Surgical Neurology International

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Original Article

Safety and efficacy of concomitant chemotherapeutic wafers and iodine-125 seeds for recurrent glioblastoma

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Received: 02 June 12 Accepted: 09 July 12 Published: 20 November 12

This article may be cited as:
Ko AL, Fink KR, Stelzer KM, Silbergeld DL. Safety and efficacy of concomitant chemotherapeutic wafers and iodine-125 seeds for recurrent glioblastoma. Surg Neurol Int 2012;3:137.
Available FREE in open access from: http://www.surgicalneurologyint.com/text.asp?2012/3/1/137/103644

Abstract

Background: Patients with recurrent malignant gliomas have a uniformly poor prognosis. However, further treatment is often warranted at the time of recurrence. Low-activity implanted brachytherapeutic devices, such as iodine-125 seeds, and implantable chemotherapeutic devices such as 1, 3-bis (2-chloroethyl)-nitrosourea (BCNU) impregnated polymer wafers (Gliadel®) have been shown to be safe and modestly effective, but a comparison of combination therapy versus Gliadel® implantation alone has not been performed.

Methods: We retrospectively examined 24 patients following re-resection of recurrent glioblastoma, with 17 patients undergoing implantation of both Gliadel® and iodine-125 seeds, and 7 patients undergoing implantation of Gliadel® only. Outcomes examined included adverse events, survival after re-resection (SAR), and time to tumor progression after re-resection (PAR).

Results: Implantation of both Gliadel® and low activity iodine-125 seeds is safe with only two wound infections noted, a complication rate comparable to previous reports. The combination appears to confer a median SAR benefit if the activity per tumor resection volume exceeds 0.8 mCi/mL (60 versus 31 weeks, $P = 0.02$), and this benefit remained significant on multivariate analysis (HR =0.26 [CI:0.07-0.93], $P = 0.03$). Gross total resection of tumor was also significantly associated with longer time to PAR (HR =5.4 [CI: 1.13-26.0], $P = 0.03$).

Conclusions: The concomitant use of Gliadel® and low activity iodine-125 seeds following re-resection of recurrent glioblastoma is safe. Our study demonstrated a significant benefit in SAR if the iodine-125 activity per tumor volume is greater than 0.8 mCi/mL. While our sample size is small, our results are in agreement with previous studies demonstrating the efficacy of combination treatment.

Key Words: Gliadel®, iodine-125, recurrent glioblastoma, surgical re-resection

Access this article online

Website: www.surgicalneurologyint.com

DOI: 10.4103/2152-7806.103644

Quick Response Code:

INTRODUCTION

Patients with recurrent malignant gliomas have a uniformly poor prognosis despite surgical resection, chemotherapy, and radiotherapy. Many patients maintain a highly functional performance status and QOL

following initial therapy. For these patients, further treatment is often warranted at the time of recurrence or tumor progression. Re-treatment options are limited, as most patients have received aggressive treatment following the initial diagnosis. Although radiotherapy is the single most effective treatment for high grade gliomas, cumulative tolerance doses to critical intracranial structures, even with conformal fractionated external beam radiotherapy, preclude retreatment with external beam radiotherapy to standard doses. Most patients have received systemic alkylating agent chemotherapy, either concomitant with or after completing radiation. Studies have shown, however, that further treatment following recurrence can improve survival.[20] In particular, re-resection in conjunction with salvage therapy appears to offer an improvement in outcome in comparison to surgery alone.[24]

Although a malignant glioma is a diffuse disease process, most recurrences occur within 2 cm of the resection margin.[25,38] Local control may not provide a cure, but it may extend length of survival (LOS) and even improve quality of life (QOL). Therapies have been devised to treat the tumor resection cavity and adjacent infiltrated brain directly. Low-activity implanted brachytherapeutic devices, such as iodine-125 seeds, allow highly focused radiation to the tumor bed. Dosages are usually calculated to a depth from surgical cavity perimeter of 0.5 cm, dropping off rapidly with approximately the 30% isodose volume at 1.0 cm depth.[29]

Implantable chemotherapeutic devices such as 1,3-bis (2-chloroethyl)-nitrosourea (BCNU) impregnated polymer wafers (Gliadel®) allow continual local chemotherapeutic agent delivery within the blood brain barrier (BBB), avoiding adverse systemic reactions. Although BCNU is detectable at some distance from implantation, the highest concentration is localized within 0.1-1.2 cm of the implant.[11] Although Gliadel® and low activity iodine-125 seed implants have demonstrated LOS benefit, this benefit is limited.[8] We examine the safety and utility of implanting both Gliadel® and low activity iodine-125 seeds following re-resection of recurrent glioblastoma. The rate of adverse events was monitored, with particular attention to wound healing and infection-related complications. Length of survival after initial diagnosis (LOS) and time to tumor progression (TTP) were assessed, and particular attention was paid to factors affecting survival after re-resection (SAR) and time to tumor progression after re-resection (PAR).

MATERIALS AND METHODS

Patient population

All malignant brain tumor resections included were performed by one surgeon from January 1999 to January 2003 at the University of Washington and were retrospectively reviewed to identify a total of 24 patients for this study. These patients underwent re-resection of a recurrent GBM and either implantation of iodine-125 seeds and Gliadel® wafers ($N = 17$) or Gliadel® wafers only ($N = 7$). Additional inclusion criteria included age of at least 18 years with a prior tissue diagnosis of glioblastoma or gliosarcoma, and previous treatment with fractionated external beam radiotherapy. Patients were excluded if they had multifocal tumors, invasion of the corpus callosum, subependymal spread, or if resection would require ventricular entry (thus precluding placement of implants). The Human Subjects Internal Review Board at the University of Washington Medical Center reviewed and approved the research protocol.

All patients had previously been treated with whole brain radiation to doses of 5400-7940 cGy of conventional radiation therapy, or 15-18 Gy of neutron beam therapy (on a research protocol). One patient received a stereotactic radiotherapy boost, and one patient underwent stereotactic radiosurgery. Some patients had received systemic chemotherapy, which included regimens of BCNU, procarbazine/CCNU/vincristine, temozolamide, cisplatin, tamoxifen, or others [Table 1]. One patient in the treatment group had received interferon therapy for melanoma prior to being diagnosed with malignant glioma.

Surgical technique

All tumors were supratentorial, and a maximal surgical resection was performed using sub-pial technique.[21] Intra-operative subgaleal and subdural cultures were obtained in all patients. Image guidance and intraoperative ultrasound were used during resection to delineate the extent of tumor. As the use of Gliadel was planned, care was taken not to enter the ventricles. If indicated, functional cortical mapping was performed to identify the limits of safe resection. Gross total resection, defined as surgical removal of all macroscopic tumor and verified with postoperative MRI, was achieved in 15 patients.

After resection, careful hemostasis was obtained. Low activity iodine-125 seeds were implanted under direct visual guidance. Seed activity was 0.588 to 0.753 mCi/seed; seeds were spaced 10 mm apart between their centers. Preoperative dosimetry was designed to deliver 230 Gy at 5 mm depth at an infinite time point. Postoperatively, dose calculation was performed based upon seed positioned on orthogonal simulation images. Seeds were placed longitudinally along the resection cavity, excluding dural surfaces. Next, eight Gliadel® wafers were placed to cover the resection cavity. Surgicel was placed over the Gliadel wafers, and thrombin glue was used to secure the seeds and wafers. A watertight dural closure was obtained, using a dural graft if needed.

Table 1: Patient characteristics

Patient	Age	Sex	KPS	Extent of resection	Pathology	RPA class	Tumor volume (mL)	I-125 activity/ volume	Chemotherapy
1	39	F	100	ST	GBM	3	41.87	0.90	
2	41	M	70	GT	GBM	4	60.71	0.58	T,C
3	48	M	80	ST	GBM	4	48.98	0.79	
4	58	M	100	ST	GBM	5	46.12	0.93	
5	41	F	100	ST	GBM	3	18.84	1.26	
6	47	M	100	GT	GBM	3	70.08	0.44	T,C
7	40	M	90	ST	GBM	3	28.26	1.25	T,B,C
8	29	F	90	GT	GBM	3	100.48	0.47	T
9	63	M	90	GT	GBM	5	37.37	0.45	T
10	53	M	70	GT	GBM	5	18.09	0.81	
11	51	F	100	GT	GBM	5	25.06	0.99	PCV
12	56	M	90	GT	GS	5	46.89	0.97	Ph,T, I
13	51	M	90	ST	GBM	5	32.03	0.88	T
14	59	F	90	GT	GBM	5	42.13	0.61	T
15	54	M	90	ST	GBM	5	24.12	1.15	T
16	47	F	80	GT	GBM	4	45.22	0.65	
17*	46	M	100	GT	GBM	3	35.59	0.98	T
18	52	F	100	GT	GBM	5	87.92	**	
19	53	M	100	GT	GBM	5	94.20	**	
20	42	M	100	GT	GBM	3	45.22	**	B
21	38	F	60	ST	GBM	4	94.20	**	B
22	57	F	90	GT	GBM	5	27.63	**	T
23	29	F	100	GT	GBM	3	46.05	**	T
24	53	M	70	ST	GBM	5	21.35	**	

T: Temozolamide, C: Cisplatin, B: BCNU, PCV: Procarbazine/lomustine/vincristine, Ph: Phenylbutyrate, I: imitinib, *=Alive, M: 14, F: 10, Med: 90, Mean: 90, GT: 15, ST: 9, **No seeds

Follow up

Patients underwent gadolinium-enhanced MR scanning within 48 h post-operatively and every 3 months thereafter. Neurologic examination and KPS evaluation were reviewed every 3 months by a neuro-oncologist. Tumor progression was defined as an increase in tumor largest cross-sectional product by 25%, appearance of new lesions, or an increased need for corticosteroids,[23] and further treatment was offered if deemed appropriate by the University of Washington Neuro-oncology Service.

Data analysis

Adverse events were tabulated. Analysis of LOS, TTP, SAR, and PAR was performed. Overall LOS was calculated from the time of initial pathologic diagnosis, and TTP was calculated as the interval between initial diagnosis and initial progression. SAR and PAR were calculated after re-resection surgery. In four cases, the patient expired prior to documented progression. These data were right-censored. Kaplan-Meier survival curves and progression curves were constructed for subgroups undergoing implantation of both iodine-125 seeds and Gliadel® wafers, and those with Gliadel® wafers only. Univariate analysis of median survival and time to progression in subgroups [age, sex, resection (gross total versus subtotal), recursive partitioning analysis (RPA) class, iodine-125 activity/volume of resection, prior treatment with chemotherapy and tumor volume] was performed with a one-sided Wilcoxon rank-sum test. Activity per volume was defined as mCi per mL of resection as defined by postoperative MRI. Multivariate analysis was performed with the same baseline factors using a Cox proportional hazards model to identify associations with post re-resection survival and post re-resection time-to-tumor progression. Statistical significance was set at $P = 0.05$.

RESULTS

Adverse events

Three patients experienced complications after repeat surgery and concomitant implantation of iodine-125 seeds and BCNU-impregnated wafers [Table 2]. Two patients developed wound infections. Both were treated successfully with antibiotics. In patient 6, intraoperative cultures were positive for coagulase negative *Staphylococcus* (presumably from the previous surgery). The patient did not manifest clinical signs of infection, and was treated successfully with a course of intravenous antibiotics. Patient 9 returned 2 weeks after resection with a superficial wound infection, and was treated with oral antibiotics. No patient required reoperation for infection.

Thus, the infection rate was 8% (though one of the two infections was present prior to surgery, as noted above). Patient 13 developed a pulmonary embolus 10 days after craniotomy and received anticoagulation therapy. No other adverse reactions were identified, and there was no perioperative mortality.

Survival and tumor control

Kaplan-Meier curves were constructed for LOS, SAR, TTP, and PAR in patients who received both Gliadel® and iodine-125 seeds versus patients who received Gliadel® only [Figure 1]. There were no significant differences between the groups in LOS, SAR, TTP, or PAR. Spearman's rank correlation did not reveal a significant correlation between time to initial progression and post-re-resection survival times ($r = 0.49$, $P = 0.15$).

The median SAR for all patients was 48 weeks. Median SAR for patients who received Gliadel® and iodine-125 seeds was 50 weeks, and was 30 weeks for those who received Gliadel® only, a result that approached statistical significance ($P = 0.09$).

Table 2: Adverse events after implantation of 1,3-bis (2-chloroethyl)-nitrosourea wafers and I-125 seeds

Pt#	Adverse event
6	Intraoperative cultures positive for coagulase-negative Staphylococcus. Treated successfully with intravenous antibiotics.
9	Superficial wound infection, postoperative day 14. Treated with oral antibiotics.
13	Pulmonary embolus, postoperative day 10. Treated with anticoagulation.

Univariate analysis was performed using age, sex, RPA class, extent of resection, previous chemotherapy, receipt of iodine-125 seeds, and tumor volume as factors contributing to survival. None of these had a statistically significant effect on LOS or TTP. For SAR, however, previous chemotherapy ($P = 0.06$) and implantation of iodine-125 seeds ($P = 0.09$) trended toward significance. Previous studies have suggested that an increased radiation activity per tumor volume may have an effect on survival,[8,17,29] and the analysis was repeated for patients receiving <0.8 mCi/mL (including patients receiving wafers only) versus those receiving a higher activity implant. This showed a statistically significant advantage in SAR (median 60 weeks and 31 weeks, $P = 0.02$) for those patients receiving the higher activity per tumor volume [Table 3] [Figure 2].

Multivariate analyses using these baseline factors showed that the activity per tumor volume had a significant effect on SAR (HR =0.26 [CI:0.07 - 0.93], $P = 0.03$). Prior chemotherapy did not show a significant effect ($P = 0.09$).

The median PAR for all patients was 15 weeks. Univariate analyses showed median time to PAR was greater for those patients aged <50 vs. those aged 50 and over (median 21.5 and 11.0, $P = 0.02$) and those of RPA class III showed later PAR than those in classes IV and V (median 21.5 and 11.0, $P = 0.02$). Neither factor remained significant on multivariate analysis. Interestingly, gross total resection on multivariate analysis was significantly associated with longer time to PAR (HR =5.4 [CI: 1.13 - 26.0], $P = 0.03$) [Figure 2].

First site of tumor progression after reoperation with gross

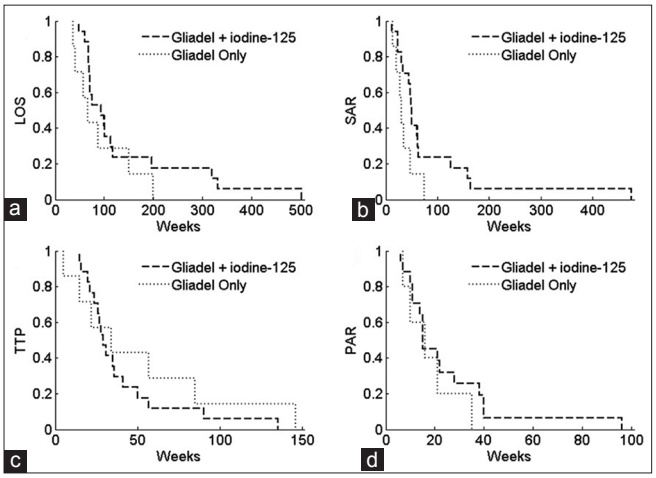

Figure 1: Gliadel® and iodine-125 versus Gliadel® alone. (a) Kaplan-Meier curves demonstrating total survival time after initial diagnosis (LOS) for patients undergoing re-resection and implantation of both chemotherapeutic wafers and iodine-125 seeds (dashed line) versus wafers only (dotted line). (b) Combination therapy did not seem to provide a significant benefit in LOS after re-resection. There did not appear to be any difference between groups with respect to (c) time to initial progression or (d) tumor progression after re-resection

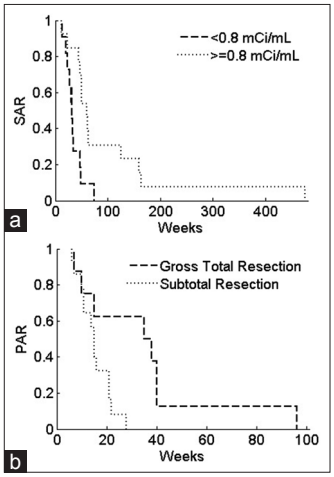

Figure 2: Significant factors effecting survival after re-resection and tumor progression after re-resection. (a) Kaplan-Meier analysis of survival after re-resection in patients with iodine-125 activity per volume greater than 0.8 mCi/mL (dashed line) versus those with less activity per volume (dotted line). The difference in median survival is 60 weeks versus 31 weeks ($P = 0.02$). (b) Gross total re-resection of tumor (dashed line) appears to have a benefit in terms of tumor progression after re-resection in comparison to subtotal resection (dotted line)

Table 3: Univariate analysis of factors affecting survival and tumor progression after re-resection

Factor	N	SAR	*P* value	PAR	*P* value
Age					
<50	12	47.5	0.69	21.5	0.02
>=50	12	41.5		11.5	
Sex					
M	14	48.5	0.43	15	0.18
F	10	33		13.5	
Resection					
GTR	15	50	0.37	35	0.18
STR	9	47		14	
RPA					
III	12	47.5	0.69	21.5	0.02
IV/V	12	41.5		11.5	
Chemotherapy					
Yes	15	49	0.07	15	0.93
No	9	28		12	
I-125 activity/volume					
<0.8 mCi/mL	11	31	0.02	11	0.14
>=0.8 mCi/mL	13	60		15	
Tumor volume					
<40 mL	10	48.5	0.98	13	0.36
>=40 mL	14	46.5		15.5	

total resection was local (less than 2 cm from resection cavity) in all cases of subsequent recurrence.

DISCUSSION

Our limited retrospective study group demonstrated that re-operation for recurrent malignant gliomas, augmented by intra-operative implantation of low-activity iodine-125 brachytherapy, and BCNU chemotherapeutic wafers, may confer some survival benefit, in particular if the iodine-125 activity per tumor volume is greater than 0.8 mCi/mL.

Patients tolerated re-operation with implantation of low activity iodine-125 seeds and BCNU-impregnated wafers well, with no adverse reactions due to the co-implantation. Because these patients had already undergone resection and radiation treatment, wound healing was monitored carefully. The 8% infection rate in this group of patients is comparable to reported rates of infection after other treatments for recurrent gliomas. Infection rates after reoperation alone of malignant glioma are reported to be 0-9.3%.[2,9,37] Infection rates after implantation of low-activity iodine-125 brachytherapy are 4.5-5%,[17,28] and after implantation of BCNU-impregnated wafers are 4-28%.[6,27,35] Other wound healing complications such as poor wound healing or CSF leaks were not manifested in this treatment group.

Pulmonary embolus is a known complication in patients with malignant glioma, and has been reported in patients undergoing reoperation alone[2] and in patients receiving BCNU-wafer implants.[36] Deep venous thrombosis has also been reported after BCNU wafer implants.[35] The patient who experienced pulmonary embolus was treated successfully with anti-coagulation therapy.

Other complications reported after either brachytherapy or chemotherapeutic wafer implantation were not seen in our study population. For example, significant radiation necrosis has been reported after iodine-125 brachytherapy,[14,17] but was not noted in this study. Malignant cerebral edema, seizures, and tumor bed cysts have been reported after BCNU wafer implantation,[6,12,26,35] but were not seen in this study. In addition, no perioperative deaths occurred.

SAR with implantation of iodine-125 seeds and BCNU wafers compares favorably in this group of patients to reported survival after reoperation alone, and reoperation with BCNU wafer implantation. SAR after re-operation alone for recurrent malignant glioma has been reported in several studies [Table 4]. Median SAR for grade IV gliomas is 13-36 weeks, and total survival is 57-82 weeks.[2,3,9,10,19,24,30,33,37] SAR after implantation of BCNU wafers is 14-47 weeks with a total survival of 47-50 weeks[5,6,35] [Table 5].

SAR in this study was comparable to that reported for iodine-125 brachytherapy alone, with median survival ranging from 47-64 weeks [Table 6]. The median PAR was 15 weeks, which appears to be less than that reported for iodine-125 alone (25-29 weeks).[17,28]

Darakchiev, *et al*., reported a median SAR of 69 weeks after concomitant iodine-125 seed and BCNU wafer placement,[7] and suggested that iodine-125 activity density was a significant factor contributing to increased survival, consistent with our findings. The median time to PAR was 47 weeks in this study,[8] which is longer than the 15 weeks found in our patient population. One possible explanation is that our study did not explicitly select patients for whom gross total resection was the goal of the operation, and consequently a larger percentage of patients in our study underwent subtotal resection (9/24 vs. 5/34). While the effect of extent of resection on survival in glioma surgery remains controversial, increasing evidence suggests cytoreduction benefits both overall and progression-free survival.[31] Even as a salvage treatment coupled with adjunct therapies such as chemotherapeutic implants, the extent of resection appears to be a prognostic factor influencing patient survival.[7] Also, a lack of standardized therapy such as the Stupp protocol prior to initiation of re-resection and salvage therapy with implantable seeds and wafers may be an additional confound.

Commensurate with these data, our multivariate

Table 4: Survival after reoperation alone for recurrent malignant glioma

Study (treatment period)	Age Med (Mean)	KPS Med (Mean)	SAR (wks) Med (Mean)	TS (wks) Med (Mean)
Harsh[19] (1975-84)	45.5	80 (78.5)	36	82
Ammirati[2] (1972-83)	48 (43.1)	70*15<70	29	76.4
Vick[37] (1989)	43	80	21.5 (28)	77 (95)
Sipos[33] (1973-92)	(36) (48)	*5<60*34<60	18.5	72.5
Dirks[9] (1978-90)	53	>50	19	57
Rostomily[30] (1986-90)	(42)	(80)	30	NR
Durmaz[10] (1985-95)	(47)		26.5	71.1
Barker[3] (1988-93)	50	(82)	36	NR
Mandl[24] (1999-2005)	51	80	13	NR

NR: Not reported

Table 5: Survival after reoperation and implantation of 1,3-bis (2-chloroethyl)-nitrosourea-impregnated wafers

Study (year)	Age Med (Mean)	KPS Med (Mean)	SAR (wks) Med (Mean)	PAR (wks) Med (Mean)	TS (wks) Med (Mean)
Brem[5] (1991)	(48.6)	(86)	47 (64)	NR	NR
Brem[6] (1989-92)	(48)	(77)	BCNU: 31 Placebo:23	NR	NR
Subach[35] (1996-98)	54		50	NR	97

NR: Not reported

Table 6: Survival after reoperation and implantation of low activity iodine-125 seeds

Study (year)	Age Med (Mean)	KPS Med (Mean)	SAR (wks) Med (Mean)	PAR (wks) Med (Mean)
Patel[28] (1994-98)	50	70	47	25
Gaspar[14]	39	*≥60	47	NR
Halligan[18] (91-95)	41	90	64	29

NR: Not reported

analysis identified extent of resection as a significant factor contributing to earlier time to progression when implanting both iodine-125 and BCNU wafers. A finding in common with previous studies was that all recurrences were within 2 cm of the resection margin.[8] These two studies provide evidence that the concomitant use of iodine-125 and BCNU wafers for recurrent GBM is safe and potentially efficacious in providing a survival benefit when achieving activity density of >=0.8 mCi/mL of tumor volume.

It is important to note that the statistical analyses employed in this study are subject to the weaknesses implicit in a retrospective, non-blinded trial. Moreover, the small numbers of patients in our series must also limit the strength of our conclusions. In particular, in our proportional hazards analysis, we analyze seven prognostic factors; traditionally, the "rule of ten" suggests ten subjects for each factor in this type of analysis, which would require 70 subjects. The number of prognostic factors in the univariate analysis also increases the risk of errors of the first kind, without correction for multiple comparisons. These statistical concerns are not unique to this paper and are shared by many small case series. Nevertheless, our results are consistent with results reported in other studies of malignant glioma with respect to the possible benefits of adjunct therapy as well as the patient factors that contribute to increase in survival.

Glioma is a diffuse disease, with tumor cells found in brain up to 4 cm away from the tumor mass.[32] Despite the diffuse nature of this disease, tumor recurrences are predominately local, defined as 2 cm from the resection margin. Wallner *et al*. reported first tumor recurrences were within 2 cm of margin in 78% of cases, within 1 cm of margin in 56% of cases, and in tumor bed in 16% of patients who underwent initial surgical resection and external beam radiation.[38] In a follow up report, a similar pattern of second recurrence was found in a limited group of patients who were suitable for reoperation, with 67% recurring within 2.0 cm.[25]

Aggressive local treatment has not convincingly changed this pattern of recurrence. Although Loeffler *et al*. reported only 10% local recurrence after treatment with temporary high-activity brachytherapy,[22] other studies report 86-88% of tumors recurring locally.[1,4] Similarly, recurrence after low-activity iodine-125 brachytherapy is local 70-90% of the time.[17,28] This is not unexpected considering the maximal radiation dose after treatment is within 0.5 cm, and drops off significantly thereafter.

BCNU wafers have been shown to release most of the chemotherapeutic agent widely, with approximately 50% of

rabbit brain exposed at 3 days,[16] but effective concentration is more limited, from 0.1 to 1.2 cm at 3 days[16,34] to 0.4 cm for the next 7-21 days. In monkeys, BCNU concentration was high within 0.3 cm of implant, and present at lower doses up to 5 cm away, but below the LD50.[13] In clinical practice, however, glioma recurrence after BCNU wafer treatment is still predominantly local, at 73%.[15,18]

In the two reports of concomitant treatment of recurrent disease with iodine-125 and BCNU wafers, it appears that while aggressive, multi-modality local treatment does not affect the pattern of local recurrence, it may confer some survival benefit.

CONCLUSIONS

Despite advances in surgery, chemotherapy, and radiation treatment, patients with malignant gliomas have a poor prognosis. Patients often have reasonable functional status at the time of glioma recurrence, and more treatment is often offered. Since most tumor recurrences are local, aggressive treatment to the tumor bed is reasonable, though not curative. Despite aggressive local treatment with either brachytherapy or local chemotherapy, most recurrences are still within 2 cm of the resection cavity. Concomitant treatment with iodine-125 brachytherapy and BCNU wafers is one option to maximize local treatment. This method is safe compared to reoperation with either iodine-125 seeds or BCNU wafers alone. Survival after resection and concomitant implant of iodine-125 seeds plus BCNU appears favorable compared to reoperation alone, and is at least comparable to implantation of either BCNU wafers or iodine-125 seeds alone. Implant of the resection site with iodine-125 seeds should be done with the goal of achieving activity density that is at least 0.8 mCi/mL of tumor volume.

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