Survival Outcomes with Two Short-Course Radiation Therapy Protocols in Elderly and Frail Patients with Glioblastoma: Results from a Retrospective Study

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Abstract:

BACKGROUND: Glioblastoma multiforme (GBM) is a fatal brain malignancy with grave prognosis despite advances in treatment, with median overall survival still dismal, which is worst in elderly and frail patients

PURPOSE: To evaluate progression free and Overall survival outcomes in elderly (aged 60 and above) or frail patients with glioblastoma multiforme (GBM) in a pilot retrospective study comparing two short-course radiation therapy fractionations.

METHODS AND MATERIALS: Retrospective two arm study. Elderly (60 years and above) and /or frail patients (with ECOG 3) with a diagnosis of GBM were studied and reviewed. Total 76 patients were reviewed into one of two arms; Arm A: short-course RT (25 Gy in five fractions 5 Gy per fraction daily over a week) or arm B using 40 Gy in 15 fractions over 3 weeks 2.667 Gy per fraction. Treatment planning was either 3D conformal planning or intensity modulated radiotherapy (IMRT). Patients were analysed for progression free survival (PFS) and overall survival (OS) according to age, Eastern Cooperative Oncology Group (ECOG) Performance Status (KPS), and extent of surgery. For patients received concurrent chemotherapy tamozolamide 75 mg / m2 dose was used. Ethical committee approval was obtained.

RESULTS: Median follow up period was 9.02 months (range: 3-16). Concurrent and adjuvant chemotherapy was given among 28/51 patients (54.9%) treated with 40 Gy in 15 fractions.

The 25 Gy/5 fractions/ 1 week RT (25 patients) was better tolerated with less use of post treatment steroid use (28% vs 35.3% in arm B). The median OS time was 7.5 months (95% CI, 6.7-8.4 months) in arm A versus 9.7 months (95% CI, 8.9-10.6 months) in arm B (P=.0001).

Median PFS and OS rates of whole cohort were 7.0 months and 9.0 months in arm A and arm B respectively. However, the median PFS was 5.4 months (95% confidence interval [CI], 4.8-6.5 months) in the five fractions (arm A) and 7.9 months (95% CI, 7.2-8.6 months) in 40 Gy/15 fx/3weeks (arm B) (P=.0.0001).

CONCLUSIONS: A short-course RT regimen of 25 Gy in 5 fractions over a week was found inferior treatment option for elderly or frail patients with GBM as compared to 40 Gy in 15 fractions/ 3 weeks. This May be due to poor Performance of the patients assigned to the shorter arm of five fractions. Further prospective studies with larger numbers are needed.

KEYWARDS: Gbm, Glioblastoma, Hypofractionation.

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Introduction:

Glioblastoma multiforme (GBM) is a fatal brain malignancy with grave prognosis despite advances in treatment, including the addition of temozolomide (TMZ) to adjuvant radiotherapy (RT) [1] with median overall survival still dismal at 16–17 months, which is still worst in elderly and frail patients [2].

60 Gy in 30 fractions of radiotherapy (LCRT) over six weeks with conventional fraction sizes of 1.8–2.0 Gy, with concurrent TMZ is considered the standard for patients with good performance status (ECOG 0-2) [3].

Most patients with glioblastoma are older than 60 years, but treatment guidelines are based on trials in patients aged only up to 70 years.[4] The landmark study by Stupp et al. [2] demonstrated a survival advantage for concomitant and adjuvant temozolomide (TMZ) chemotherapy added to a standard course of RT (60 Gy in 30 daily fractions over 6 weeks) compared to RT alone. The overall survival benefit of this aggressive treatment, however, was attenuated in older or poor performance status patients Additionally, this study excluded patients older than 70 years of age [5]

RT in elderly patients with GBM is associated with improved survival and quality of life (QoL) compared to best supportive care (BSC) [6]. Both temozolomide and hypofractionated radiotherapy should be considered as standard treatment options in elderly patients with glioblastoma [4]

However, Optimal dose fractionation of radiation therapy and additional benefit of chemotherapy in this population are being investigated [7]. Nordic Clinical Brain Tumour Study Group (NCBTSG) reported better efficacy of hypofractionated radiotherapy (34 Gy in 10 fractions) with TMZ in elderly patients aged above 60 years with GBM [4]. Roa W, et al found no difference in survival outcomes between elderly and frail patients with GBM receiving 60 Gy in 30 fractions radiation therapy comparted to short-course 40 Gy in 15 fractions radiotherapy [8].

Recently a phase III trial showed that short-course radiotherapy regimen of 25 Gy in 5 fractions is an optimal treatment option for elderly patients, mainly those with a poor performance status or contraindication to chemotherapy [9].

We aimed to retrospectively assess progression free survival (PFS) and overall survival (OS) outcomes for two different short course radiotherapy regimens (25 Gy in 5 fractions or 40 Gy in 15 fractions) in our elderly and frail patients (>60 years and ECOG 3) with GBM, and to determine the prognostic factors for survival outcomes.

Methods:

After formal approval from Institutional ethical committee, we retrospectively reviewed newly diagnosed GBM patients aged 60 years and above or frail patients (ECOG 3) were enrolled at radiation therapy department in our hospital. Each participant was required to consent in writing.

Eligibility criteria:

a. Age ≥ 60 and / or ECOG 0-3 .
b. Histologically confirmed GBM.

Exclusion criteria:

a. Previous cranial RT,
b. Synchronous malignancy.
c. Failure to commence radiation therapy for GBM within 6 weeks of surgical diagnosis,
d. Inability to comply with follow-up requirements.
e. Unavailability of pre operative and postoperative imaging studies for review.

Treatment

Data of patients reviewed were studied in two groups were studied. Arm A short course radiotherapy (25 Gy in 5 fractions over one week) or Arm B adjuvant short course radiotherapy (40 Gy in 15 fractions over 3 weeks). RT started within 6 weeks of surgery. All patients were treated in one phase radiotherapy. The planning target volume (PTV) was based on preoperative computed tomography (CT) and magnetic resonance imaging (MRI) studies and included the enhancing tumor plus peritumoral edema with a 2-cm margin or a 2.5-cm margin if there was no peritumoral edema. A photon energy of 6 MV or higher was used. Treatment planning was either 3D conformal planning or intensity modulated radiotherapy (IMRT). Efforts were made to limit the dose of radiotherapy to the optic chiasm (54 Gy), retina (50 Gy), and brainstem (54 Gy), provided this could be accomplished without compromising gross tumor volume (GTV). If the location of the tumor was such that these critical structures would inadvertently receive higher doses, the patient was informed in advance of the potential for radiation toxicity. Chemotherapy (TMZ) was allowed in concurrent or adjuvant setting with 40 Gy in 15 regimen. For patients received concurrent chemotherapy tamozolamide 75 mg / m2 dose was used.

Outcomes and Patient Assessments

The primary end point of the study was overall survival (OS), measured from the date of treatment to death from any cause. The secondary end points were progression free survival (PFS), the proportion of patients alive at 6 months, quality of life (QoL), and the steroid requirement of the two groups. Retrospective assessment. At each follow-up, assessment of ECOG, symptoms and steroid use. Imaging assessment was done every 3 months.

Statistical analysis

The target sample size was calculated following the method of Makuch and Simon. [10]. Survival curves were generated using the Kaplan-Meier method. A one-sided 95% CI for the difference in the proportion of patients surviving at 6 months was calculated. Descriptive analysis was performed for frequency and percentage calculation.

Results:

All patients underwent surgical resection. Gross total resection (GTR) was performed in 31 patients (40.8%) and sub-total resection (STR) in 45 patients (59.2%).

Between 2014 and 2016, 76 patients were Retrospectively reviewed between two arms: Arm A: 25 Gy in 5 fractions over a week, 5 Gy per fraction (25 patients) and Arm B; 40 Gy in 15 fractions over 3 weeks (51 patients). All patients completed the treatment protocol without major violations. Chemotherapy was given in 28 (54.9%) patients in arm B. At the time of final analysis, all patients had died.

Baseline and post treatment characteristics are shown in (| Table 1). Mean age of cohort was 64.8 years (range: 60-71). ECOG performance status was 2 in 47 patients (61.8%) and 3 in 29 patients (38.2%).

Median follow up period was 9.02 months (range: 3-16). Median PFS and OS rates of whole cohort were 7.0 months and 9.0 months respectively (Figure 1, Figure 2).

The 25 Gy/5 fractions RT (arm A) was better tolerated in terms of:

- less post treatment steroid use (28% vs 35.3% in arm B; P =0.02),
- headaches (28% vs. 33.3% in arm B) ,
- nausea and vomiting (4% vs. 13.7% in arm B).
- Grade 3 toxicity was seen only in one patient in arm B.

The median PFS and OS in Arm A was inferior to arm B. Median PFS in arm A was 5.4 months (95% confidence interval [CI], 4.8-6.5 months) compared to 7.9 months (95% CI, 7.2-8.6 months) (P=.0.0001) (Figure 1). while the median OS time was 7.5 months (95% CI, 6.7-8.4 months) in arm A versus arm B; 9.7 months (95% CI, 8.9-10.6 months) (P=.0001) (Figure 2). The lower bound of the one-sided 95% CI for the difference in survival at 6 months was 10.6%. Further subset analysis of arm B patients, no difference in PFS (7.6 months vs. 8.5 months; P=0.52) or OS was seen with or without TMZ (9.2 months Vs.10.6; P 0.63).

Discussion:

Retrospective study of patients aged 60 years or older with GBM, we found that patients who were treated with 25 Gy in 5 fractions had inferior progression free and overall survival compared to patients treated with 40 Gy in 15 fractions with or without TMZ. Patients treated with 25 Gy in 5 fractions tended to have more comorbidities, and were not candidates to receive chemotherapy.

Our finding that 25 Gy in 5 fractions is associated with inferior survival outcomes compared to 40 Gy in 15 fractions which differs from the results of several published randomized trials (Table 2).

Our overall survival outcomes were better than previous studies, which may be due to higher percentage of gross tumour resection rates (40.8%) in our cohort which is well established prognostic factor for survival in GBM, although there may be a survival benefit of subtotal resection over biopsy alone [11].

ECOG, another important prognosticator, was also different in the two arms with better ECOG 2 more in longer treatment course [12].

In our study, all included patients completed their radiation course, and 54.9% of 40 Gy in 15 fractions patients received chemotherapy.

With respect to post treatment Quality of life (QoL) and steroid use, patients receiving 25 Gy in 5 fractions had better evaluations. However, we recommend more comprehensive evaluation tools like the FACT-Br, which may be difficult as only few many patients would alive to complete the detailed FACT-Br questionnaire [13].

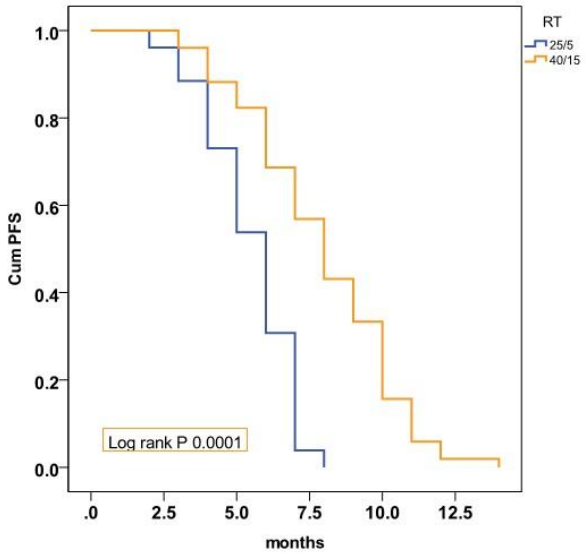

Figure 1: Progression free survival curves

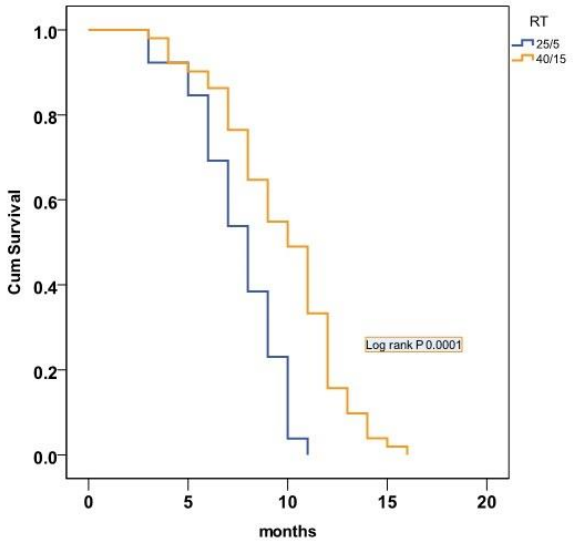

Figure 2: Overall survival curves

Table 1:Characteristics of Patients

Variables	25 Gy in 5 fractions	40 Gy in 15 fractions
Age		
Mean (years)	65.12	64.92
SD	± 3.47	± 4.36
Gender		
Female	13 (52.0%)	26 (50.9%)
Males	12 (48.0%)	25 (49.1%)
ECOG		
2	12 (48.0%)	35 (68.6%)
3	13 (52.0%)	16 (31.4%)
Extent of surgery		
STR	14 (56.0%)	29 (56.8%)
GTR	9 (36.0%)	22 (43.2%)
TMZ	-	28 (54.9%)
Post RT steroid use	7 (28.0%)	18 (35.3%)
Post RT headaches	7 (28.0%)	17 (33.3%)
Post RT N&V	1 (4.0%)	7 (13.7%)

Table 2: Previously published studies of hypofractionated radiotherapy outcomes in Elderly and frail patients with GBM

Hypofractionated RT	Study	PFS (months)	OS (months)
25 Gy in 5 fractions	Guedes de Castro D [8]	4.3	6.8
40 Gy in 15 fractions	Perry JR, et al [1]	3.9	7.6
	Cao J, et al [4]	-	6.9
	Minniti J, et al [5]	-	12.4
	Roa W, et al [6]	-	5.6
	Guedes de Castro D [8]	3.2	6.2

In conclusion, results of our study do not support routine use of 25 Gy in 5 fractions in elderly or frail patients with GBM over 40 Gy in 15 fractions with or without TMZ. This May be due to poor Performance of the patients assigned to the shorter arm of five fractions. Further prospective studies with larger numbers are needed.

We recommend prospective studies incorporating 30 Gy in 6 fractions [close approximation to tumor biological effective dose (BED)] in elderly and frail patients to assess survival outcomes [14, 15].

Authors' contributions

EA—concept and design of study.
EA, MT data collection and tabulation.
EA, MT and TS—data analysis and results.
EA, MT and TS—manuscript drafting and preparation.
EA, MT, TS and HB —manuscript editing and preparation for final publication.
EA, TS and HB-Manuscript revision.
EA, TS and HB— revision and reformatting, submission and correspondence.
All authors have read and approved the manuscript.

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Availability of data and materials

The raw data and materials are available upon request.

Ethics approval and consent to participate

Ethical approval was not required as this is a dosimetry study with no patient randomization.

No consent was required as the study is auditing practice retrospectively.

Consent for publication

Yes, by all authors.

Competing interests

Authors declare no conflict of interest

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