gliadel® in the therapy of newly diagnosed glioma is important to analyze for several reasons. First, Gliadel® has been shown to improve both six-month and median survival when used in the therapy of recurrent malignant glioma.[3] Second, BCNU is advocated, although not universally accepted, as a standard adjuvant therapy in newly diagnosed glioblastoma. Gliadel® wafers provide a means to administer BCNU locally without the time commitment and risk of the systemic side effects associated with intravenous BCNU. Finally, it is possible that Gliadel® might improve upon the results of systemic BCNU as the therapy is deposited directly into the tumor bed at high local concentration immediately after surgery when tumor burden is at its lowest.

There is significant available data about survival outcome with Gliadel® in newly diagnosed patients. An initial 22 patient phase I trial[1] testing Gliadel® therapy in newly diagnosed patients found that median survival was 42 weeks with four of 22 surviving >18 months in a population with Karnofsky performance status (KPS) of at least 60 and median age 60. Ten of the patients from that trial received Gliadel® at Johns Hopkins and are included in our current analysis. Toxicities during radiotherapy were not specifically described. Subsequently, a 32 patient randomized trial

conducted in Europe[5] has provided information demonstrating that Gliadel® may be safe and efficacious as part of the initial therapy of GBM. Patients treated with Gliadel® had a median survival of 13.5 months whereas those who received placebo had survival of 9.3 months ($p=.012$). When the analysis was confined to those with GBM only, the survivals were 12.3 months versus 9.3 months ($p=.008$). This study had been planned to accrue more patients, but was ended when the supply of Gliadel® was interrupted. It was reported that five Gliadel® patients and four placebo patients had serious postoperative complications, but no information was provided about toxicities during radiotherapy. Most importantly, initial survival but not toxicity results have been presented from a 240 patient European randomized trial that demonstrates median survival significantly improved to 14 months from 11.6 months.[6]

Our results confirm that it is safe to place Gliadel® in patients with newly diagnosed malignant glioma as the incidence of significant surgical complications is low. Only one of 45 (2%) patients experienced a superficial wound infection, whereas none of 45 had deep infection. A randomized trial of 222 patients by the Polymer-Brain Tumor Treatment Group,[3] who were treated with Gliadel® for recurrent gliomas (after prior radiotherapy) did not demonstrate significant increases in postoperative complications as measured by seizure incidence [41/110 (37%) vs. 32/112 (29%), infection rate (4/110 (4%) vs. 1/112 (1%)], and requirements for steroids. More recently a single institutional series of patients with recurrent disease using gliadel after prior radiotherapy raised the question of increased infectious complications with four of 17 (24%) Gliadel® treated patients having wound infection versus one of 45 (2%) infections in patients undergoing surgical procedures without Gliadel® at the same institution during a similar time period.[7] Our results confirm a low infection rate with Gliadel® use as one of 45(2%) had superficial wound infection and none of 45 had a deep wound infection. One patient in our series required reoperation within 30 days of initial surgery to remove a symptomatic clot. In addition, the length of hospital stay and incidence of reoperation in the present series are within expected ranges for surgery alone.

The particular toxicities and Decadron requirements experienced by patients during radiotherapy after Gliadel® placement were also analyzed. This issue is of interest because experiments in primate models have demonstrated that Gliadel® wafers can cause an inflammatory response in the brain.[8] Primate studies have demonstrated that some edema could be seen radiographically by day 14 but that it resolved by day 72. Autopsy revealed that a subacute cellular inflammatory response was seen on postoperative day 16 and changed to a chronic inflammatory response by day 72.

The toxicity of radiotherapy after Gliadel® placement in newly diagnosed malignant glioma patients was acceptable, suggesting that there is no need to reduce the dose of radiotherapy utilized in this clinical setting. Although good baseline data is not available for neurologic events of minimal to moderate severity occurring during radiotherapy alone, our sense is that there was not a substantial increase in toxicity when radiotherapy was given after Gliadel® placement. Four of 28 patients had severe complications requiring hospital admission during radiotherapy, including one fatal pneumonia, one treated pneumonia, severe phenytoin reaction, and lethargy during dexamethasone taper. Only the later serious event was considered to be potentially related to Gliadel®.

The dexamethasone requirements during radiotherapy were assessed for patients treated at Johns Hopkins. Given the inflammation or edema that potentially can be induced by either Gliadel® wafers or radiotherapy alone, this issue is of particular interest. Fifteen out of 27 (56%) of surviving patients were still on dexamethasone one month after completing RT, and 13 of 24 (54%) patients developed neurologic symptoms requiring an increased dose during attempted dexamethasone taper. Although baseline information is not available for patients receiving radiotherapy after resection of glioblastoma, these data lead us to recommend close supervision of patients treated with Gliadel® and radiotherapy as they undergo dexamethasone taper.

Histopathological findings for patients reoperated for a new contrast-enhancing lesion indicate that treatment effects can radiographically mimic the findings of recurrent tumor in a proportion of patients. Fifteen of 45 (33%) patients had reoperation for a new local contrast enhancing lesion, and in five out of 15 (33%) of these cases the histopathology revealed treatment effect or necrosis without evidence of active tumor. In general candidates for repeat resection had recurrence at the initial site of disease considered suitable for gross total resection. The demonstration of treatment effect/necrosis in five of 45 (11%) of patients may represent an underestimate of the true incidence. Most patients received additional treatment at the time of recurrence without any attempt at pathologic confirmation. In addition, in two patients the specimen was primarily treatment effect with only a foci of active tumor. It is also important to note that this effect may be persistent over time as treatment effect or necrosis without active tumor was demonstrated in three of four

patients undergoing a later third resection, including two of the five patients who had treatment effect or necrosis at the initial reoperation and one patient who had treatment effect with a foci of active tumor at the initial reoperation.

These pathologic findings, which could indicate enhanced biologic activity, demonstrate that clinicians should be aware that a recurrent lesion at the primary site, the predominant mode of failure for glioblastoma, might in fact not represent recurrent disease in a proportion of patients treated with Gliadel® followed by radiotherapy. We did not utilize preoperative PET scanning or MRI spectroscopy in any of the reoperation patients, but this might be an excellent population of patients in which to test the ability of these imaging modalities to distinguish necrosis/treatment effect from recurrent disease. In glioblastoma, where local recurrence is generally universal and rapid, distinguishing the effects of treatment from true tumor recurrence may be of limited importance because there is always viable tumor present, even if the surgical resection specimen contains only necrosis/treatment effect, in all patients with glioblastoma. Indeed, the survival of patients with necrosis or treatment effect seen in the surgical specimen is consistent with the survival of patients with glioblastoma in general. However, Gliadel® is also under evaluation in disease entities such as brain metastasis, where the relative incidence of local recurrence is lower and, therefore, distinguishing treatment effect/necrosis from tumor would be potentially even more important. For the present, we recommend that patients with locally recurrent lesions, as defined by radiological studies,after therapy with Gliadel® and radiation be excluded from therapeutic trials until histologic confirmation of recurrent malignancy is obtained. Inclusion in clinical trials of patients who may have ''radiological recurrence'' that does not represent true disease growth has the potential to bias response outcome. It should be noted that another possible explanation for these findings is that significant viable tumor was present at the edges of the tumor bed but that resection was confined to areas with necrosis or treatment effect.

It is not possible to draw conclusions about efficacy of Gliadel® with radiotherapy from our analysis of the current series since there were not were not clear prospective patient selection criteria and the patient population was not large enough. However, we evaluated survival to verify that unexpected early deaths were not occurring, which might suggest toxicity. The survival results do not suggest any adverse effect of Gliadel® on overall survival. In fact, our survival results are similar to the favorable results described for the patients randomized to radiation plus Gliadel® in the initial 32 patient and subsequent 240 patient European randomized trials described above, which showed a significant survival benefit with Gliadel® in newly diagnosed glioblastoma. The median survival was 12.8 months for glioblastoma patients in our study, in comparison with 12 months in the earlier 32 patient European trial[5] and 14 months and in the subsequent 240 patient European trial.[6] We observed that for patients over 55 years old, the median survival was 9.6 months, whereas it was 15.9 months for younger patients. The lack of effect of preoperative performance status on outcome potentially reflects the difficulty in retrospectively determining performance status.

Finally, we examined whether there was a substantial risk that Gliadel® would be placed in patients with a diagnosis other than malignant glioma. In the newly diagnosed patient, Gliadel® is frequently placed only with the availability of frozen section diagnosis. We found that, in our series, all patients who received Gliadel® ultimately had a final diagnosis of malignant glioma, of which 87% had glioblastoma.

In summary, Gliadel® wafers do not significantly increase postoperative risks or the short term toxicities of full dose radiotherapy, although an emphasis should be placed on close supervision during dexamethasone taper. The median survival for glioblastoma patients appears to be greater than one year suggesting that there are not long term toxicities that significantly impact upon overall survival. A significant portion of locally recurrent contrast enhancing lesions will primarily represent treatment effect or necrosis, and obtaining histopathologic confirmation of recurrence should be considered prior to enrolling such patients in clinical trials or instituting potentially toxic therapies.

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