

Treatment of recurrent high-grade gliomas with GliSite brachytherapy: a prospective mono-institutional Italian experience

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ABSTRACT

Aims and background. The present study evaluated toxicity, local control, and survival in patients with relapsed high-grade glioma after surgery and external beam radiation therapy and treated with re-operation and GliSite brachytherapy.

Methods. Between 2006 and 2008, 15 patients with recurrent high-grade glioma underwent re-operation and GliSite brachytherapy. Ten patients were males and 5 females. Median age was 40 years (range, 20-71). Karnofsky performance status was ≥ 70 . All patients but one received GliSite irradiation of the surgical cavity wall at the dose of 4500 cGy at a depth of 1 cm.

Results. No severe acute side effects were observed during GliSite brachytherapy. Pathologically documented, symptomatic late radiation necrosis was observed in 3 patients (20%); 2 subsequently died of further complications. Two patients were alive at a median follow-up 13 months (range, 1-30). Median overall survival after GliSite brachytherapy was 13 months.

Conclusions. Patients with recurrent high-grade glioma can be treated with additional surgery and GliSite brachytherapy, delivering 4500 cGy at 1 cm depth without significant acute side effects but with a significant rate (20%) of late radiation necrosis, resulting in 13% of treatment-related deaths. Compared with the literature, survival results in our study appear to be satisfactory, but they may be related to patient selection criteria. Re-intervention followed by GliSite brachytherapy should not be offered as a standard treatment for recurrent high-grade glioma, because of the high rate of late complications, treatment-related deaths, and high treatment costs.

Introduction

Despite macroscopically radical surgery followed by adjuvant chemoradiation, long-term survival is rare in high grade gliomas (HGG). The standard treatment at diagnosis includes surgery and postoperative external beam radiotherapy (EBRT) plus chemotherapy¹. Malignant gliomas typically relapse locally within 2 cm of the surgical cavity margins²⁻⁵.

Surgery of local relapse is feasible in only a few patients for poor general conditions or location of recurrence. In addition, because of the concern for radiation brain-tissue injury, further radiation, with or without chemotherapy, is hardly ever delivered. However, in a previous experience, we assessed the feasibility of external reirradiation and concomitant-sequential oral lomustine in recurrent brain gliomas, reporting a modest subjective and objective response rate but a remarkable median overall survival of 13.7 months from relapse⁶.

Key words: brachytherapy, GliSite, high-grade glioma, local recurrence.

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We report the first Italian experience with surgery and re-irradiation using the GliaSite Radiation Therapy System (GS-RTS, Proxima Therapeutics/Alpharetta, GA, USA) in relapsed HGG after primary surgery and postoperative EBRT.

Patients and methods

Between February 2006 and July 2008, 15 patients with recurrent grade 3 or 4 glioma (10 glioblastoma multiforme, 4 anaplastic astrocytoma, 1 anaplastic xanthoastrocytoma) were treated with surgical resection and GliaSite brachytherapy. Ten patients were male and 5 were female. Median age was 40 years (range, 20-71). Median Karnofsky performance status (KPS) before reoperation was 90 (range, 70-100). All patients but one had previously received adjuvant EBRT for their primary disease; the radiation dose delivered was 6000 cGy in 12 of 14 patients. All patients but one had been previously treated with chemotherapy (BCNU, temozolomide, or other agents) after the first operation. The interval from first operation to GliaSite implantation ranged from 7 to 70 months (median, 28). Patient characteristics are reported in Table 1.

In the presurgical staging and during follow-up, all patients were evaluated with brain magnetic resonance imaging (MRI) and 7 were also studied with PET/CT with infusion of O-(2-[18F]-fluoroethyl)-L-tyrosine.

Patient selection criteria

Eligibility criteria included age 18 years or older, histologically proven HGG with radiologically documented recurrence after primary surgery and EBRT, and minimum KPS score of 70. All patients had to be good candidates for safe surgical resection, with an estimated li-

fe expectancy of at least 6 months. Patients were excluded from treatment with the GS-RTS if the staging MRI documented leptomeningeal tumor spread, tumor size exceeding the maximum volume provided by the balloon (maximum diameter, 4 cm), marked edema or significant midline shift not expected to be corrected by tumor resection. Patients were also excluded if the tumor approximated or invaded critical brain structures, such as the brainstem or optic chiasm, with an unacceptable risk of severe radiation injury.

Acute and late toxicity was scored according to RTOG criteria⁷. The study obtained the approval of the Institute Ethics Committee for clinical trials. A written informed consent was obtained from the patients who entered the study.

The GliaSite-Radiation Therapy System

The combination of a medical device with the radioactive solution for brachytherapy in relapsed brain tumors is known as the GliaSite-Radiation Therapy System (GS-RTS, Proxima Therapeutics). The device is composed of a dual silicone balloon (inner and outer balloon) connected through a catheter to an infusion port. The internal balloon contains the radioactive solution during the period of irradiation, whereas the external balloon acts as a safety barrier in case of inner balloon rupture. The device is supplied with balloons of 2, 3 or 4 cm in diameter for allocation in surgical cavities of different sizes.

The radioactive solution (IotrexTM) contains sodium 3-(¹²⁵I) iodo-4-hydroxybenzenesulfonate (¹²⁵I-HBS) acting as an internal brachytherapy source. It is delivered in nominal 1.0 ml vials containing a minimum of 150 mCi at the time of calibration by the licensee. Net after-loaded activity ranges from 75 to 1200 mCi depending on the prescribed radiation dose, treatment depth, and

Table 1 - Patient characteristics

Patient no.	Sex	Age (yr)	Tumor location (side)	Histology at first diagnosis	Histology at recurrence	EBRT (cGy)	Chemotherapy	KPS pre-GliaSite
1	M	20	Frontal (R)	Astrocytoma III/GBM	GBM	6000	TMZ	100
2	F	64	Frontal (R)	GBM	GBM	6000	TMZ	90
3	M	38	Temporo-parietal (R)	GBM	GBM	6000	TMZ	100
4	M	31	Frontal (L)	Xanto-astrocytoma III	Xanto-astrocytoma III	6000	PCV	100
5	M	59	Frontal (L)	GBM	GBM	2500	TMZ	70
6	M	57	Temporo-insular (L)	GBM	GBM	6000	TMZ	90
7	M	39	Fronto-parietal (L)	Astrocytoma III	Astrocytoma III	6000	PCV-TMZ	80
8	M	40	Frontal (L)	Astrocytoma III	Astrocytoma III	-	-	100
9	F	36	Frontal (L)	Astrocytoma III	GBM	6000	TMZ	90
10	F	59	Occipital (R)	GBM	GBM	6000	TMZ	90
11	F	47	Frontal (R)	GBM	GBM	6000	TMZ	80
12	M	38	Temporal (L)	GBM	GBM	6000	TMZ	100
13	M	71	Frontal (L)	GBM	GBM	6000	TMZ	90
14	M	36	Fronto-parietal (R)	GBM	GBM	6000	TMZ	100
15	F	64	Parieto-occipital (L)	GBM	GBM	6000	TMZ	100

R, right; L, left; GBM, glioblastoma multiforme; EBRT, external beam radiation therapy; TMZ, temozolomide; PCV, procarbazine, carmustine, vincristine; KPS, Karnofsky performance status.

balloon diameter. The low energy emission (27-35 KeV photons) of ^{125}I results in a rapid attenuation over short distances leading to a rapid dose falloff. In this way, IotrexTM allows the delivery of a high radiation dose to the surface of the surgical cavity, avoiding irradiation of large portions of the surrounding normal brain tissue.

Description of the procedure

After resection, a Gliasite balloon fitting the diameter of the cavity was placed in the resection cavity. The balloon was then filled with saline and the reservoir secured to the skull. Unenhanced and gadolinium-enhanced MRI was performed within 24 to 48 h to ensure accurate placement of the device, to assess any residual tumor, as well as to allow dosimetric planning. To visualize the adherence of the balloon surface to the surgical cavity wall, after a period of 2 to 4 weeks, a repeat MRI was obtained, filling the balloon with a volume of saline equal to the volume of IotrexTM planned for irradiation.

Based on the volume of the solution to be infused in the balloon and the dose to be administered at a set depth, the duration of brachytherapy was calculated using the "Iotrex Calculation Booklet" (provided by Proxima Therapeutics). The duration of brachytherapy in our group of patients ranged from 3 to 4 days in an in-patient setting, and the radioactive solution was then removed from the device. To avoid personal and environmental contamination, specific precautions were taken throughout the procedure. Removal of the device was planned in the weeks following irradiation.

Statistics

Data on overall and disease-free survival were obtained through an active follow-up of the patients including radiologic examinations. Overall and disease-free survival were calculated from the date of beginning treatment to death and to date of relapse, respectively. Survival analysis was computed by the Kaplan-Meier method⁸.

Results

A total of 15 patients with recurrent HGG underwent surgical re-intervention and GS-RTS brachytherapy. The extent of surgical resection of recurrence was macroscopically radical in 14 patients and non-radical in 1 (close proximity to the motor cortex). In 13 patients, histology was the same as the first operation, whereas in 2 cases the original anaplastic astrocytoma histology changed to glioblastoma multiforme.

Brachytherapy with the GS-RTS was performed in all patients in an in-patient setting. Fourteen patients received a dose of 4500 cGy at 1 cm depth, whereas the patient who had refused the first EBRT received a dose of 6000 cGy at the same depth. Infusion and removal of the

IotrexTM solution were easily carried out in approximately 30 min. There was no evidence of staff or environment contamination. Details of Gliasite treatment are summarized in Table 2.

Acute side effects after the operation were observed in 1 patient, who showed both transient hemiparesis and dysphasia, which recovered in 6 months. No acute side effects were observed during the procedures of emptying and filling the balloon. During the period of Gliasite brachytherapy, side effects were reported in 4 patients: 1 headache, 1 headache and partial epileptic seizure, 1 headache and insomnia, 1 motor deficit in one arm. All the symptoms resolved with corticosteroids and symptomatic treatment.

Three cases of late toxicity were observed: 1 patient died because of multi-organ failure, 1 patient died of hydrocephalus. One patient, previously untreated with EBRT and who was the only patient who received a Gliasite dose of 6000 cGy, is alive and free of disease at 30 months from brachytherapy but with very frequent episodes of severe headache and epileptic seizures. These 3 patients had a radiological diagnosis of radionecrosis and underwent a further operation; histological examination of the material retrieved by surgical curettage confirmed the diagnosis of radiation necrosis without evidence of tumor. The volume of IotrexTM solution infused in these 3 patients (10 ml, 10 ml and 14 ml, respectively) did not differ substantially from the volume infused in the 12 patients who did not experience any radionecrosis.

Local relapse was documented in 11 of 15 patients: in 6 patients (54.5%), relapses occurred within 1 cm of the surface of the surgical cavity, whereas in 5 patients (45.5%) they occurred 1 cm beyond the cavity. No differences in the ability to localize the site of recurrence was found between MRI and PET/CT diagnostic procedures.

At a follow-up of 1 to 30 months (median, 13), only 2 patients were alive. One patient was free of disease after 30 months from Gliasite brachytherapy, and 1 patient

Table 2 - Details of Gliasite treatment

Patient no.	Balloon diameter (cm)	Balloon-filled volume (ml)	Activity ^{125}I (mCi)	Dose (cGy)	Depth (cm)	Dwell time (d)
1	3	15	327	4500	1	3
2	3	15	306	4500	1	3
3	3	15	303	4500	1	3
4	3	10	325	4500	1	3
5	3	10	336	4500	1	3
6	3	10	315	4500	1	3
7	3	14	369	4500	1	3
8	3	10	292	6000	1	4
9	3	10	314	4500	1	3
10	4	12	325	4500	1	3
11	3	10	320	4500	1	3
12	3	15	333	4500	1	3
13	3	14	348	4500	1	3
14	3	18	419	4500	1	3
15	3	14	292	4500	1	3

was alive with a further relapse 6 months after the procedure.

Overall survival from first diagnosis of HGG was calculated from the date of first diagnosis to the time of death or last follow-up. Median overall survival from first diagnosis was 38 months (Figure 1). Overall survival after Gliasite brachytherapy was calculated from the device implantation to the time of death or last follow-up. The median overall survival from Gliasite brachytherapy was 13 months (Figure 2). Disease-free survival after Gliasite brachytherapy was calculated from the device implantation to subsequent relapse, and median disease-free survival from Gliasite brachytherapy was 7 months (Figure 3).

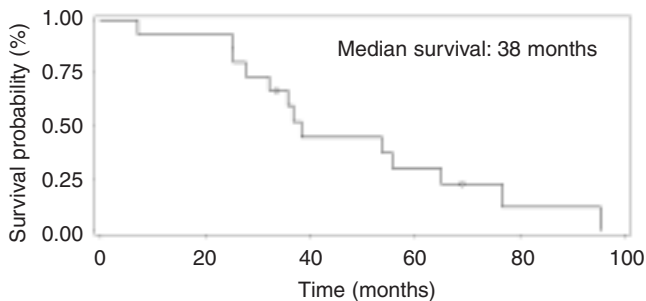


Figure 1 - Kaplan-Meier overall survival from first diagnosis of high grade gliomas.

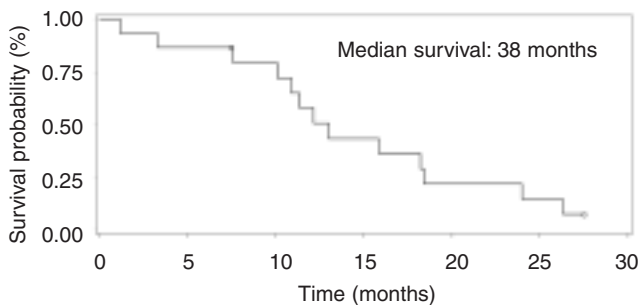


Figure 2 - Kaplan-Meier overall survival from Gliasite brachytherapy.

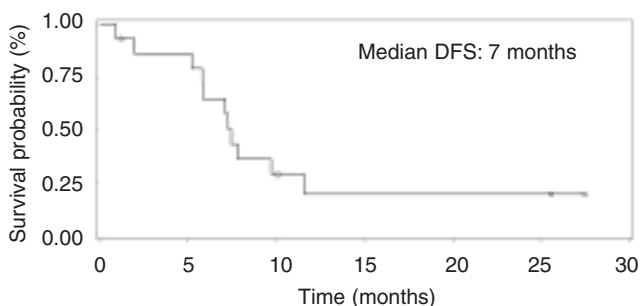


Figure 3 - Disease-free survival (DFS) from Gliasite brachytherapy to subsequent relapse.

The average cost of each Gliasite brachytherapy treatment delivered in an in-patient setting was 24,000 Euro.

Discussion

The standard treatment for brain HGG is surgical resection followed by postoperative EBRT given with conventional fractionation plus chemotherapy¹. Since 2005, EBRT with concomitant and sequential temozolomide has been increasingly used⁹⁻¹¹. Despite an aggressive local treatment, HGG tends to relapse locally and typically within 2 cm of the surgical cavity margins²⁻⁵. The standard treatment of local relapse is additional surgery when feasible (10-13% of cases in our experience). These patients have an ominous prognosis due to repeated disease relapses. In order to prolong the relapse-free period, various local treatments have been attempted, such as EBRT using stereotactic radiosurgery¹²⁻¹⁵, low-dose rate brachytherapy with ¹²⁵I permanent seed implant^{16,17} and carmustine wafer implant¹⁸. Of these therapies, only carmustine wafers have been proven to be superior over resection alone in a randomized clinical trial¹⁸.

The GS-RTS was approved by the Food and Drug Administration in 2001 for use in patients with malignant brain tumors following tumor resection. Compared with other radiation therapy modalities, GS-RTS offers an extremely selective irradiation of the target volume, because the balloon containing the radioactive solution acts as a point source. The low energy emission of ¹²⁵I results in a selective irradiation of the volume at highest risk of recurrence, namely the tissue adjacent to the surgical cavity wall.

Up to now, three papers on GS-RTS for the treatment of recurrent HGG have been published¹⁹⁻²¹. In 2003, Tatter *et al.*¹⁹ reported the results of the first study carried out on 21 patients with glioblastoma or anaplastic astrocytoma recurrence and treated in six centers, with doses ranging from 4000 to 6000 cGy to a depth of 5 to 10 mm. The primary end points were to evaluate the successful implantation and delivery of brachytherapy and to assess the safety of the device. The authors observed no serious adverse treatment-related events. In particular, no symptomatic radiation necrosis was observed. A median overall survival of 12.7 months from the time of device insertion was observed. The authors concluded that the GS-RTS safely and efficiently performs and delivers a readily quantifiable dose of radiation to tissues at the highest risk of tumor recurrence.

In 2005, Chan *et al.*²⁰ reported the results of a monoinstitutional trial on 24 patients treated for relapsed glioblastoma. In the study, the prescribed radiation dose was individually tailored taking into account the potential risks and benefits of higher and lower doses. The dose delivered to a depth of 5 to 10 mm ranged from 2990 to 8000 cGy. Acute and late side effects were mild

and rare, with 2 cases (8.3%) of symptomatic pathologically confirmed radiation necrosis. The median overall survival from GliSite treatment was 9.1 months. The authors concluded that only in patients with KPS ≥ 70 does median overall survival (9.3 months) compare favorably with other series of patients treated with additional resection alone, chemotherapy alone, or additional EBRT. They also concluded that there was no difference in overall survival between patients receiving 4500 cGy or a higher dose.

In 2006, Gabayan *et al.*²¹ reported the results of a trial including 95 patients with recurrent grade 3 or 4 glioma treated at 10 institutions. A median dose of 6000 cGy was delivered to an average depth of 10 mm. The median overall survival from GliSite placement was 36.3 weeks (8.5 months). Analysis of various prognostic factors revealed that only KPS significantly influenced survival. Three cases (2.8%) of pathologically documented radiation necrosis were observed. The authors concluded that re-irradiation with GliSite after resection is feasible and that comparison with historical controls suggests that the procedure may provide a modest improvement (about 3 months) in survival compared with surgery alone.

The present paper reports on the first Italian experience with GliSite in the treatment of relapsed HGG previously treated with surgery and postoperative EBRT. Based on the conclusions of Chan *et al.*²⁰, we decided to exclude patients with KPS < 70 and to deliver a radiation dose of 4500 cGy. In our experience, treatment with GS-RTS, at the dose of 4500 cGy at 1 cm depth, appeared to be feasible and without significant acute side effects in patients with KPS ≥ 70 . However, severe late complications were reported in 3 patients: 3 cases (20%) of symptomatic radiation necrosis requiring surgical curettage were observed and pathologically documented. Two of these patients subsequently died because of further complications (multi-organ failure and hydrocephalus) with no evidence of further relapse; these have to be considered treatment-related deaths (13%). The rate of symptomatic radiation necrosis observed in our study appears to be remarkably higher than that reported by Tatter *et al.*¹⁹, Chan *et al.*²⁰, and Gabayan *et al.*²¹ accounting for 0%, 8.3%, and 2.8% respectively.

Despite the use of a radiation dose of 4500 cGy, 54.5% of relapses occurred within 1 cm of the surgical cavity wall, thus suggesting that this dose is inadequate to sterilize any neoplastic foci in the surgical bed. Median disease-free survival indicates that 50% of tumor recurrences after GliSite treatment occur within 7 months from brachytherapy and that all documented recurrences occurred within 12 months. Overall survival after GliSite brachytherapy (13 months) is comparable to that reported by Tatter *et al.*¹⁹ (12.7 months), but more favorable than that reported by Gabayan *et al.*²¹ (8.5 months) and Chan *et al.*²⁰ (9.3 months; all patients with glioblastoma multiforme).

Survival in our patients can be reasonably compared to that reported by Brem *et al.*¹⁸ with surgery plus carmustine wafers (median overall survival, 7.2 months). To our knowledge, this is the only randomized study that compares surgery alone *versus* a combined treatment, and which also demonstrates the advantage of a combined treatment over surgery alone.

It should be noted that overall survival in the present study is comparable to that reported in our previous experience with surgery, when feasible, and EBRT combined with oral lomustine (median overall survival, 13.7 months)⁶, in which only 50% of patients underwent surgical resection.

Conclusions

Patients with resectable local relapse from HGG can be treated with surgery and brachytherapy with the GS-RTS, delivering a dose of 4500 cGy at 1 cm depth without any significant acute side effect. However, symptomatic radiation necrosis appears to be a main late side effect in as many as 20% of patients, resulting in 13% of treatment-related deaths. In addition, the rate of local relapse in the brain tissue within 1 cm of the cavity wall remains as high as 54.5% of all documented subsequent relapses.

Relapsed HGG have an ominous prognosis, and the median overall survival of 13 months obtained in our study appears to be a positive outcome compared with the findings reported in the literature. However, whether this result is ascribable to the eligibility criteria (KPS ≥ 70), resulting in a favorable selection of patients, is an issue that cannot be addressed by the present study. It should be noted that we obtained a comparable median overall survival in our previous study with surgical resection (when feasible) followed by EBRT plus concomitant oral carmustine, which was, in fact, a less demanding and less expensive treatment. From the patient's point of view, a "single shoot" brachytherapy might be a favorite option compared with multi-fractionated EBRT.

However, in our experience, GliSite brachytherapy was associated with a higher risk of symptomatic radiation necrosis as well as higher costs for the healthcare facility. In our opinion, although we observed a modest improvement in survival compared with the results reported in the literature, surgery plus GliSite brachytherapy cannot be recommended as a routine treatment in HGG relapsed after surgery plus EBRT, but it should be considered only in selected cases.

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