ORIGINAL ARTICLE

HYPOFRACTIONATED RADIOTHERAPY IN GLIOBLASTOMA MULTIFORME

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Abstract

Purpose: The purpose of this study was to assess the outcomes in glioblastoma patients treated with hypofractionated radiotherapy.

Materials and Methods: We reviewed all glioblastoma patients treated at our specialist cancer centre over 7 and a ½ years using hypofractionated radiotherapy (HRT) postoperatively. The HRT regimen was 48 Gy given at 3 Gy/fractions in 16 fractions. We calculated overall survival using time to event analyses.

Results: A total of 62 patients were identified of whom 44 (71%) were male. The median age of these patients was 50 years (range: 20–71 years). Eastern Cooperative Oncology Group (ECOG) performance status was 0 in 47 (76%) and 1 in 15 (24%) patients. 7 (11%) of the patients underwent gross total resection, 52 (83%) had subtotal resection and 3 (5%) had a biopsy only. Response assessment on magnetic resonance imaging at 3-month post-HRT showed that 14 (22%) patients had regression, 21 (34%) were stable and 22 (35%) had a progressive primary tumour. 5 (8%) patients were lost to follow-up. With a median follow-up of 7.8 months, the median overall survival was 9 months. Patients with ECOG-0 showed a median survival of 7 months as compared to 6 months for those with ECOG-1. Patients with stable or partial response showed a median overall survival of 8 months in comparison to 6 months for those with progressive disease. There were no significant differences in median survival based on the extent of surgery. A Cox multivariate model confirmed significant correlation of age and response to radiotherapy with survival.

Conclusion: HRT consisting of 48 Gy in 3 weeks can be used for selected glioblastoma patients to reduce the overall treatment time of conventional radiotherapy by 35–40% without apparent increased toxicity or decrement in survival in a low resource environment.

Key words: Chemoradiation, glioblastoma, hypofractionated radiotherapy, survival

Introduction

Nearly 700,000 new cases of primary brain tumours are diagnosed each year.[1] Glioblastoma multiforme (GBM) is the most common malignant primary brain tumour accounting for 54% of all gliomas. It is also the most aggressive variety.[1] The incidence of GBM increases after the age of 65 years.[2-4] Treatment of GBM is challenging and has limited success. Median survival following surgery alone is about 4 months.[2] The benefit of post-operative radiotherapy in the treatment of GBM has been documented in randomised controlled trials.[5,6] However, even with post-operative radiotherapy, the median survival time is increased to 9–12 months and the 2-year survival rate remains around 10%. The current standard of care for young patients with good performance status is post-operative chemoradiation followed by adjuvant temozolomide. This intense, long and relatively expensive course of treatment gives a median survival of 14 months, and the overall outcome remains poor. Published data have shown that there can be a worsening of the quality of life after aggressive treatment schedules.[7-9] In patients with GBM, it is desirable to minimise the period of treatment and hospitalisation.[8] In developing

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countries, most patients present at an advanced stage and are offered a selective regimen of hypofractionated radiotherapy (HRT) rather than the standard regimen. We reviewed our data to assess the outcomes amongst GBM patients treated with HRT at our institution.

Materials and Methods

This study was carried out in the Department of Radiation Oncology at Shaukat Khanum Memorial Cancer Hospital and Research Centre (SKMCH and RC), a 189-bed specialist cancer centre in Lahore, Pakistan. We reviewed the medical records of all GBM patients treated at our centre between January 2006 and July 2013. All patients had a histologically confirmed GBM with Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1. Patients with poor performance status (ECOG >1) were excluded from the study. The extent of surgical resection was determined by reviewing the medical records, as well as pre-operative and 4-week post-operative CT or magnetic resonance imaging (MRI) brain scans, the histopathology and by discussion with the neurosurgeon. Gross total resection (GTR) was defined as the radiographic absence on MRI of any persistent enhancement. Any MRI enhancement thought to represent residual tumour after resection was categorised as subtotal resection (STR). HRT was started within 4–6 weeks of the surgical procedure. All patients were treated using a 6 MV linear accelerator and cobalt 60.

The total dose was 48 Gy in 16 fractions of 3 Gy each, with five fractions per week given to the enhancing tumour (GTV), as delineated with the help of MRI scans. Clinical target volume (CTV) was marked with a margin of 2.5 cm, including editing from the natural barriers (bone). Customised Cerrobend blocks or multileaf collimators were used to reduce normal brain irradiation. During radiotherapy, dexamethasone (6–12 mg daily) was given in combination with a proton-pump inhibitor, as well as antiepileptic medication, as needed. After completion of treatment, the dose of dexamethasone was slowly tapered. Temozolomide could not be given to any patients, due to cost constraints. Overall survival was calculated using the Kaplan–Meier method. This study was approved by the Institutional Review Board of SKMCH and RC.

Results

The median age of our patients was 50 years (range 20–71 years) with 44 (71%) males and 18 (29%) females. Patients' demographic characteristics are shown in Table 1. Performance status according to the World Health Organisation criteria was ECOG-0 in 47 (76%) and ECOG-1 in 15 (24%) patients. 7 (11%) patients underwent GTR, 52 (83%) had subtotal resection and 3 (5%) had biopsy only. Response assessment on MRI at 3 months after HRT showed that 14 (22%) patients had regression, 21 (34%) had stable disease and 22 (35%) patients had progressive primary tumour. 5 (8%) patients were lost to follow-up. Radiation toxicity was not recorded formally. With a median follow-up of 7.8 months, the median overall survival was 9 months. Patients with ECOG-0 showed a median survival of 7 months as compared to 6 months for those with ECOG-1. Patients with stable or partial response showed a median overall survival of 8 months in comparison to 6 months for those with progressive disease. There was no significant association of median survival with the extent of surgery. A Cox multivariate model confirmed a significant correlation of age and response to radiotherapy with overall survival [Figures 1-3].

Discussion

Patients with GBM have a dismal prognosis. Surgery followed by chemoradiation and adjuvant temozolomide is considered the standard treatment.[6]

Table 1: Patient characteristics

Patient characteristics	*n* (%)
Median age: 50 years (20-71 years)	
Median follow-up: 7.8 months	
Gender	
Male	44 (71)
Female	18 (29)
Performance status	
ECOG 0	47 (75.8)
ECOG 1	15 (24.2)
Surgery	
Complete	7 (11.3)
Debulking	52 (83.9)
Biopsy	3 (4.8)

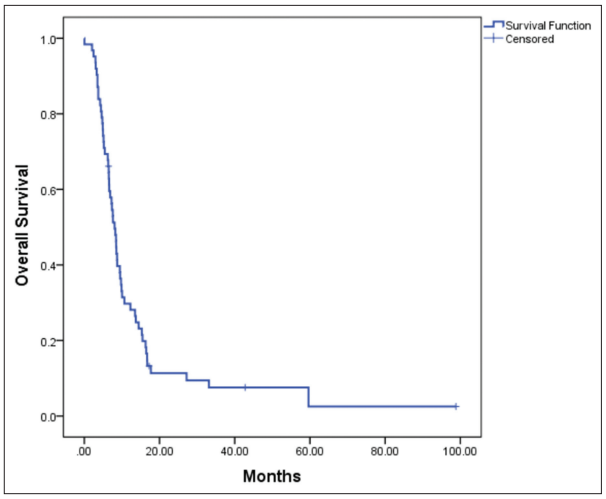

Figure 1: Overall survival of patients

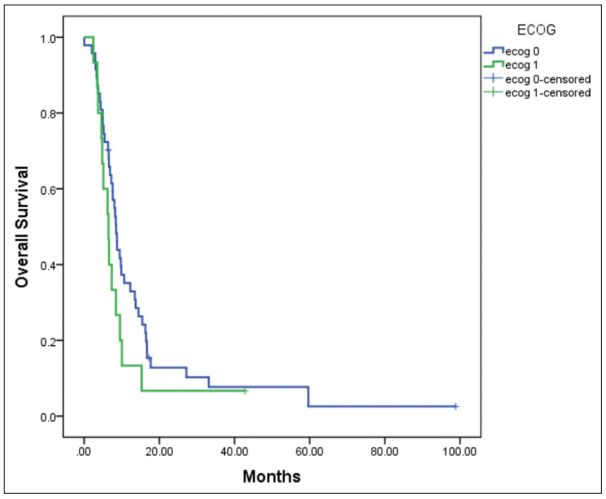

Figure 2: Overall survival of patients stratified by the Eastern Cooperative Oncology Group performance status

The usual dose of conventional radiotherapy for the treatment of GBM with 2.0 Gy/fraction is around 60 Gy.[10] Literature has not shown an improvement in overall survival by increasing the total dose >60 Gy.[10-12] Altered fractionation schemes also do not result in longer survival.[10,13-16] In the studies on accelerated hyperfractionated radiotherapy, using three to four fractions per day, total doses of 36–50 Gy have been delivered in 2–3 weeks, without an increase in toxicity compared to conventional radiotherapy.[13,14]

Hypofractionation is defined as giving a dose per fraction >2.0 Gy with a reduced total number of fractions. Hypofractionation lowers the therapeutic ratio between the tumour and late responding normal tissues. Late normal tissue toxicity is of little clinical relevance in patients with GBM due to their short overall survival. GBM tumours have a rapid doubling time so that standard or hyperfractionated radiotherapy schedules can compromise the outcome due to rapid tumour repopulation.[15] The published data show that almost 12–37.5% of patients show progression at the end of treatment. Hypofractionation provides a dual benefit: First, there is increased cell kill, and second, it reduces the accelerated repopulation of tumour cells.[15]

As calculated by the linear quadratic equation using an alpha/beta 3 Gy for late effects, the biologically effective dose (BED) of 48 Gy/16 fractions in terms of conventional fractionation is 57.6 Gy.[17] This is almost equivalent to the 60-Gy standard established by the Brain Tumour Study Group.[15] The safety of large dose fractionation with one fraction per day has also been documented in patients with GBM.[18-21] We found HRT to be medically well tolerated and a more convenient approach for our patients, as many of our patients came from remote areas. It is also a more resource-friendly radiation treatment schedule. The median survival of patients with GBM is measured in months rather than in years due to their shortened overall survival. Therefore, it is of paramount importance to decrease the duration of treatment and hospitalisation.[22,23] We have used a short radiation schedule with an overall treatment time of 3.5 weeks. The survival rates recorded in this study are comparable to those achieved with conventional radiotherapy schedules, without the use of concurrent or adjuvant chemotherapy. Trials where radiation is used as a monotherapy have shown survival of up to 12 months. We could not assess toxicity in our study due to inadequate data present in our database. Other studies have suggested that important prognostic factors for GBM are age,[10,17,24,25] performance status[10,11,17,24] and extent of surgery.[10,17,24] In an analysis of 645 patients from three radiation therapy oncology group trials, age, Karnofsky performance status, extent of surgery and primary tumour site were identified as independent prognostic factors.[17] In this study, the median survival of patients with ECOG-0 was almost 7 months compared to 6 months in patients with ECOG-1.

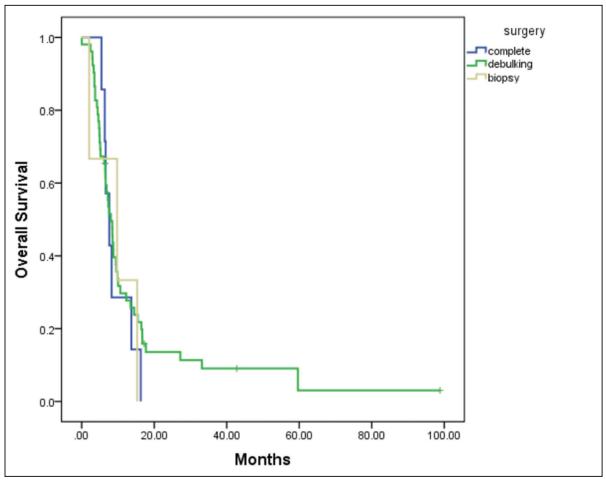

Figure 3: Overall survival of patients stratified by the extent of surgical resection

Limitations of this study

This study has several limitations. First, it was a retrospective review. Second, we were unable to collect data on radiation toxicity amongst our patients. Third, due to cost constraints, we were unable to offer temozolomide to our patients. However, this study offers some evidence that HRT might be appropriate for certain patient populations.

Conclusion

HRT alone is mainly used in elderly patients and those with poor performance status. However, it is a good alternative in good performance status patients when resources are limited. It is a resource-sparing treatment strategy with an acceptable overall survival.

Conflict of Interest

The authors declare that they have no conflict of interest.

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