3D Conformal Radiotherapy and Cisplatin for Recurrent Malignant Glioma

Lauren VanderSpek, Barbara Fisher, Glenn Bauman, David Macdonald

ABSTRACT: **Purpose:** To determine the maximum tolerated dose of 3D conformal radiotherapy in combination with Cisplatin for patients with recurrent malignant gliomas. **Methods:** From 1999-2003, nine patients with recurrent malignant glioma received fractionated radiotherapy and Cisplatin (20 mg/m²/d IV on days 1-5) in a Phase I radiation dose escalation trial. Three sequential dose levels were evaluated: 25 Gy, 30 Gy, and 35 Gy, using 5 Gy fractions. All patients received prior external beam radiation (median dose 59.4 (20-60) Gy) and five patients received prior chemotherapy. **Results:** Six male and three female patients were enrolled with a median age of 52 years, and a median Karnofsky performance status score of 70. The median re-irradiated tumor volume was 18.9 (0.1-78.5) cm³ and the median follow-up was 8.8 (3.2-31.2) months. One patient (30 Gy/6 fractions) experienced medically reversible acute grade 3 toxicity. A second patient (35 Gy/7 fractions) experienced acute grade 2 toxicity and histology showed tumor and radiation effect. A third patient (25 Gy/5 fractions) experienced late grade 3 toxicity from radiation necrosis. The radiological responses consisted of complete response (1 patient), partial response (1 patient), and stable disease (2 patients). The median overall survival was 8.8 months (95% CI 8.0-9.9), and the median disease free interval was 2.0 months (95% CI 1.4-4.4). Seven patients received chemotherapy following re-irradiation and Cisplatin. **Conclusion:** The maximum tolerated dose of 3D conformal fractionated radiotherapy was 30 Gy in 6 fractions with low dose Cisplatin, which was well tolerated in terms of acute toxicity for our patient population. This regimen demonstrated only modest efficacy in the treatment of recurrent malignant glioma. Combinations of conformal re-irradiation and other systemic agents may merit investigation. Currently our recommended dose is 30 Gy in 6 fractions for selected patients.

RÉSUMÉ: Radiothérapie conformationnelle 3D et cisplatine dans le traitement de la récidive du gliome malin. **But :** Il s’agit d’une étude visant à déterminer la dose maximale tolérée de radiothérapie conformationnelle 3D en combinant avec l’administration de cisplatine chez les patients qui présentent une récidive de gliome malin. **Méthodes :** Neuf patients présentant une récidive d’un gliome malin ont reçu de la radiothérapie fractionnée et du cisplatine (20 mg/m²/j IV les jours 1 - 5) au cours d’une étude clinique de phase I à dose croissante. Trois niveaux séquentiels de doses ont été évalués : 25 Gy, 30 Gy et 35 Gy, en fractions de 5 Gy. Tous les patients avaient reçu précédemment de la radiothérapie externe (dose médiane 59,4 Gy ; écart de 20 à 60 Gy) et cinq patients avaient reçu de la chimiothérapie. **Résultats :** Six hommes et trois femmes, dont l’âge médian était de 52 ans et le score médian à l’échelle de Karnofsky était de 70, ont été inclus dans l’étude. Le volume médian de la tumeur réirradiée était de 18,9 cm³ (0,1 à 78,5 cm³) et la durée médiane du suivi était de 8,8 mois (3,2 à 31,2 mois). Un patient, qui avait reçu 30 Gy/6 fractions, a présenté une toxicité aiguë de grade 3 réversible avec le traitement médical. Un second patient, qui avait reçu 35 Gy/7 fractions, a présenté une toxicité aiguë de grade 2 et à l’examen anatomopathologique on a constaté des phénomènes liés à la tumeur et à l’irradiation. Un troisième patient, qui avait reçu 25 Gy/5 fractions, a présenté une toxicité tardive de grade 3 causée par la nécrose due à l’irradiation. Les réponses radiologiques étaient les suivantes : réponse complète (1 patient), réponse partielle (1 patient) et maladie stable (2 patients). La survie globale médiane était de 8,8 mois (IC de 95% : 8,0 à 9,9), et la survie médiane sans récidive était de 2,0 mois (IC de 95% : 1,4 à 4,4). Sept patients ont reçu de la chimiothérapie après la réirradiation et du cisplatine. **Conclusion :** La dose maximale tolérée de radiothérapie conformationnelle 3D était de 30 Gy en 6 fractions associée à du cisplatine à faible dose. Ce traitement a été bien toléré en ce qui concerne la toxicité aiguë chez nos patients. Ce régime de traitement s’est avéré modestement efficace dans le traitement de la récidive du gliome malin. La combinaison de réirradiation conformationnelle à d’autres agents systémiques mérite d’être étudiée. Nous recommandons actuellement la dose de 30 Gy en 6 fractions chez des patients sélectionnés.


Malignant gliomas present therapeutic challenges due to their location, aggressive biologic behavior and diffuse, infiltrative growth. Median survival after initial treatment is approximately 10-15 months for glioblastoma multiforme (GBM), and 40-50 months for anaplastic astrocytoma and anaplastic oligodendrogliomas. Recurrences occur within 2 cm of the original lesion in approximately 90% of cases after whole-brain radiation, and up to 100% of cases after 3-D conformal...
Radiation. At the time of relapse, median survival with supportive care alone is approximately two months.

Treatment options at the time of recurrence include surgery, chemotherapy, stereotactic radiosurgery (SRS) or 3D CRT, and brachytherapy. A systematic review of 1415 patients with recurrent high-grade astrocytomas treated with a variety of treatment modalities showed a median survival of 28 weeks with a median time to further progression of 14 weeks. The rate of radiation necrosis has been reported as high as 20% for SRS and ranging from 4-40% for stereotactic radiotherapy (SRT) or 3D CRT.

The addition of chemotherapy to radiation treatment of recurrent malignant glioma is another treatment strategy. Cisplatin has been evaluated as a radiosensitizer in several tumor types, such as anal, cervical, head and neck, and bladder cancers. Weekly Cisplatin with external beam radiotherapy has been shown to be tolerated for treatment of malignant brain tumors. Cisplatin at a dose of 20mg/m²/day x 5 days together with 125I implants also has acceptable toxicity. For the current study, a dose of Cisplatin 20mg/m²/day IV on days 1-5 of radiation was chosen based on these demonstrated tolerances in the literature.

To determine the maximum tolerated dose of radiation when in combination with Cisplatin for treatment of recurrent malignant glioma, a dose escalation schedule for this study was based on Shepherd et al who treated 29 patients with high-grade glioma to doses ranging from 20-50 Gy in 5 Gy/fraction. A total dose of ≥40 Gy was found to be a major predictor of radiation damage (p < 0.005). In the current study three sequential dose levels were evaluated: 25 Gy, 30 Gy, and 35 Gy, using 5 Gy per fraction.

**Methods**

**Patient and tumor characteristics**

From March 1999 to June 2003, nine patients with recurrent malignant glioma received fractionated radiotherapy and low-dose Cisplatin in an Institutional Review Board approved Phase I radiation dose escalation trial at the London Regional Cancer Program. Tumor progression following initial treatment was documented by imaging characteristics in all cases and also with histology in three patients. The patient and tumor characteristics are shown in Table 1.

The most recent histology prior to re-irradiation was as follows: GBM (six patients), AA (one patient), and mixed anaplastic glioma (two patients). Initial surgery consisted of partial resection (two patients) and gross total resection (six patients), and one patient had a biopsy at recurrence. Multiple resections were performed in three patients. All patients previously received fractionated external beam radiation with a median dose of 59.4 Gy (range 20–60 Gy). The median interval from completion of initial radiotherapy to the start of re-irradiation was nine months (range 2-93 months). Five patients received prior chemotherapy: PCV (Procarbazine, Lomustine, Vincristine) (two patients), modified PCV (one patient), Temozolomide (two patients), Topotecan (one patient), SU101 (one patient) and Marimastat (one patient).

Patients were enrolled on the study if they had histological confirmation of malignant glioma and radiological (CT/MRI) evidence of recurrence/progression and met the following additional criteria: (1) Karnofsky Performance Score (KPS) ≥ 50; (2) neurological function status 0-3; (3) no cytotoxic chemotherapy < 1 month prior to protocol therapy; (4) age ≥ 18 years; (5) absolute neutrophils ≥ 1500/mm³, platelets ≥ 100,000/mm³, BUN ≤ 30 mg, creatinine ≤ 1.8 mg, bilirubin ≤ 2 mg, serum glutamate pyruvate transaminase (SGPT) or serum glutamic-oxaloacetic transaminase (SGOT) ≤ 2 x upper limit of normal (ULN); (6) prior external beam radiation ≥ 2 months prior to re-treatment; and (7) recurrent tumor diameter < 6 cm. Patients with brainstem tumors (midbrain, pons, medulla), multiple intracranial lesions, no measurable tumor, leptomeningeal metastases or subependymal spread were excluded.

**Study endpoints**

Central nervous system (CNS) toxicity was defined as the development of any new treatment-related neurological symptoms or signs (± CT and/or MRI abnormalities) following the radiation treatment that were felt attributable to the treatment. Toxicities were scored according to the Radiation Therapy Oncology Group (RTOG) CNS toxicity subscale. For each dose level, an observed rate of ≥ 25% grade ≥ 3 acute, medically irreversible, CNS toxicity was considered unacceptable and would result in suspension of accrual and the previous dose would be accepted as the maximally tolerated dose. Acute toxicity was within 90 days from the start of re-irradiation. Radiological response was defined by the Macdonald criteria: complete response was disappearance of all clinical
evidence of tumor, determined by two observations ≥ 4 weeks; partial response was ≥ 50% reduction in the volume of the lesions for ≥ 4 weeks duration; stable disease was response < 50% or progression < 25% for ≥ 4 weeks duration; progressive disease was unequivocal increase in the volume of the tumor of ≥ 25%. Clinical response consisted of either an objective improvement in neurological status or no neurological deterioration with a stable or decreasing steroid dose. There must also have been stable or regressing tumor on imaging.

Survival was determined from the start of re-irradiation to the date of death. Progression free interval was also determined from the start of re-irradiation to the time of clinical recurrence. Survival curves were calculated by the method of Kaplan and Meier.31

All patients registered for the study were included in the analysis, with none being lost to follow-up. No patient died or withdrew from the study prior to treatment completion.

**Treatment planning and delivery**

Informed written consent was obtained from all study patients. Each patient was positioned and immobilized with an individualized thermoplastic mask with treatment planning CT slices ≤ 0.5 cm through the regions of interest. Gross tumor (GTV), clinical (CTV), and planning (PTV) target volumes were defined based on the treatment planning CT, with registration to MRI when possible, in accordance with the 1993 International Commission on Radiation Units and Measurements (ICRU).32

Treatment was delivered to the PTV by fields determined by 3-D planning to produce the optimal conformal plan. The use of beam intensity modulation was not allowed (except for wedges, compensating filters, and static beam shaping devices such as multileaf collimators [MLC]).

Treatment was delivered using daily fractions of 5 Gy for all patients. Three sequential dose levels were evaluated: 25 Gy (four patients), 30 Gy (three patients), and 35 Gy (two patients). Treatment details are shown in Table 2.

Cisplatin was administered as an intravenous infusion over 30-40 minutes at a dose of 20 mg/m² daily on radiation treatment days 1-5. The average time between chemotherapy and radiation was 56 minutes (range 10 minutes to 2 hours and 45 minutes), though data was incomplete for three patients. There was no dose escalation of Cisplatin. None of the patients required dose modification, which was based on absolute neutrophil count, and all patients received the full course of Cisplatin.

**RESULTS**

**Acute Toxicity**

All patients received the scheduled treatment except one patient without toxicity who declined the final of six fractions.

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**Table 2: Treatment parameters and outcome**

<table>
<thead>
<tr>
<th>Patient</th>
<th>KPS</th>
<th>NF</th>
<th>Treatment prior to relapse</th>
<th>Surgery at relapse</th>
<th>Reirradiation schedule</th>
<th>Treatment post study</th>
<th>PFI (mo)</th>
<th>OS (mo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>80</td>
<td>1</td>
<td>Total resection RT (60 Gy/30 fractions) Topotecan, SU101</td>
<td>Partial resection</td>
<td>25 Gy/5 fractions</td>
<td>PCV, Temozolomide</td>
<td>0.8</td>
<td>8.6</td>
</tr>
<tr>
<td>2</td>
<td>80</td>
<td>2</td>
<td>Total resection RT (60 Gy/30 fractions) Marimastat</td>
<td>No</td>
<td>25 Gy/5 fractions</td>
<td>PCV</td>
<td>1.4</td>
<td>8.8</td>
</tr>
<tr>
<td>3</td>
<td>70</td>
<td>2</td>
<td>Total resection (x 2) RT (59.4 Gy/33 fractions) Modified PCV</td>
<td>No</td>
<td>25 Gy/5 fractions</td>
<td>Partial resection</td>
<td>31.2*</td>
<td>31.2</td>
</tr>
<tr>
<td>4</td>
<td>70</td>
<td>1</td>
<td>RT (20 Gy/5 fractions, whole brain)</td>
<td>Biopsy</td>
<td>25 Gy/5 fractions</td>
<td>Lomustine</td>
<td>1.3</td>
<td>8.0</td>
</tr>
<tr>
<td>5</td>
<td>70</td>
<td>1</td>
<td>Total resection RT (60 Gy/30 fractions)</td>
<td>No</td>
<td>30 Gy/6 fractions</td>
<td>Lomustine</td>
<td>4.7</td>
<td>9.9</td>
</tr>
<tr>
<td>6</td>
<td>70</td>
<td>2</td>
<td>Partial resection (x 3) RT (54 Gy/30 fractions) PCV, Temozolomide</td>
<td>Ommaya reservoir insertion</td>
<td>30 Gy/6 fractions</td>
<td>Etoposide</td>
<td>1.7</td>
<td>3.2</td>
</tr>
<tr>
<td>7</td>
<td>80</td>
<td>1</td>
<td>Total resection RT (60 Gy/30 fractions)</td>
<td>No</td>
<td>30 Gy/6 fractions</td>
<td>Temozolomide, Etoposide</td>
<td>2.1</td>
<td>9.7</td>
</tr>
<tr>
<td>8</td>
<td>100</td>
<td>0</td>
<td>Partial resection (x 2) RT (54 Gy/30 fractions) PCV, Temozolomide</td>
<td>Total resection</td>
<td>35 Gy/7 fractions</td>
<td>Partial resection Etoposide, Tamoxifen</td>
<td>2.0</td>
<td>14.1</td>
</tr>
<tr>
<td>9</td>
<td>70</td>
<td>2</td>
<td>Total resection RT (60 Gy/30 fractions)</td>
<td>No</td>
<td>35 Gy/7 fractions</td>
<td>No</td>
<td>4.4</td>
<td>5.0</td>
</tr>
</tbody>
</table>

* this patient had radionecrosis and no objective relapse. KPS (Karnofsky Performance Status), NF (Neurologic Function), RT (radiation therapy), PCV (Procarbazine, Lomustine, Vincristine), PFI (progression free interval), OS (overall survival), MO (months)
This patient was replaced at the 30 Gy level. One patient treated with 30 Gy in six fractions experienced acute grade 3 toxicity with decreased level of consciousness six days after the first re-irradiation fraction. The patient had an Ommaya reservoir that required drainage prior to and during treatment, which improved her level of consciousness. One patient treated with 35 Gy in seven fractions had acute grade 2 toxicity at 60 days after the first re-irradiation fraction (word-finding difficulties and slurred speech). This patient underwent partial resection and tumor as well as radiation effect was seen on histology. The study was terminated at the 35 Gy level due to the radiation effect seen on histology.

Late Toxicity

A patient who received 25 Gy in five fractions experienced grade 3 confusion and weakness with falls on day 21 after the initial re-irradiation fraction. Increased steroid initially stabilized the patient’s neurological function. Surgery was performed 7.4 months after the initial re-irradiation fraction and radiation induced necrosis with scant residual treated glioma was reported. This patient survived 31 months from the start of re-irradiation with no equivocal tumor recurrence.

Response

Radiological response according to the Macdonald criteria consisted of complete response (one patient), partial response (one patient), stable disease (two patients) and progression (five patients). The patient with the complete response developed late radiation necrosis. The patient with the partial response on imaging was clinically worsened due to the steroid itself. The clinical response for the two patients with stable disease on imaging consisted of neurological improvement in one patient for four months with no steroid prescribed, and stable neurological symptoms with decreased steroid requirement for three months, respectively.

The median follow-up was 8.8 months (3.2-31.2) from the start of re-irradiation. The median overall survival was 8.8 months (95% CI 8.0-9.9) (Figure 1), and the median disease free interval was 2.0 months (95% CI 1.4-4.4) (Figure 2). All patients were deceased at the time of analysis.

Additional therapy

Seven patients were treated with further chemotherapy consisting of PCV (two patients), single agent Lomustine (two patients), Etoposide (three patients), Temozolomide (two patients), and Tamoxifen (one patient).

DISCUSSION

Recurrent malignant gliomas continue to have a poor prognosis with modest response to various surgical and radiation techniques. Dose escalation studies for initial radiation have shown no significant increase in morbidity with conformal fields up to doses of >70 Gy but series evaluating escalating doses up to 80-90 Gy in limited volumes have not improved local control. The treatment strategy in this study was to add low dose Cisplatin (20 mg/m²) IV daily on re-irradiation treatment days 1-5 to a dose escalation regimen based on the dose escalation study by Shepherd et al. The addition of chemotherapy to radiation for the treatment of recurrent malignant glioma has been described in the literature for several chemotherapeutic agents (Table 3).

In the Shepherd study, a total dose of > 40 Gy was a significant predictor of radiation damage. The median survival was 11 months for 32 patients with recurrent high-grade glioma (including three patients with high grade oligodendroglia)
Table 3: Re-irradiation with chemotherapy series

<table>
<thead>
<tr>
<th>Author</th>
<th>n</th>
<th>Histology (n)</th>
<th>Median Radiation Dose and Schedule</th>
<th>Chemotherapy</th>
<th>Median Survival (months)</th>
<th>Progression-Free Survival (months)</th>
<th>Graded Toxicity / Radiation Necrosis (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arcicasa</td>
<td>24</td>
<td>High-grade glioma (24)</td>
<td>34.5 Gy/1.5 Gy per day/5 days per week</td>
<td>Lomustine</td>
<td>13.7</td>
<td>8.4</td>
<td>G4 thrombocytopenia (1) G3 leucopenia (3)</td>
</tr>
<tr>
<td>Larson</td>
<td>26</td>
<td>GBM (14) AA (8) AO (1) Malignant glioma (3)</td>
<td>16.5 Gy to the prescription isodose</td>
<td>Marimastat</td>
<td>17 (grade 3) 9.5 (grade 4)</td>
<td>7.8 (grade 3) 3.8 (grade 4)</td>
<td>G3 MSK (2) G3 thrombocytopenia (4) G3-4 leukopenia (3) Radiation necrosis (3)</td>
</tr>
<tr>
<td>Glass</td>
<td>20</td>
<td>Malignant astrocytoma: Grade 3 (7) Grade 4 (13)</td>
<td>42 Gy/6 Gy once-twice per week</td>
<td>Cisplatin</td>
<td>13.8</td>
<td>4.6</td>
<td>Radiation necrosis (7)</td>
</tr>
<tr>
<td>Lederman</td>
<td>88</td>
<td>GBM</td>
<td>24 Gy/6 Gy per week x 4</td>
<td>Paclitaxel</td>
<td>7.0</td>
<td>Not reported</td>
<td>Radiation necrosis (7)</td>
</tr>
<tr>
<td>Schafer</td>
<td>14</td>
<td>GBM (5) AA (7) High-grade oligodendroglia (2)</td>
<td>30 Gy/2 Gy per day/5 days per week</td>
<td>Temozolomide</td>
<td>7.5</td>
<td>5.0</td>
<td>Mental degradation (1) Severe cephalgia (1) No late toxicities reported</td>
</tr>
<tr>
<td>Schonekaes</td>
<td>25</td>
<td>High-grade glioma (25)</td>
<td>20-30 Gy (2 x 1.2 Gy per day)</td>
<td>Temozolomide</td>
<td>9.3</td>
<td>7.0</td>
<td>No G3-4 toxicity</td>
</tr>
<tr>
<td>Current Study</td>
<td>9</td>
<td>GBM (6) AA (1) Mixed anaplastic glioma (2)</td>
<td>30 Gy/5 Gy per day/5 days per week</td>
<td>Cisplatin</td>
<td>8.8</td>
<td>2.0</td>
<td>G3 CNS toxicity (2) (One patient had radiation necrosis)</td>
</tr>
</tbody>
</table>

GBM (glioblastoma multiforme), AA (anaplastic astrocytoma), AO (anaplastic oligodendroglia), G3 (grade 3 toxicity), G4 (grade 4 toxicity), MSK (musculoskeletal), CNS (central nervous system)

As pointed out by Ernst-Stecken et al., reliable data on the effects of hypofractionated SRT for recurrent glioma on both tumor and normal tissue is limited, whereas in SRS the tolerance doses have been described. For larger volume recurrences, hypofractionated SRT may result in higher efficacy than standard fractionation by the use of relatively high single doses. SRT has also been shown to have a lower risk of late complications as compared to SRS.

Late effects from radiation therapy correlate with cumulative radiation dose, fractionation, treatment volume, patient age, and use of chemotherapy. For conventional fractionated radiotherapy, the radiation dose associated with a 5% probability of radiation necrosis (TD5) is estimated to be between 45-60 Gy. There is no concise data on recovery of normal brain tissue after radiation, however, it has been suggested that there is a ‘remembrance’ of approximately 50% of the dose by 1-2 years after the original radiation. In regard to SRS, there is an inverse relationship between the volume irradiated and the total radiation dose such that as the volume of irradiated tissue increases, the dose that results in radiation necrosis decreases. In clinical practice, this inverse relationship may not be apparent because of the concern of late effects may prompt physicians to decrease dose and/or volumes to avoid complications. Radiation Therapy Oncology Group 94-11 tested the hypothesis that...
radiation therapy of smaller volumes would allow the safe administration of higher doses of radiation compared to patients with large volumes of tumor.\textsuperscript{51} There was a trend toward increased survival with higher radiation dose in recursive partitioning analysis Class III/IV patients, but this may be due to smaller tumor sizes in that arm of the trial. Retrospective data shows better outcomes with smaller tumors post surgery\textsuperscript{29,52} and similarly, tumors ≤ 4 cm that are eligible for SRS have a better prognosis.\textsuperscript{28,53} Lead-time and length bias are also issues with smaller tumors.\textsuperscript{28} In our study tumors greater than 6 cm were excluded to minimize potential late toxicity and this may have influenced the modest effect of the treatment.

For newly diagnosed GBM the standard of care is concurrent radiation with oral Temozolomide followed by adjuvant Temozolomide.\textsuperscript{10,54-56} For recurrent malignant glioma, however, there is no consensus regarding salvage chemotherapy.\textsuperscript{10}

Cisplatin increases the slope of radiation dose-response curves in mammalian cells \textit{in vitro} and inhibit repair of sublethal radiation damage\textsuperscript{57} and enhances radiation effect \textit{in vivo}.\textsuperscript{57-60} Cisplatin has also been shown to radiosensitive human glioma cell lines with a dose-modifying factor of 1.2-1.7.\textsuperscript{61} Penetration of Cisplatin through the blood-brain barrier is limited due to the size of the molecule.\textsuperscript{62} Thompson found that the concentration of Cisplatin was 0.17 $\mu$g/kg in brain tissue in three patients who received Cisplatin 50 mg/m$^2$ monthly, which is felt by Sheleg\textsuperscript{62} to be insufficient for achieving an antitumor effect.\textsuperscript{63} Other authors argue that concentrations of Cisplatin as low as 1 $\mu$g/ml are radiopotentiating and that intracerebral concentrations of platinum in this range are attained with doses of 20 to 25 mg/m$^2$.\textsuperscript{64} Following intravenous administration of Cisplatin, Stewart found low concentrations of platinum in normal brain parenchyma, but high concentrations in intra-cerebral tumor and the surrounding edema. This difference was attributed to disruption of the blood-brain barrier within the tumor vasculature.\textsuperscript{64} In the current study, Cisplatin did not appear to provide significant radiosensitization. Glass demonstrated similar results with weekly Cisplatin (40 mg/m$^2$) and external beam radiotherapy for the treatment of malignant brain tumors in a study of 20 patients with recurrent, progressive or persistent malignant astrocytoma, with SRT once or twice weekly.\textsuperscript{15} There was manageable acute toxicity and one patient had a partial response, eleven had stable disease, and eight patients progressed. Surgery was required in five patients for either tumor progression or radiation necrosis. Median survival for all patients was 55 weeks and the median response duration was 18.5 weeks. Median survival was 8.5 months for a subgroup with an interval of ten weeks or more between initial EBRT and SRT, whereas median survival for a subgroup treated at less than a ten week interval for progression or potential for tumor progression based on SPECT imaging was 16.6 months.

Investigation into combinations of other systemic agents with conformal re-irradiation may be merited. Targeted therapies currently under investigation for recurrent high-grade gliomas may also merit investigation in the future in combination with radiotherapy. For example, the epidermal growth factor receptor (EGFR) inhibitor, Gefitinib (ZD1839 or Iressa), has demonstrated a median survival for patients with recurrent GBM or 39.4 weeks after first relapse.\textsuperscript{10,65} Thalidomide was well tolerated and median survival was 28 weeks in a phase II study for patients with recurrent high-grade glioma.\textsuperscript{10,66} Alternate forms of delivery of chemotherapy, such as the placement of Gliadel Wafers (MCI Pharma Inc, Bloomington, MN),\textsuperscript{10,67} may also provide novel approaches to treatment in combination with radiation.

The maximum tolerated dose of 3D conformal fractionated radiotherapy was 30 Gy in six fractions with low dose Cisplatin, which was well tolerated in terms of acute toxicity for our patient population. There is a risk of late radiation necrosis in long-term survivors and the rate of radiation necrosis in this study is comparable to other salvage regimens in the literature. The regimen demonstrated only modest efficacy in the treatment of recurrent malignant glioma. Currently at our centre re-irradiation is offered to patients with a good performance status, a long interval from previous radiation, for which surgery is not an option, and chemotherapy or a clinical trial have been refused or are unavailable. The recommended dose is 30 Gy in six fractions. Combinations of conformal re-irradiation and other systemic agents may merit investigation.

**Acknowledgement**

The authors thank Frances Whiston for all of her work with the statistics.

**References**


4. Hochberg FH, Pruitt A. Assumptions in the radiotherapy of cerebraltumor and the surrounding edema. Thisdifference was felt by Sheleg\textsuperscript{62} to be insufficient for achieving anantitumor effect.\textsuperscript{63} Other authors argue that concentrations of Cisplatin as low as 1 $\mu$g/ml are radiopotentiating and that intracerebral concentrations of platinum in this range are attained with doses of 20 to 25 mg/m$^2$.\textsuperscript{64}


