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ORIGINAL ARTICLE

Postoperative hypofractionated radiotherapy in glioblastoma multiforme

M. Arslan, A.N. Karadeniz, G. Aksu, M. Güveli, M. Fayda, A.K. Doğan, F. Akyüz

Department of Radiation Oncology, Institute of Oncology, Istanbul University, Istanbul, Turkey

Summary

Purpose: *To evaluate the safety and efficacy of hypofractionated radiotherapy (HRT) in glioblastoma multiforme (GM) patients in terms of overall and progression-free survival.*

Patients and methods: *Adult patients with GM were prospectively treated with HRT after total, subtotal or partial tumor excision. HRT was applied 3 days a week with a tumor dose of 3.33 Gy per fraction. At the first phase of treatment 12 fractions and at the second phase 3 fractions with smaller fields were delivered. The total dose was 50 Gy/15 fractions/5 weeks. The results were compared with a historical control group of GM patients treated with conventional RT.*

Results: *20 patients with GM were treated between 1997-2000 at our department. The tumor was multifocal in one (5%) case. The types of operations used were total tumor excision 10 (50%) cases, subtotal excision 5 (25%) cases and partial excision 5 (25%) cases. For the historical control group the corresponding operations were 19 (56%), 6 (18%) and 9 (26%). In the study group one-year survival was 50% and median survival 12 months. Mean overall survival was 13.5 (11.3 months for the historical control group, p=0.16) and progression-free survival 6.8 months (5.6 for the historical control group, p=0.36). Treatment was well tolerated. Acute toxicity was minimal and only one HRT patient had late toxicity (brain necrosis).*

Conclusion: *The mean overall survival with HRT was better but statistically non significant compared with the historical control group. Our study supports that HRT can be used instead of conventional and hyperfractionated radiotherapy and studies of HRT with higher doses may be meaningful.*

Key words: brain tumor, glioblastoma multiforme, hypofractionated radiotherapy, survival

Introduction

Glioblastoma multiforme is one of the most common primary brain tumors in adults [1]. Half of the brain tumors in adults are GM [1,2]. Although its incidence can range in different countries, it occurs in 4-5 per 100,000 people per year. The incidence of this disease increases after the age of 40 [1,3-7].

Despite improvements in diagnostic and treatment modalities in the last 15 years, overall prognosis and the natural course of GM remain unchanged [1,3,8-11]. GM has the worst prognosis and the highest mortality and morbidity rates of all primary brain tumors in adults [1,3]. The standard therapeutic approach is surgical excision followed by conventional radiotherapy. In the literature the median survival ranges between 9 and 12 months [1,6,8,9,12]. Two-year survival is about 10% [1,13], 3-year survival 3-6% [1] and 5-year survival 0-5% [1,14].

As the prognosis is poor with standard postoperative radiotherapy, different fractionation schedules were tested. Hyperfractionated [15,16] and accelerated fractionations were tried [17]. Different radiation techniques [10,18] and radiation types [3,19] were reported. HRT has been reported in relatively less trials [20].

In 1997 we designed a prospective study to evaluate the safety and efficacy of postoperative HRT in GM patients in terms of overall and progression-free survival. This was the first prospective clinical trial with HRT at our institution.

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Author and address for correspondence:

Mehmet Arslan, MD
Bademlik mh. M. Aralığı sk. 17/12
Beyoğlu, Istanbul
Turkey
Tel: +90 532 6864659
Email: marslan19@ yahoo.com

Patients and methods

Between 1997-2000, 20 adult patients operated for GM were irradiated with HRT and compared with a historical control group treated with conventional RT (n=34). The types of operations used for the study group and the historical control group, respectively, were: total tumor excision 10 (50%) and 19 (56%) cases; subtotal excision 5 (25%) and 6 (18%); partial excision 5 (25%) and 9 (26%). One-year overall and progression-free survival times were calculated from the date of operation using the Kaplan-Meier method.

The diagnosis was confirmed by the pathologic examination of the surgical specimen. Only GM patients were included in this study. Anaplastic astrocytomas and grade 3-4 astrocytomas (Kernohan's grading system) were excluded.

HRT started after wound healing 3 weeks postoperatively on average and was delivered with Co-60 teletherapy unit. The irradiated volume was determined by preoperative computed tomography or magnetic resonance imaging and perioperative findings. In the first phase of treatment the abnormal contrast-enhancing zone and edema around the tumor were irradiated with 2-3 cm margin from the normal brain tissue. In the second phase the tumor region was irradiated. HRT was applied 3 days a week with a tumor dose of 3.33 Gy per fraction. At the first phase of treatment 12 fractions and at the second phase 3 fractions with smaller fields were applied. The total dose was 50 Gy/15 fractions/5 weeks.

Conventional RT consisted of the delivery of a total dose of 60 Gy in 30 fractions within 6 weeks.

Daily dexamethasone 16 mg i.v. push was given as antiedematous treatment to all patients during HRT. Post-HRT 40% of the patients continued maintenance dexamethasone 4 mg p.o. daily for about 6 weeks with gradual discontinuation. Antiepileptic treatment with carbamazepine 200 mg p.o. twice daily was given continuously.

After the completion of HRT the patients were seen one month later and then they were followed up every 2 months. In case of suspected relapse or the appearance of new symptoms, the patients were evaluated clinically and radiologically. Two such patients were operated due to relapsed tumor and one was re-irradiated.

Results

Eleven males and 9 females with median age 57 years (range 37-86) formed the study group (Table 1). Fifteen (75%) of them presented with symptoms of increased intracranial pressure i.e. headache, nausea, vomiting, mental changes and visual defects. Forty per cent of the patients had hemiparesis-hypoesthesia and 30% had seizures. Median symptom duration was 8 weeks (range 1-96). All patients had supratentorial tumors. In 73% of the patients the tumor dimension was 4 cm or less. Except one patient all of them had unifocal tumor.

Twenty patients were irradiated with HRT after the operation. Ten out of 20 (50%) had macroscopic total tumor excision, 5 (25%) had subtotal excision and in 5 patients (25%) the tumor was partially excised.

Treatment was well tolerated. During HRT serious acute side effect were not observed. However, one patient had a grave late toxicity in the form of brain necrosis.

All 20 patients were followed up regularly until death. The mean follow up was 10 months (range 2-29). One-year survival was 50% and median survival 12 months (range 2-29) (Figure 1). Mean overall survival was 13.5 months (range 9.5-17.4) and progression-free survival 6.8 months (range 3.8-9.7) (Figure 2). Mean overall survival for the historical conventional RT group was 11.3 months (range 9.4-13.1) (Figure 1) and progression-free survival 5.6 months (range 4.2-7.1) (Figure 2). Differences between study and control groups were non significant (overall survival p=0.16, progression-free survival p=0.36; Table 2).

Table 1. Patient clinical characteristics

Characteristic	*Conventional radiotherapy (%) n=34*	*Hypofractionated radiotherapy (%) n=20*	*p-value*
Age (years)			
≤50	23.5	33.3	0.63
>50	76.5	66.7	0.43
Sex			
Male	73.5	52.4	2.57
Female	26.5	47.6	0.11
ECOG performance status			
<III	35.3	57.1	2.52
≥III	64.7	42.9	0.11
Symptom duration (weeks)			
≤6	67.6	42.9	3.28
>6	32.4	57.1	0.07
Epilepsy			
Yes	68.8	61.9	0.27
No	31.3	38.1	0.61
Cranial nerve symptoms			
Yes	28.1	11.1	1.9
No	71.9	88.9	0.15

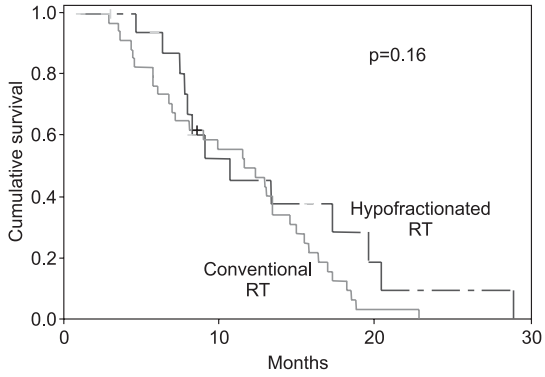

Figure 1. Overall survival of patients treated with hypofractionated and conventional radiotherapy.

Discussion

The treatment of GM is a serious clinical problem. If no adjuvant treatment is given after the operation the median survival time is no longer than 4 months [1,8]. Surgery plus postoperative radiotherapy is standard and optimal treatment [5,21]. Randomized trials have shown that postoperative radiotherapy can prolong survival and improve quality of life [22].

The standard and optimal total dose of conventional radiotherapy is 60 Gy. The dose per fraction is between 1.8-20 Gy [5,23]. There is no clear evidence that improved results can be taken with increasing the dose beyond 60 Gy [23,24]. Hyperfractionated or accelerated regimens cannot improve the results either [7,17,20,21,23].

Postoperative HRT has been tested in some trials [11,20,25]. Slotman et al. [26] treated 30 patients with HRT. Sixty-seven per cent of them had total/subtotal excision, 27% had their tumor excised partially and in 6% only biopsy was taken. HRT consisted of 42 Gy given in 3 weeks (5 daily fractions of 3 Gy each per week). The median follow up time was 24 months and 80% of the patients recurred after 6.5 months. Age, Karnofsky performance status and maximal tumor excision were found as prognostic factors. The authors

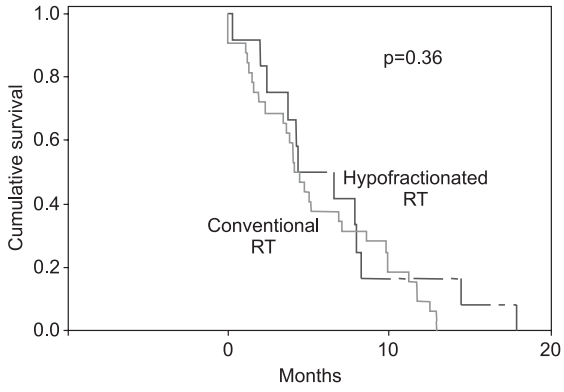

Figure 2. Progression-free survival of patients treated with hypofractionated and conventional radiotherapy.

Table 2. Conventional and hypofractionated radiotherapy survival results

Survival	*Conventional radiotherapy*	*Hypofractionated radiotherapy*	*p-value*
Overall, months, median	11.3	13.5	0.16
Progression-free, months, median	5.6	6.8	0.36

reported that their results were similar with conventional radiotherapy. None of the patients experienced severe acute or late complications.

Lang et al. [27] irradiated 29 patients with partial excision and 9 patients with stereotactic biopsy only. 3.5 Gy per fraction were given with 5 fractions per week up to a total dose of 42 Gy. Median survival was 11.5 months (45.7 weeks; range 29.6-63.6). There were no serious acute or late radiation toxicities and this regime was found as effective as the conventional one.

Glinski et al. [28] compared 44 patients treated with HRT or conventional radiotherapy in their randomized prospective trial. Two-year survival was 10% in the conventional arm and 23% in the HRT arm (p=0.05). Treatment in both arms was well tolerated.

Hayakawa et al. [29] compared 31 patients irradiated with HRT and 54 patients irradiated with conventional radiotherapy. Survival was better in the HRT arm.

Hulshof et al. [30] in their study found no difference between HRT and conventional radiotherapy arms and they claimed that HRT could be given to patients with intermediate or poor prognostic factors.

In our institute we designed this study to evaluate the effectiveness of tumor control with HRT. The results were compared with a group of GM patients treated in the past with conventional radiotherapy. No survival difference was seen between these two fractionation regimens. Survival in the HRT arm was better but not statistically significant. Overall survival and progression-free survival were 13.5 and 11.3 months, and 6.8 and 5.6 months for HRT and conventional radiotherapy historical group, respectively. In our series our patients' survival was identical with results reported in the literature [1,6,8,9,13].

Although prognosis of GM is ominous, some characteristics of the patient, tumor and treatment can affect the natural course of this neoplasm. Known and reported prognostic factors related to patient and tumor characteristics are patient's age [1,8,11,26,31], performance status before the operation [1,11,26,31], tumor localization [32], tumor size [11], and symptoms and their duration [13,31]. Important factors related to treatment are the extent of tumor excision [11], the type of operation [1,11,13,23,26,31,32], the presence of residual tumor [33], delivery of radical radiotherapy

[8,11,13] and re-operation of relapses [1,10,34].

Considering the results of this preliminary study we believe that decreasing the number of fractions can be considered in patients with transportation limitations and poor performance status. Studies including greater numbers of patients are needed in order to clearly evaluate if HRT is an efficacious alternative treatment.

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