Hypofractionated radiotherapy versus conventional radiotherapy in treatment of glioblastoma multiforme

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Abstract

Purpose : This study was planned to evaluate the safety and efficacy of hypofractionated radiotherapy(HRT) in treatment of glioblastoma multiforme (GM).

Patients and methods : Twenty adult patients with (GM) were prospectively treated with (HRT) after surgical excision. HRT was given 3 days a week with a tumor dose of 3Gy/fraction. There were two phases of treatment, the first phase was 12 fractions, and the second phase was three fractions with smaller field size. The total dose was 50 Gy/15 fraction. The results were compared with a control group retrospectively treated with conventional radiotherapy.

Results : Twenty patients with GM were treated. Excisional biopsy was done in 15% of cases , 25% of cases underwent subtotal excision while 60% of cases were operated with total excision. As regard historical group 20% of cases underwent excisional biopsy ,subtotal excision in 30% and total excision in 50% of cases . The study revealed that median overall survival 6.5 months and 6 months for (HRT) and conventional group respectively. The progression free survival was 6 months and 5 months for the (HRT) and conyentional group respectively. Treatment was well tolerated with minimal acute toxicities.

Conclusion: Although HRT didn't improve overall survival or progression free survival in GM compared with conventional group but the treatment duration was reduced which may be of palliative benefit in such group of patients. Further studies could be useful to determine the optimal fraction size for GM when HRT is used as an adjuvant treatment.

Introduction

Glioblastoma multiforme is one of the most common primary brain tumors in adults(1). Half of the brain tumors in adults are GM(2). The incidence of this disease increases after the age of forty (3).

Although brain tumors are uncommon in comparison with other cancers such as breast or lung cancer. They exert a tremendous toll upon the patients, their spouses and families because of the sever neurologic disability they produce. The incidence and mortality from primary brain tumors appears to be rising, particularly amongst the elderly(4).

High grade primary brain tumors such as anaplastic astrocytoma and glioblastoma are feard because of their aggressive course. In spite of intensive therapy with surgical resection, radiotherapy and chemotherapy the prognosis for malignant gliomas remains poor, with median survival of one year(5).The improvement in diagnostic and treatment modalities in the last years doesn't affect the overall prognosis and natural course of GM(1).

Although GM carries a fatal prognosis, postoperative radiotherapy has been shown to increase the median survival compared with that for patients treated with surgery alone(6) .

The standard dose of radiation given after surgical resection is 60 Gy delivered in 1.8 – 2.0 Gy / fration. Dose escalation through standard fractionation to 70 – 90 Gy has recently been attempted with conformal techniques, although changes in the pattern of failure have been observed, survival improvement hasn't been achieved(7) .

Hyperfractionation (giving a smaller fraction size twice daily) to a total dose 72 Gy has shown no specific benefit for GM(8) .

From the radiobiologic standpoint, late responding tissues such as neural tissue should be more responsive to fewer, but larger dose fractions of radiation, therefore to control CNS tumors such as GM adequately, it is likely that the radiation dose given must exceed the tolerance of the surrounding brain tissue, resulting in an unacceptable side effect profile. However, this basic problem may be overcome if the tumor alone is treated to these higher doses, and the normal tissue is spared(9).

Several prospective trials have been performed using hypofractionated radiation dosing for the treatment of primary GM(9). A randomized study from Maria Slodowska – Curie Memorial Center, Poland evaluated 44 patients with GM who were treated with three split courses of hypofrationated radiotherapy to a total dose of 50 Gy and such study gave a statistically significant 2-year survival benefit compared with conventional therapy(10).

In Royal Marsden Hospital, a phase I – II study had been performed using 5-Gy fractions of stereotactic RT to 20 – 50 Gy proved to be efficacious and tolerable(11).

In 1997 Arslan and his colleagues designed a prospective study to evaluate the safty and efficacy of postoperative HRT in GM patients in terms of overall and progression – free survival, treatment was well tolerated, acute toxicity was minimal and the study supported that HRT could be used instead of conventional and hyperfractionated radiotherapy(12).

A non randomized study involved 30 patients treated with a hypofractionated course of 42 Gy in 14 fractions. The median survival and toxicity were comparable to that after standard fractionation(13).
Although the methods of such trials varied as regard fraction size, total dose, and the overall treatment time, all were shown to have an acceptable toxicity and encouraging results.

The aim of this study was to evaluate the safety and efficacy of adjuvant hypofractionated radiotherapy for patients with GM

Patients and Methods

From December 2007 to January 2009,twenty adult patients diagnosed histologically as GM were referred to clinical oncology department Zagazige University Hospitals. These cases were enrolled in group A which were treated with hypofractionated radiotherapy and were compared with a historical control group treated with conventional radiotherapy. Table(1)shows patient characteristics .

The types of operation which were performed for the study group and the control group ,respectively, were : total tumor excision 12 (60%) and 10 (50%); subtotal excision 5 (25%) and 6 (30%); biopsy 3 (15%) and 4 (20%) .

The diagnosis was confirmed to be GM by the pathologic examination of the surgical specimen. After wound healing; on the average 3 weeks postoperatively; HRT was delivered with linear accelerators . The irradiated volume was determined by preoperative compeutrized tomography or the magnetic resonance imaging. The gross target volume (GTV) for both the initial volume (GTV1) and the conedown volume(GTV2) is obtained from the MRI. GTV1 includes the contrast enhancing lesion, the surgical resection cavity and surrounding edema; a 2.0-cm margin is added to form PTV1. GTV2 for the conedown treatment should include the contrast enhancing lesion (without edema) plus a 2.5-cm margin to form PTV2. In the first phase of treatment, the tumor and edema around were irradiated with 2-3cm margin from the normal brain tissue. In the second phase the tumor region only was irradiated.

The HRT was applied 3 days a week with a tumor dose 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 fraction 15 weeks.

The historical control group were treated with conventional radiotherapy with total dose 60 Gy in 30 fractions over 6 weeks one year overall survival and progression free survival times were calculated from date of operation using the Kaplan meier method.

Daily dexamethasone 16 mg I.V was given as a brain dehydrating measure to all patients during HRT. After HRT 50% of patients continued maintenance dexamethasons 4 mg daily for about 6 weeks with gradual discontinuation also antiepileptic treatment was given continuously.

After Radiotherapy completed, patients were evaluated monthly by physical examination, neurologic examination and determination of performance status. Radiological examination **by** C.T or MRI were done every three months.

Results

Twenty patients were included in the study group, 12 males (60%) and 8 females (40%) the mean age was 55 years (rang 40 – 72). All patients had an initial Karnofsky performance status > 70 . 75% of the study group had tumor dimension 4 cm or less all patients had supratentorial tumor. Sixteen patients (80%) presented with symptoms of increased intracranial tension i.e headache, nausea, vomiting, mental changes and blurring of vision. Forty percent of the patients had hemiparesis–hypoesthesia and 30% had seizures.The mean duration of illness was 10 weeks (range 2 – 72).

The patients of the study group were irradiated with HRT after the operation. Treatment was well tolerate and acute toxicities were mild, serious acute side affect were not observed. In all cases, radiation necrosis as identified on MRI appeared to be within the high does area which determined during treatment planning.

All twenty patients were followed up regularly until death the overall survival and time to disease progression were measured from the day of radiotherapy completion.

The median overall survival of the study group was 6.5 months (range1-14) and the median of progression free survival was 6 months (range 1-15).

As regard the historical conventional group the median overall survival was 6 months (range 2-18) while the progression free survival was 5 months (range 2-14) Table(2) fig 1,2.

Discussion

Although prognosis of GM is ominous, some characteristics of the patients, tumor and treatment can affect the natural course of this neoplasm. Known and reported prognostic factors related to patients and tumor characteristics are patients age, performance status before operation, tumor size, tumor localization and symptoms of their duration.The treatment of glioblastoma is a serious clinical problem. If no adjuvant treatment is given after operation, the median survival time is about 4 months(1). Surgery plus post operative radiotherapy is standard and optimal treatment (14).

With respect to survival duration, the optimum dose of radiation defined in randomized studies is 60 Gy in 30 fractions given over 6 weeks (15). The dose per fraction is between 1.8 – 2 Gy (14) .

A meaningful improvement in survival from doses above 60 Gy has not been demonstrated (16). Postoperative HRT has been tested from the radiobiologic stand point, GM are relatively radioresistant and respond more like neural tissue, which is a late responding tissue the a/B ratio is small for late responding tissues this implies that a late responding tissue should be more sensitive to fewer, higher dose fractions (HRT) (9).Postoperative HRT has been tested in some trials (12). Hypofractionated radiotherapy has three advantages over standard therapy.

First, fewer overall treatment session are needed and the total treatment time is shorter. With a uniformly fatal disease such as GM this is an important concern in terms of quality of life owing to the significant time commitment required to undergo RT. This regimen offers a treatment course that is completed in 2, instead of 6 weeks which may be preferable in certain subsets of patients such as those with poor performance status unresectable disease when palliation is the primary treatment goal. Second, the reduced number of treatment sessions confers a cost advantage over standard therapy. Finally radiobiologic advantage to hypofractionation with GM my exist (9). The general consensus is that conventional intensive treatment which carries morbidity may not be appropriate for patients with adverse prognostic features who may have a limited gain in life expectancy. These patients tend to be offered either supportive care alone or short palliative radiotherapy with the aim of avoiding both prolonged treatment which would take up a large part of remaining life and prolonged side effects of intensive radiotherapy (17).

Slotman etal (18) treated thirty patients with HRT in the form 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 patients recurred after 6.5 months, Age performance status and type of operation were found as prognostic factors.

Such study reported that the results of HRT were similar with conventional radiotherapy. None of the patients experienced sever acute or late complications. Glinski et al (10) 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. Treatment in both arms was well tolerated.

Lang et al (19) treated 38 patients, diagnosed as glioblastoma multiforme with HRT where 3.5 Gy per fraction were given with 5 fractions per week up to total dose of 42 Gy. Median survival was 11.5 months (45.7 weeks; rang 29.6 – 63.6). There were no serious acute or late radiation toxicities and this regmine was found as effective as the conventional arm.

Arslan et al (12) designed a study to evaluate the effectiveness of tumor control with HRT in cases of GM and compare them with group previously treated with conventional radiotherapy concluded that no survival difference was seen between the two fractionation regimens. Survival in HRT arm was better but not statistically significant. Overall survival and progression free survival were 13.5 and 11.3 months for HRT arm while it was 6.8 and 6.5 months for conventional arm.

Phillips et al (20) had performed the first randomized comparison of conventional fractionated radiotherapy with short course of hypofrectionated treatment in GM and AA A statistically significant survival difference between the two arms could not be demonstracted and they recommented further studies to support this result. Mc Aleese, et al (17) had treated two groups of poor prognosis malignant glioma patients one group with HRT 5 Gy/fraction biweekly up to 30 Gy the other group was treated with conventional RTH they concluded that HRT offered reasonable, but lesser survival benefit than that would obtained with conventional RTH.

In the randomized trial conducted at sites in seven European countries, researchers recruited 342 patients with newly diagnosed glioblastoma.

Patients were assigned standard 60 Gy radiotherapy delivered in 2 Gy fractions for 6 weeks (n=100), hypofractionated 34 Gy radiotherapy delivered in 3,4 Gy fractions for 2 weeks (n=123), or 200 mg/m2 temozolomide daily on days 1 to 5 every 4 weeks for 6 cycles (n=119).

Median survival was 8.3 months for temozolomide, 7.5 months for hypofractionated radiation 34 Gy and 6 months for standard radiation. There was no significant difference in survival for patients treated with temozolomide or 34 Gy radiation.

“These results indicate that standard 60 Gy radiation could replaced by HRT or temozolomide in patients with glioblastoma(21)

In our study, we compare HRT with conventional radiotherapy in treatment of GM patients. No survival difference was seen between both group but it was noticed that survival was slightly better in HRT group and of no statistical significance. Overall survival and progression free survival were 6.5 and 6 months ,and 6 and 5 months for HRT and conventional radiotherapy groups respectively, and these results greatly coincide with the results of most trials which were mentioned in the literature.

We concluded that HRT could be an option in treatment of GM patients where most of such patients are with poor performance status and the lesser number of fraction with HRT could be more suitable for them. Mostly HRT could be received three times a week or five times a week in the above mentioned studies a further studies is recommended to compare between both and choose the most effective. So studies with greater number of patients are advised to evaluate if HRT is an effective alternative treatment in GM and to determine the optimal fraction size when HRT is used as an adjuvant treatment of GM.

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Table 1 shows patient characteristics

Characteristics	Hypofractionated		Conventional	
	NO	%	NO	%
Age <50 >50	 9 11	 45 55	 6 14	 30 70
Sex male female	 12 8	 60 40	 13 7	 65 35
ECOG	 7 13	 35 65	 11 9	 55 45
Duration of symptoms <10 week >10week	 14 6	 70 30	 12 8	 60 40
Increase ICT Present absent	 16 4	 80 20	 17 3	 85 15
Surgery Complete Subtotal Biopsy	 12 5 3	 60 25 15	 10 6 4	 50 30 20

Table 2: Difference between the study group and control groups were non significant statistically

Survival	Hypofractionated	Conventional	P – value
Median – over all survival	6.5 month	6 month	0.509
Progression free survival	6 month	5 month	0.967

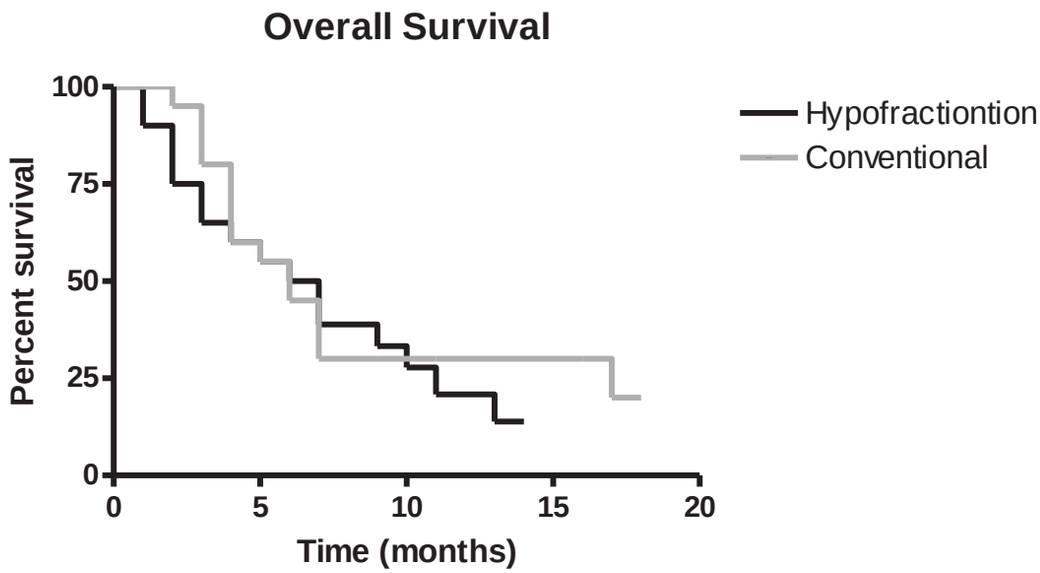

Fig 1: over all survival

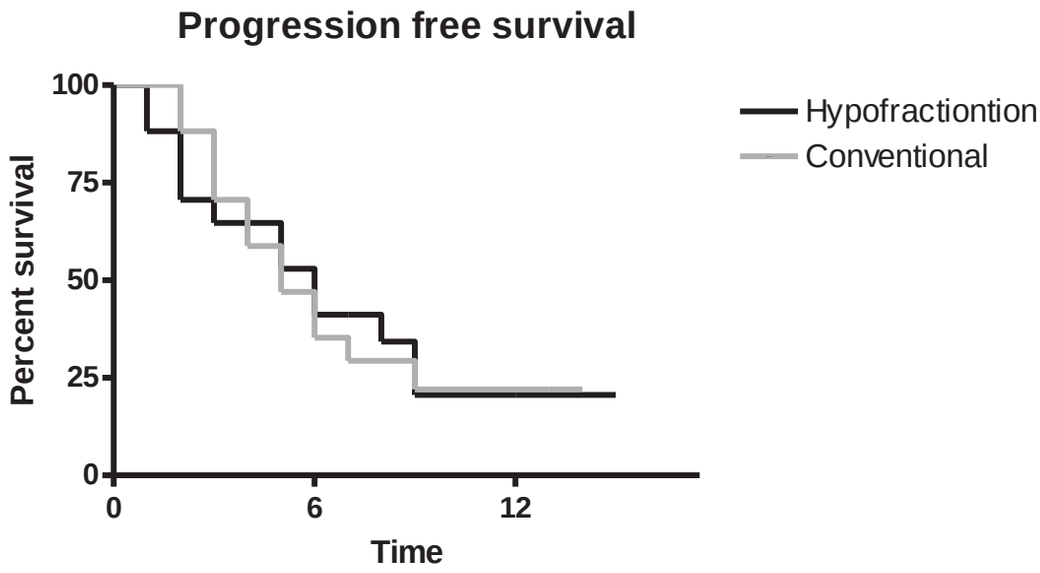

Fig 2: Progression free survival