

Concurrent Hypofractionated Three-dimensional Re-irradiation and Temozolomide in Recurrent Malignant Glioma

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Abstract

Background: This study determines the efficacy and tolerability of hypofractionated three-dimensional conformal radiotherapy in conjunction with daily temozolomide in treatment of previously irradiated recurrent malignant glioma.

Methods: We enrolled 21 patients diagnosed with recurrent or progressive malignant glioma who previously underwent external beam irradiation. All patients had hypofractionated three-dimensional conformal radiotherapy to a total dose of 30 Gy in six fractions, over a two-week period, concurrent with daily temozolomide (75 mg/m²).

Results: At the median follow up of 9.5 months (range: 2.5-42), there were 18 (86%) patients who had died. Median overall survival from the onset of hypofractionated three-dimensional conformal radiotherapy was nine months and median time to progression was five months. There was no detectable severe toxicity. Salvage surgery prior to hypofractionated three-dimensional conformal radiotherapy and planning target volume significantly influenced patient outcome according to multivariate analysis.

Conclusion: Hypofractionated conformal re-irradiation concurrent with daily temozolomide is a feasible, well-tolerated treatment for recurrent malignant glioma. Patients with surgical re-resection and smaller planning target volumes have the most favorable outcomes.

Keywords: Recurrent malignant glioma, Hypofractionated re-irradiation, Temozolomide

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Introduction

Malignant gliomas are the most frequently diagnosed primary brain tumors in adults.¹ Despite recent advances in neuroimaging, surgical techniques, postoperative external beam radiotherapy, and

chemotherapy,²⁻⁵ malignant gliomas still have dismal prognoses and the vast majority of patients experience local recurrence at some point in time during their follow up.⁶⁻⁸

Currently there is no standard treatment for recurrent malignant

gliomas. Treatment options include surgical resection,^{9,10} systemic chemotherapy,^{11,12} and radiation therapy.¹³⁻¹⁶

In the past, re-irradiation as a salvage treatment option was limited by severe treatment-related toxicities to surrounding normal brain tissues.¹⁷ Subsequently, several studies have proposed that re-irradiation may not be followed by the high incidence of side effects as feared. When certain treatment volume and dose limits are respected, re-irradiation appears to be associated with acceptable toxicities.^{4, 14-18} Nevertheless, there is still no general agreement on which radiation technique and fractionation is most appropriate, and the choice often depends upon the radiotherapy options available to the treating physician.¹⁹ Radiotherapeutic options for recurrent gliomas include single fraction stereotactic radiosurgery (SRS), fractionated stereotactic radiotherapy (SRT), brachytherapy, and three-dimensional conformal radiation therapy (3D-CRT).⁴

The objective of this study was to determine the efficacy and toxicity of hypofractionated 3D-CRT (H3D-CRT) in conjunction with daily temozolomide for treatment of recurrent malignant gliomas.

Patients and Methods

This study was conducted in the Department of Clinical Oncology and Nuclear Medicine and Neurosurgery, Mansoura University Hospital, Egypt. (Study protocol approved by local Institutional Review Board).

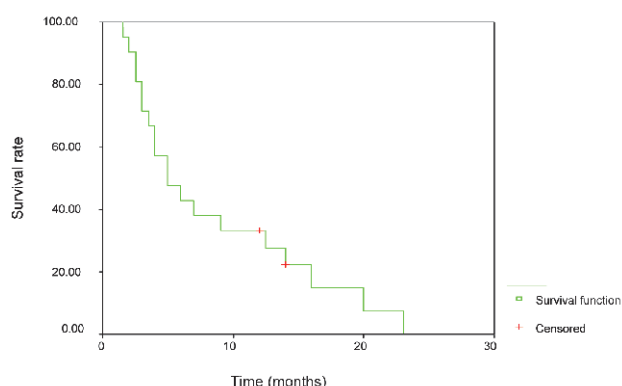


Figure 1. Time to progression (TTP) from onset of re-irradiation.

Inclusion criteria

Included, patients had histologically proven supratentorial malignant gliomas that recurred or progressed after initial treatment as identified by characteristics of tumor progression visualized on subsequent follow up imaging (CT and/or MRI) studies, either with or without histological confirmation of progression. Other criteria included: age >18 years, Karnofsky performance score (KPS) ≥ 60 , adequate hematologic function (neutrophils $\geq 1500/\text{m}^3$, hemoglobin ≥ 10 gm/dl, and platelets $\geq 100,000/\text{mm}^3$), adequate renal function (serum creatinine ≤ 1.5 mg/dl), adequate liver function [serum bilirubin, serum glutamate pyruvate transaminase (SGPT), serum glutamic oxalacetic transaminase (SGOT), all $\leq 1.5 \times$ the upper limit of normal (ULN)], prior external beam irradiation ≥ 6 months, and tumor volume that could be included within a 10×10 field. Eligible patients were required to sign informed consents regarding the study treatment.

Exclusion criteria

Patients were excluded if they had evidence of tumor infiltration into the brain stem, corpus callosum, ventricles, contralateral site, multiple intracerebral lesions or leptomeningeal metastases.

Treatment planning

An individual immobilization thermoplastic mask was manufactured for each patient with treatment planning post-contrast CT brain scans obtained at every 3 mm slices. Gross target volume (GTV) was defined by the contrast enhanced

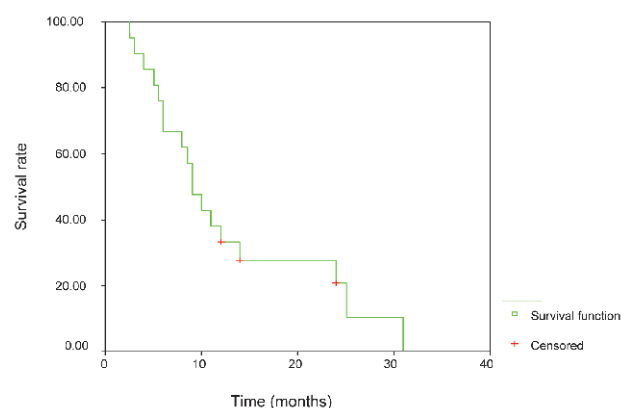


Figure 2. Overall survival (OS) from the onset of re-irradiation.

Table 1. Patient characteristics.

| Characteristics | | N | (%) |
|--|-------------------------------|------------|------|
| Age (years) | Median: | 50 | |
| | Range | 22-68 | |
| Sex | | | |
| | Male | 12 | 57.1 |
| | Female | 9 | 42.9 |
| Karnofsky Performance status (KPS) | Median: | 80 | |
| | Range: | 60-100 | |
| Initial surgery | | | |
| | Gross total resection | 10 | 47.6 |
| | Partial resection | 8 | 38.1 |
| | Biopsy | 3 | 14.3 |
| Initial histopathology | | | |
| | Astrocytoma II | 5 | 23.8 |
| | Astrocytoma III | 6 | 28.6 |
| | Oligodendroglioma III | 1 | 4.7 |
| | Glioblastoma multiforme (GBM) | 9 | 42.9 |
| Adjuvant chemotherapy | | | |
| | PCV | 10 | 47.6 |
| | Temozolomide | 2 | 9.5 |
| Salvage surgery | | | |
| | Gross total resection | 4 | 19.0 |
| | Partial resection | 7 | 33.3 |
| | Biopsy | 2 | 9.5 |
| Recent histology | | | |
| | Astrocytoma III | 6 | 28.6 |
| | Glioblastoma multiforme (GBM) | 15 | 71.4 |
| Salvage chemotherapy | | | |
| | PCV* | 5 | 23.8 |
| | Temozolomide | 7 | 33.3 |
| | ICE* | 2 | 9.5 |
| Reirradiation PTV (cm³) | Median: | 67.4 | |
| | Range: | 15 – 137.5 | |
| Interval from primary radiation to reirradiation (months) | Median: | 13 | |
| | Range: | 7 – 69 | |

*PCV: Procarbazine, lomustine, and vincristine ICE: Ifosfamide, Carboplatin, and Etoposid.

tumor edge on the planning CT. Planning target volume (PTV) was defined as GTV plus a margin of 5 mm. In patients with resection, the pretreatment enhancing tumor volume was used for treatment planning.

Treatment was delivered with 6 MV photon energy from an ELEKTA linear accelerator. Treatment planning was three-dimensional in order to deliver an optimal conformal plan prescribed to the 95% isodose line of the PTV. A total dose of 30 Gy in six fractions over a two-

week period was delivered with concomitant daily temozolomide (75 mg/m²) administered within two hours before radiotherapy. Complete blood counts were performed weekly during treatment. All patients had prophylactic treatment for brain edema, in the form of daily doses of dexamethasone (16 mg, qd).

Post-treatment evaluation

All patients were assessed clinically and radiologically with CT and/or MRI brain scans at

6 to 12 weeks after radiotherapy, then at three-month intervals thereafter. Response was defined by the Macdonald criteria.²⁰

Toxicity was evaluated at every follow up visit and any adverse event that included worsening of neurological status was reported and scored according to Radiation Therapy Oncology Group (RTOG) toxicity criteria.²¹

Statistical analysis

Overall survival (OS) was measured from the first day of H3D-CRT to the date of death or last follow up. Time to progression (TTP) was measured from first day of H3D-CRT to the time of radiologically proven tumor progression. Survival curves of these intervals were calculated using the Kaplan-Meier method. We evaluated the impact of prognostic factors on survival by conducting log-rank tests for univariate analysis and the Cox regression model for multivariate analysis. Significance level was $P < 0.05$. We used SPSS software program version 10 for statistical analyses.

Results

Between January 2009 and June 2011, we included 21 patients with recurrent high grade glioma in this study. No patient died or withdrew from the study prior to treatment completion. Patients' characteristics are listed in Table 1. The median age was 50 years (range: 22-68). The initial histology was astrocytoma (grade II) in 5

patients, astrocytoma and oligodendroglioma (grade III) in 7 patients, and glioblastoma multiforme [grade IV; (GBM)] in 9 patients. At the time of re-irradiation, there were 6 patients with astrocytoma and 15 patients who had GBM. Initial surgical intervention was as follows: gross total resection in 10 patients, partial resection in 8, and 3 patients only underwent biopsies. Prior to re-irradiation, 13 patients underwent additional surgery which consisted of complete resection in 4 patients, partial in 7 and biopsy in 2 patients. All patients underwent pretreatment with post-operative involved field conventionally fractionated radiotherapy to a median dose 60 Gy (range: 54-60) at least six months before H3D-CRT. Twelve patients received prior adjuvant chemotherapy and 14 received salvage chemotherapy. The most common chemotherapy protocols were procarbazine, lomustine, and vincristine (PCV) in 15 patients and temozolomide in 9 patients.

Treatment toxicity

Hypofractionated 3-DCRT was well tolerated. All patients completed the scheduled radiation without interruption and no patients developed severe acute toxicities. Experienced toxicities included mild to moderate headaches in five patients, three developed temporary attacks of focal convulsions that were controlled by antiepileptic medications, and two experienced worsening of pre-existing motor disturbances. In

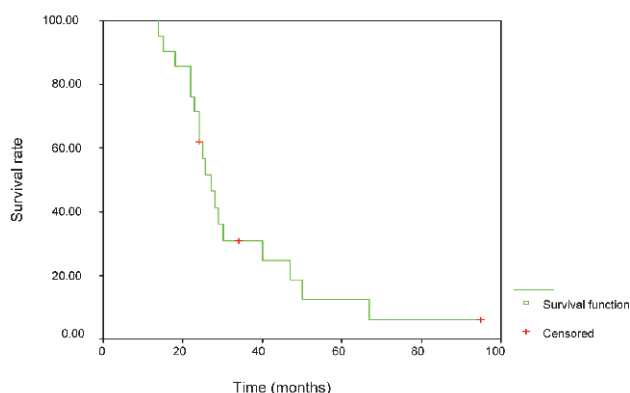


Figure 3. Overall survival (OS) from the onset of primary radiation.

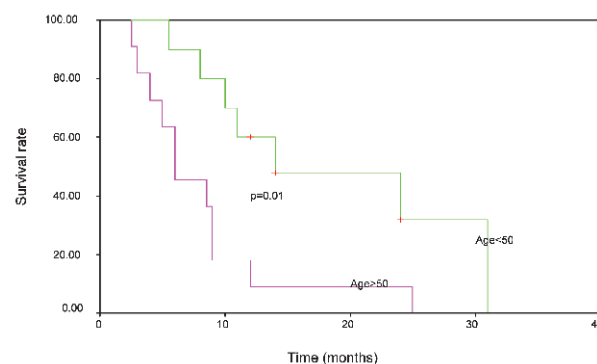


Figure 4. Overall survival (OS) from the onset of re-irradiation by age (years).

these, follow up CT scans showed enlargement of perifocal edema that partially resolved with an escalating steroid dose.

Late toxicity from re-irradiation was suspected in 4(19%) patients: of these, 2 suffered from increasing somnolence, one patient developed memory disturbance associated with dysphasia, and one had evidence of progressive motor disturbance. Three patients underwent additional surgery over a six-month period following re-irradiation; histological examination showed tumor in two of these patients and predominant necrosis with scant tumor involvement in the other patient.

Response

We evaluated all patients for evidence of clinical and radiological responses with CT and/or MRI scans at 6-12 months after H3D-CRT. Four patients had complete response(CR) and three achieved partial response (PR). Stable disease was reported in eight patients and progressive disease in six patients.

Survival

After a median follow up of 9.5 months (range:2.5-42) from the start of re-irradiation, 18 patients with recurrent high grade glioma died; 3 patients were still alive at 12, 14,and 24 months after treatment with no sign of tumor progression in two patients.

Median TTP was five months (95% CI: 2.01-7.99; Figure1). Median OS was nine months (95% CI: 6.76-11.24). Survival rate at one year after

H3D-CRT was 42.9%, whereas it was 19% at two years after treatment (Figure2). Median survival from time of initial diagnosis was 27 months (95% CI: 22.79-31.21; Figure 3).

We analyzed various prognostic factors for their impact on outcome. At the time of re-irradiation, patients' younger age; KPS; tumor grade; salvage surgery; and smaller PTV significantly influenced TTP and OS according to univariate analysis (Table 2). Multivariate analysis of these factors revealed that salvage surgery and smaller PTV were the only significant predictors of progression and survival (Table 2).

Patients who underwent salvage resection had a median TTP of 14 months compared to 3 months for the group that had no resection ($P= 0.000$). Patients with PTV $<50 \text{ cm}^3$ had median TTP of 16 months versus 3.5 months for those with a PTV $>50 \text{ cm}^3$ ($P= 0.000$). Median OS from time of re-irradiation in patients <50 years of age was 14 months compared to 6 months for those over the age of 50 years ($P=0.012$; Figure 4). Median OS in patients who underwent salvage resection was 24 months versus 5.5 months in the other group ($P= 0.000$; Figure 5). Patients with PTV $<50 \text{ cm}^3$ had a median OS of 25 months compared to 6 months for those who had a PTV $>50 \text{ cm}^3$ ($P= 0.000$; Figure 6).

Discussion

Despite the combined treatment modalities of surgery, post-operative radiotherapy, and

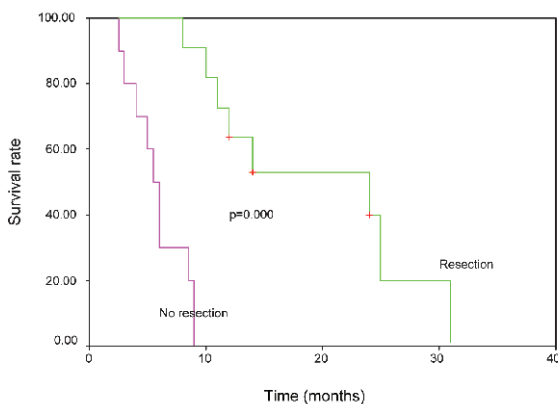


Figure 5. Overall survival (OS) from the onset of re-irradiation by salvage surgery.

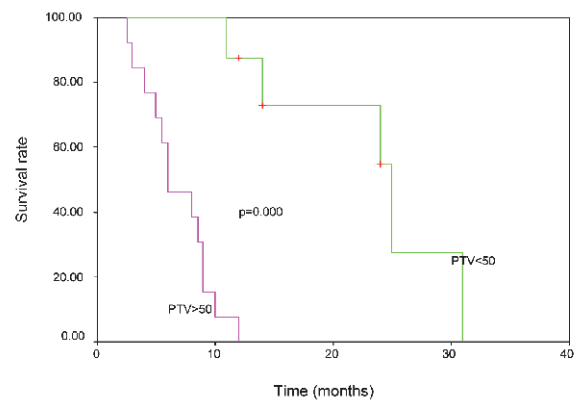


Figure 6. Overall survival (OS) from the onset of re-irradiation by PTV.

Table 2. Prognostic factors for re-irradiation outcome measures.

| | TTP* | | OS* | |
|---|------------|--------------|------------|--------------|
| | Univariate | Multivariate | Univariate | Multivariate |
| Age (years) (<50 vs. ≥ 50) | 0.018 | 0.911 | 0.012 | 0.55 |
| Sex | 0.757 | - | 0.661 | - |
| KPS* (<90 vs. ≥ 90) | 0.002 | 0.528 | 0.017 | 0.353 |
| Initial histology (Grade II/III vs. GIV) | | | | |
| Initial surgery (complete vs. incomplete) | 0.073 | - | 0.006 | 0.063 |
| Adjuvant chemotherapy (yes vs. no) | 0.134 | - | 0.095 | - |
| Salvage surgery (resection vs. no resection) | 0.000 | 0.037 | 0.000 | 0.013 |
| Recent histology (Grade III vs. G IV) | 0.001 | 0.496 | 0.013 | 0.059 |
| Salvage chemotherapy (yes vs. no) | 0.672 | - | 0.419 | - |
| PTV*(cm ³) (<50 vs. ≥ 50) | 0.000 | 0.027 | 0.000 | 0.018 |
| Interval (months) (< 20 vs. ≥ 20) | 0.741 | - | 0.785 | - |

*KPS: Karnofsky performance status; PTV: Planning target volume; TTP: time to progression; OS: Overall survival.

frequently chemotherapy, most patients with malignant high grade glioma ultimately recur locally.^{18,22} In recurrent malignant glioma palliative chemotherapy is relatively well established; nevertheless patients should be evaluated for the possibility of re-irradiation and/or secondary neurosurgical resection. Some seem to benefit from secondary local treatment.²²⁻²⁵ As recently shown, re-irradiation is a safe, feasible therapeutic option for recurrent malignant glioma. Modern conformal treatment approaches allow brain re-irradiation with a low to acceptable probability of radiation necrosis.²⁶

The treatment strategy in our study was to re-irradiate patients who presented with recurrent high grade glioma, using short term hypofractionated irradiation and concurrent daily temozolomide. The total dose of 30 Gy in 5 Gy fractions used in our study was associated with acceptable toxicity. We chose this dose schedule based on a dose escalation study by Shepherd et al.²⁷ These researchers noted that a total dose of >40 Gy and a single fraction of >5 Gy were

significant predictors of radiation damage. VanderSpek et al.²⁸ recommended 30 Gy in six fractions as the maximal safely tolerated dose of H3D-CRT. Similar findings were reported by other investigators.^{18,29}

From the onset of re-irradiation, we reported a median TTP of five months and a median OS of nine months. Median survival time from initial irradiation was 27 months. Similarly, Vordermark et al.¹⁸ performed a retrospective analysis of 19 patients with recurrent high grade glioma treated with hypofractionated stereotactic radiotherapy (HFSRT) to a median dose of 30 Gy (range: 20-30 Gy) and a median single dose of 5 Gy (range: 4-10 Gy). They observed that patients attained a respective median OS of 9.3 months and a median TTP of 5 months from the time of HFSRT. VanderSpek et al.²⁸ in their phase I/II radiation dose escalation trial used three dose levels: 25 Gy, 30 Gy, and 35 Gy at 5 Gy fractions to re-irradiate nine patients with recurrent malignant glioma. Patients from their study demonstrated a median OS of 8.8 months and median TTP of 2 months.

Our survival data correlated with results of various published series with hypofractionated re-irradiation, either as a single modality or combined with chemotherapy.²⁹⁻³²

In the current study, we researched the role of different prognostic factors on progression and survival from re-irradiation and found significantly better outcomes in patients of younger age, better KPS, grade III histology, surgical re-resection, and smaller PTV, according to univariate analysis restricted to surgical re-resection and smaller PTV by multivariate analysis.

Henke et al.²² confirmed a positive prognostic significance in patients of younger age (<50 years), smaller PTV (<30 ml), better KPS, and longer interval between primary irradiation series and re-irradiation. According to Bartsch et al.,³³ their study reported significant advantages in both TTP and OS from the onset of re-irradiation for patients who had a second surgical resection. Patients with recent grade III histology were found by Vordermark et al.¹⁸ to have significantly longer median survival from the time of HFSRT. Fogh et al.²⁵ conducted the largest retrospective series of HFSRT in recurrent malignant glioma and suggested that younger age ($P < 0.001$) and smaller PTV ($P = 0.025$) positively affected survival time from the onset of re-irradiation. In addition, they observed an excellent median survival time (11 months) in patients who experienced recurrence within six months of initial irradiation, which suggested that patients should not be denied the chance for re-irradiation or other salvage therapy.

Currently, a number of anti-angiogenic agents have been evaluated in patients with recurrent glioblastoma, of which the most established is bevacizumab.³⁴⁻³⁶ At present, the NCCN guidelines include bevacizumab with or without chemotherapy as a treatment option for recurrent glioblastoma.⁵ Clinical studies have demonstrated the feasibility of combining bevacizumab plus radiation and/or chemotherapy³⁷⁻⁴⁰ or with targeted agents such as erlotinib and cetuximab^{41,42} for patients with newly diagnosed or recurrent malignant gliomas. Preliminary results were encouraging. However, the ideal chemotherapy

partner, optimal chemotherapy agents, and treatment schedules have yet to be identified.

Conclusion

The use of H3D-CRT concomitant with temozolomide is a feasible, well-tolerated treatment for recurrent high grade glioma that results in a modest survival benefit. Small tumor volume and surgical re-resection are associated with better outcome. Larger prospective trials that combine re-irradiation with other salvage treatment, including targeted agents are warranted to establish the most advantageous schedule for individual patients.

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Conflict of interest

No conflict of interest emerged during the implementation of this work. The paper has not been presented at any previous congress.

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