Re-Irradiation in Recurrent High-Grade Glioma

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Abstract

**Background and Purpose:** Despite the progress in treatment modalities such as neurosurgery and radiotherapy, almost all patients treated with malignant gliomas develop recurrent tumors and die of their disease. The aim of this study was to determine response, survival and treatment toxicities after re-irradiation of relapsing primary malignant brain gliomas.

**Material and Methods:** Twenty patients with recurrent or progressive primary brain glioma were subjected to re-irradiation. 3-D conformal radiotherapy with a median target total dose of 35 Gy (BED = 66.5 GY\(^2\)) was applied using 1.8-2 Gy daily; 5 days per week with a 6 MV linear accelerator.

**Results:** Patients were assessed as regard response, survival and treatment complications. Median progression free and overall survival was 3 and 9 months respectively. As regard subjective response; 50% of cases showed improvement symptoms. Radiographic indices were stabilized or improved in about 60% of patients. Brain necrosis was noted in 10% of patients.

**Conclusion:** Re-irradiation of recurrent brain gliomas allows the survival prolongation and delays disease progression or recurrence, with acceptable toxicities.

**Key Words:** Malignant glioma – Brain glioma – Re-irradiation.

Introduction

HIGH-GRADE glioma (HGG) constitutes the most common primary central nervous system tumor in adults, as it is accounting for more than 60% of all brain tumors [1]. Surgery and radiotherapy are the main line of their therapeutic management, nevertheless, the outcome of patients affected by this disease is still dismal and recurrence is a very common event [2]. In the last ten years treatment outcome of glioblastoma (GBM) have improved with the use of radiotherapy (RT) plus concomitant and adjuvant temozolomide (TMZ) with a median survival 14.6 months and 2-year survival 27% [3]. Because of the infiltrating nature of gliomas, they frequently recur and despite an increase in survival rates the majority of patients progress within 1-2 years [4].

Many options are available for the salvage treatment of recurrent HGG after initial RT, including surgical re-resection, re-irradiation, or systemic chemotherapy, but up till now no standard of care is recommended [5]. Extensive parenchymal infiltration of recurrent disease makes optimal surgical resection so difficult, with a high risk of morbidity. Only few patients with recurrent HGG are fit for re-surgery due to the patient's medical condition and the probability of further neurological compromise [6,7]. Chemotherapy has been the mainstay of treatment for patients with recurrent disease. However, poor general conditions of those patients as well as the related development of side effects make the use of chemotherapy regimen of limited role and mainly result in a modest palliation [2]. Re-challenging with non-conventional TMZ regimen has become a common practice in treatment of recurrent HGG [8]. More recently several targeted therapies such as anti-VEGF antibody EGFR, PKC/PI3K/AKT and integrin inhibitors have been introduced in clinical practice and in clinical trials with very preliminary results [9]. In most cases though, these agents are likely to produce cytostatic effects, hence they will need to be given in combination with conventional cytotoxics, and such combinations may be limited by reduced bone marrow reserve as a result of previous treatment [10]. In these circumstances the use of re-irradiation may have important advantages since it avoids any systemic side effects and the available data are supporting both the feasibility and the survival lengthening capability of re irradiation in comparison with supportive care only [2]. An improvement in radiotherapy and imaging techniques has improved target definition. 3-D conventional radiotherapy using co-registered magnetic resonance imaging (MRI) has improved target definition and...
allows for a reduction of the dose to normal structures. Re-irradiation for brain tumors is now attracting more interest as understanding of the tolerance of the brain evolves. Developments in radiation technology and imaging also mean that highly accurate targeting of biologically relevant tumor volumes is possible [4]. The aim of this study was to evaluate survival and quality of life after re-irradiation of relapsing high grade glioma.

Patients and Methods

Between November 2007 to July 2011 twenty patients were subjected to re-irradiation for recurring primary brain gliomas (7 cases were astrocytoma G II-III, 6 were an plastic astrocytoma and 7 were GBM). The interval between 1st & 2nd radiation courses was at least 8 months. Before starting radiotherapy, all patients were subjected to complete history taking, thorough clinical and neurological examinations. Assessment of performance status using ECOG scale [11], with determination of corticosteroid dose that control symptoms of increased intracranial tension. Also, laboratory investigations including complete blood picture, liver & kidney function tests, and brain CT or MRI to determine pre-treatment size of the recurrent tumor. Routine chest X-ray and pelviabdominal ultrasound to exclude possibility of distant metastasis. After an informed consent; all patients were subjected to 3-D conformal radiotherapy with a median target total dose of 35 Gy (BED=66.5 GY2) (range 20-55 Gy, BED=38-99 GY2) was applied using 1.8-2 Gy daily; 5 days per week with a 6 MV linear accelerator. Patients were assessed weekly during treatment as regard subjective response and corticosteroid medication. After Radiotherapy has completed; patients were evaluated monthly by physical and neurologic examination. The radiological response was assessed by reviewing all available CT- and MRI-films. During follow-up, corticosteroid medication and the WHO-performance were registered. Progression free survival and overall survival was evaluated using appropriate statistical methods.

Results

Twenty patients were included in this study, 12 males (60%) and 8 females (40%) the mean age was 50 years (rang 35-65). According to ECOG performance status; grade 2 was 40%, grade 3 was 30% and grade 4 was 30% of cases (Table 1). All cases complaint of headache and blurring of vision but of variable degrees. Other neurological symptoms presented according to sites of recurrent or progressive brain gliomas. Dose of steroid that control symptoms of increased intracranial tension before re irradiation ranged from 8mg to 32mg (median 16mg) (Table 4). Initial course of radiation was radical in intent for all patients using conventional fractionated radiotherapy; 1.8-2 Gy / fraction with total dose 55-65 Gy (BED=110-130 GY2). Median interval between radiation courses was 14 months (range: 8-24). Re irradiation volumes overlapped previous treatment in 18 patients (90%) and were none overlapping in 2 patients (10%). Cumulative maximum overlap dose within the CNS ranged from 85-111 Gy (BED=168-209 GY2) (median: 79.7 GY BED=156.5 GY2). Retreatment was completed as planned in 18 patients and was aborted in 2 cases due to clinical deterioration. As measured from the time of retreatment median progression free and overall survival was 3 and 9 months respectively. As regard subjective response; 50% of cases showed improvement of headache and blurring of vision while 40% showed stabilization of symptoms and 10% showed deterioration of symptoms (Table 2). Radiographic indices were stabilized or improved in about 60% of patients evaluable at a median of 3 months post treatment (Table 3). Dose of steroid post treatment ranged 0-16mg (median 8mg). Complications (early or late) potentially attributable to re treatment were noted in 6 (30%) of patients. Brain necrosis was noted in 2 (10%) of patients and the actuarial risk of necrosis was 20% at 1 year following re treatment.

Table (1): Patients characteristics.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>No.</th>
<th>%</th>
<th>Range</th>
<th>Mean</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td>35-65</td>
<td>50</td>
</tr>
<tr>
<td>Sex:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>12</td>
<td>60</td>
<td></td>
<td></td>
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<tr>
<td>Female</td>
<td>8</td>
<td>40</td>
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<td></td>
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<tr>
<td>ECOG:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade II</td>
<td>8</td>
<td>40</td>
<td></td>
<td></td>
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<tr>
<td>Grade III</td>
<td>6</td>
<td>30</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade IV</td>
<td>6</td>
<td>30</td>
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</table>

Table (2): Subjective response to treatment.

<table>
<thead>
<tr>
<th>Response</th>
<th>No.</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Improvement of symptoms</td>
<td>10</td>
<td>50</td>
</tr>
<tr>
<td>Stabilization of symptoms</td>
<td>8</td>
<td>40</td>
</tr>
<tr>
<td>Deterioration of symptoms</td>
<td>2</td>
<td>10</td>
</tr>
</tbody>
</table>

Table (3): Response to treatment based on CT findings.

<table>
<thead>
<tr>
<th>Response</th>
<th>No.</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stable disease (SD)</td>
<td>12</td>
<td>60</td>
</tr>
<tr>
<td>Progressive</td>
<td>8</td>
<td>40</td>
</tr>
</tbody>
</table>
Discussion

Despite the progress in neurosurgery and radiotherapy, almost all patients treated with malignant gliomas develop recurrent tumors and die of their disease [12]. The vast majority of gliomas recur within 2 cm of the original surgical site [13]. At relapse, treatment options have included further surgical resection, systemic chemotherapy and more recently, re-irradiation but currently, there is no agreed standard of care [4]. The currently available clinical data as regard re-irradiation in glioma are retrospective and generally used a variety of radiotherapy doses, techniques and volumes focusing on the fact that no standard approach to re-irradiation exists in this context. Nevertheless, the available clinical data suggest that re-irradiation may be a relatively safe and effective approach in properly selected patients [14]. Re-irradiation for gliomas has attracted controversy in the past but is receiving more attention due to advances in radiotherapy techniques and imaging modalities, which may reduce concerns related to the risk of late neurological toxicity [4]. Mayer and Sminia [15] have published a systematic review of 21 studies of the effects of re-irradiation of brain tumors. This review excluded patients treated with brachytherapy, but evaluated treatment outcome in patients treated with fractionated external beam or radiosurgery approaches. Details of important variables including time between radiation courses and treatment volumes were rarely available in such studies. They also make the point that the incidence of toxicity, including radionecrosis, may be significantly under-reported in these data sets since only symptomatic necrosis is likely to be recorded. According to their analysis, the major factor contributing to necrosis was the total dose received. There was no correlation between time to re-irradiation and the development of necrosis although the minimum time interval between treatments in this data set was 3 months. Importantly, they concluded that the incidence of necrosis did not increase significantly until the total cumulative dose was 100 Gy.

Seven series were published between 1996 and 2009 where 144 patients (74 GBM and 70 HGG) were included in those studies. The patients had a median age ranging from 10 to 50 years and a median Karnofsky performance status (KPS) between 60 and 90. Four of such studies [16,18,19,22] had used combined regimens of chemotherapy as a concurrent treatment with radiotherapy. Re-irradiation started after a median interval time of 14-38 months after the first irradiation. After calculation a cumulative biologically effective dose (BED) of 163.1-197.5 Gy 2 was given to the re-irradiated patients. About half of the re-irradiated patients had previously received some form of second surgery. The treatment was quite well tolerated: Only a minor number of radio necrosis was reported [16,20-22], in two studies [16,22] some patients were re-operated, and in two studies [18-21] the use of corticosteroid was increased or maintained for a long period. The mean overall survival (OS) was 9.4 months. Hayat et al. [18], and Arcicasa et al. [19] reported a better results with the use of combined chemotherapy with a median OS after irradiation of 13 and 13.7 months respectively in comparison to 7-10.2 months of the other studies not using chemotherapy [16-17,20-22]. In general, neurologic toxicity was mild. The radionecrosis rate ranged between 4.5% and 30% (median, 6.5%). Recent data assessing response to re-irradiation using either radiosurgery or fractionated stereotactic radiotherapy reported a median survival of 8.5 months, radiographic tumor response or stable disease was observed in (40%) of patients [23]. A reported case-control study comparing re-irradiation with chemotherapy, response rates may be at least as good as systemic treatment with nitrosoureas [24]. Data need to be compared with expected outcomes in this patient group. There are very few data on the quality of life after re-irradiation, which is an important consideration in a poor prognostic group. Overall available data, suggest that there may be a selected group of patients with recurrent glioma, where re-irradiation may be a safe and an effective approach [28].

Our study was performed on twenty patients with recurrent high grade glioma the median cumulative dose after reirradiation was 79.7 Gy. Overall survival and progression free survival was 9 and 3 months respectively. Symptoms of increased intracranial tension was improved in 50% of cases while 10% showed deterioration of symptoms, radiation necrosis was noted in 10% of retreated cases. Results of our study didn’t show great difference when compare it with the above-mentioned studies that used similar treatment regime. Analysis of the available data demonstrated that, re-irradiation can represent a valuable salvage treatment option that provides comparable outcomes with respect to re-operation and chemotherapy. Re-irradiation can be performed by different tech-

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Table (4): Dose of steroid before and after treatment.

<table>
<thead>
<tr>
<th>Dose of steroid</th>
<th>Range</th>
<th>Median</th>
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<tbody>
<tr>
<td>Before treatment</td>
<td>8mg-32mg</td>
<td>16</td>
</tr>
<tr>
<td>After treatment</td>
<td>0-16mg</td>
<td>8mg</td>
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niques and seem to be equally effective but the results should be interpreted taking into account several issues. Some of them might even represent areas of improvement and/or future research [26]. The suitability for re-irradiation must be considered on an individual basis and when the potential for benefit outweighs the risks. The impact on an individual’s quality of life from late toxicity must not be underestimated. Patients may get a worsening of their presenting symptoms due to the original tumor, including focal neurological deficits. Any high dose brain irradiation is also associated with a risk of memory problems, cognitive impairment and personality change. Focal normal tissue damage as a result of re-irradiation may also be associated with higher seizure risk, and an expanding mass related to radio necrosis may require surgical intervention to relieve pressure symptoms [4]. Wong and colleagues [27] have suggested that the use of bevacizumab (Avastin) can reverse radiation induced necrosis in the central nervous system. Combination of bevacizumab with reirradiation for glioma has recently been demonstrated to be practical [28]. If these data are confirmed in larger studies, the use of highly targeted radiotherapy in combination with similar agents will become more appealing [10].

Conclusion:

In conclusion re-irradiation using high precision techniques allows the survival prolongation and delays disease progression or recurrence. However, it is not a curative treatment and it is limited to selected subgroups of patients. Therefore, a further therapeutic improvement is needed. The radio chemotherapy combination as well as alternative treatment modalities should be investigated.

References


