Journal of Neuro-Oncology and Neuroscience
ISSN: 2572-0376

Open access Research Article

A Randomized Study of Radiation Therapy with or without Temozolomide in Elderly and/or Frail Patients and Newly Diagnosed Glioblastoma (GBM)

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ABSTRACT

Addition of temozolamide to standard radiotherapy has shown survival benefit in patient with age 70 or younger. But there has been so far no robust randomized trial evaluating the efficacy of temozolamide with hypo-fractionated radiotherapy. So we in our centre studied the role of Temozolomide with short course (1 week) hypofractionated Radiotherapy in elderly/frail patients.

Aims: To compare Overall Survival (OS) and Progression-Free Survival (PFS) between the two arms.

Settings and design: The Study was Randomized trial of hypofractionated radiotherapy (25 Gy in 5 fractions) with temozolomide (arm A, N=35) or without temozolomide (arm B, N=35). This study was conducted at Department of Radiotherapy, Postgraduate Institute of Medical Education and Research, Chandigarh, India.

Methods and material: Total 70 patients with newly diagnosed Glioblastoma (post-operative) were enrolled and were randomized into two groups using computer generated randomization table.

Statistical analysis used: The t test was used to compare the continuous variables of the two study arms, and chi square tests were used to compare the categorical variables. All tests were two-tailed and a P=0.05 was taken significant.

Results: Median PFS was longer in arm A than in arm B (3.65 and 2.33 months, P=0.028) but median OS was similar (4.86 and 4.033 months, P=0.146).

Conclusions: Addition of temozolomide to hypofractionated radiotherapy (25 Gy in 5 fractions) is a feasible and effective treatment option with limited morbidity for elderly and frail newly diagnosed GBM patients.

Keywords: Radiation; Hypofractionated radiotherapy; Glioblastoma

INTRODUCTION

Glioblastoma is one of the most frequent and aggressive brain tumours. The median age of diagnosis is 64 years and its incidence is increasing in elderly patients. Survival in elderly/frail patients with glioblastoma is grim. This is due to associated comorbidities which decreases the tolerance of standard treatment regimen. The standard of care for glioblastoma has been maximal safe resection followed by concurrent chemo-radiotherapy and adjuvant chemotherapy with temozolomide for 6 months [1]. Stupp et al. have show survival benefit in patients who received standard course of radiotherapy 60 Gy in 30 fractions over 6 weeks with concurrent chemo radiation and adjuvant chemotherapy with temozolomide. In view of limited survival, attempts have been made to curtail the duration of radiotherapy without affecting disease control [2]. Roa et al. showed non-inferiority of shorter course radiotherapy 40 Gy in 15 fractions over 3 weeks compared to standard course radiotherapy 60 Gy in 30 fractions in terms of survival. Perry

Received:	13-May-2020	**Manuscript No:**	IPJNO-20-4091
Editor assigned:	18-May-2020	**PreQC No:**	IPJNO-20-4091 (PQ)
Reviewed:	01-June-2020	**QC No:**	IPJNO-20-4091
Revised:	03-August-2022	**QI No.**	IPJNO-20-4091 (QI)
		Manuscript No:	IPJNO-20-4091 (R)
Published:	31-August-2022	**DOI:**	10.21767/2572-0376.7.4.48

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Citation Subhash T (2022) A Randomized Radiation Therapy with or without Temozolomide in Elderly and/or Frail Patients and Newly Diagnosed Glioblastoma (GBM). J Neuro Oncol 7:48.

et al. showed the advantage of combining concurrent and adjuvant temozolomide with shorter course radiotherapy 40 Gy in 15 fractions. Further attempts have been made to decrease the duration of treatment. Roa et al. showed no difference in Overall Survival OS progression free survival PFS and quality of life QOL with shorter course radiotherapy 25 Gy in 5 fractions over 1 week compared to 40 Gy in 15 fractions over 3 weeks. In view of shorter duration of treatement, 1 week treatment was recommended [3]. These two trials suggested that a shorter course radiotherapy with concurrent and adjuvant temozolomide can be a reasonable treatment option for elderly and frail patients. We attempt to combine the shorter course of radiotherapy 25 Gy in 5 fraction over 1 week with concurrent and adjuvant temozolomide in elderly and frail patients [4].

MATERIALS AND METHODS

90 patients aged>60 years were enrolled at Department of Radiotherapy, PGIMER, Chandigarh, India between 20/08/2018 to 24/04/2019. All these patients were post-operative cases of histopathologically diagnosed glioblastoma. Among these19 were excluded due to various reasons. They were randomly assigned to one of two groups. Pre-treatment evaluation were done for all patients at randomization. Data collected were clinical history and examination, date of surgery, kps score and extent of resection. The extent of surgery was based on the surgeon note and post-op imaging [5].

After randomization and pre-treatment evaluation, patients in arm A received hypofractionated radiotherapy (25 Gy in 5 fractions over 1 week) along with concurrent temozolomide (175 mg/m^2) followed by adjuvant temozolomide (175 mg/m^2, day 1 to day 5 every 28 days) until disease progression. Patients in arm B received only hypofractionated radiotherapy (25 Gy in 5 fractions over 1 week). Radiation was delivered using 3 dimensional conformal radiotherapy technique. Target was determined with post-operative MRI fused with planning CT images [6]. Only one volume was considered throughout. GTV was defined as the entire postoperative enhancing tumour and surgical cavity. Clinical target volume was made by giving a 20 mm margin to GTV with no expansion beyond any anatomical barriers. PTV was drawn giving 5 mm margin to CTV in all directions. The Organs At Risk (OARs) contoured were bilateral eyes, lens, optic nerves, optic chiasm, bilateral temporal lobes, brainstem and spinal cord [7].

Response Evaluation

All patients were evaluated with MRI-Brain at 3 month, 6 month and 9 month post completion of radiotherapy. Disease progression was evaluated according to the response assessment criteria for high grade gliomas (RANO criteria) [8].

Statistical Analysis

Overall Survival (OS) was defined as the time interval between the start of radiotherapy and that of death [9]. Progression Free Survival (PFS) was defined as the interval between date of start of radiotherapy and the date of progression of disease. Progression was defined either as clinically or radiologically. The OS and PFS were calculated using the Kaplan-meir method and compared using the log rank test. Probability value of <0.05 was considered statistically significant.

RESULTS

Patient Characteristics

A total of 90 patients were selected for study, but 19 were excluded. Total of 71 patients were enrolled in the study. The study was held from January 2017 to September 2018 [10]. All 71 patients were randomly assigned patients (36 in arm 1 and 35 in arm 2) were included in the intention to treat analysis. Almost all the patients were followed until they died: 34 (94.44%) assigned to radiotherapy plus temozolomide (arm 1) and 34 (97.4%) assigned to RT alone (arm 2). For the small group of patients who remained alive, the median follow up was 15 months **(Table 1)**.

Table 1: The median age was 63 years. Baseline characteristics and stratification variables were well balanced between the two groups.

Characteristics	No. of patients (%) arm 1 (n=36) RT + TMZ	No of patients (%) arm 2 (n=35) RT alone
Age, years	Median age: 63.22	Median age: 61.63
Gender		
Male	18 (52.9)	19 (51.4)
Female	18 (48.6)	16 (47.4)
KPS	Mean: 70	60
Surgical procedure		
NTE	18 (52.9)	16 (47.1)
GTE	18(48.6)	19 (51.4)
Corticosteroid therapy		
Yes	30	23
NO	6	12

Types of Surgery

Out of 34 patients who underwent NTE, 18 (52.9%) were in arm 1 and 16 patients (47.1%) in arm 2 whereas out of 37 patients who underwent GTE, 18 (48.6%) were in arm 1 and 19 (51.4%) in arm 2. Survival analysis according to extent of resection was done using Kaplan-meier test. The median OS in GTE was 159 days *vs* 129 days in NTE group **(Figure 1)**.

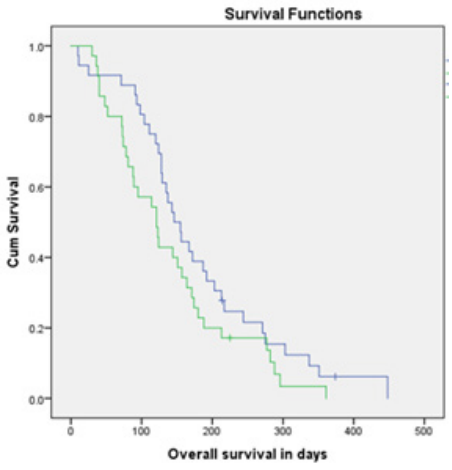

Figure 1: The median OS in GTE was 159 days vs. 129 days in NTE group. **Note:** (⌐¬) GTE,(⌐¬) NTE, (⌐¬) GTE censored, (⌐¬) NTE censored.

Location of tumour: Outl 71 patients, 38 (53.5%) patients had lesion on the right side and 33 (46%) had lesion on the left side

of the brain. The most common lobe affected was temporal (25.4%), frontal (18.3%) and parietal (13%).

Clinical examination at randomization: Out of all patients, 69 (97.2%) were conscious and oriented to time, place and person at presentation, 1 patient was semiconscious and 1 patient was comatose.

The most common neuronal deficit was decreased power in one side of body and normal power in contralateral side (45.1%) followed by decreased power in all limbs (12.7%). No patients had any sensory or cranial nerve deficit at randomization. Most patients had normal gait (35.2%), followed by waddling gait (26.8%). 4.2% patients were not able to walk at all.

Overall Survival

The median overall survival in arm 1 was 146 days whereas median overall survival in arm 2 was 121 days (P=0.146) **(Figure 2)**.

Progression free survival: The median progression free survival in arm 1 and arm 2 were 109.50 days and 77 days respectively with P value of 0.028 (statistically significant) **(Figure 3)**.

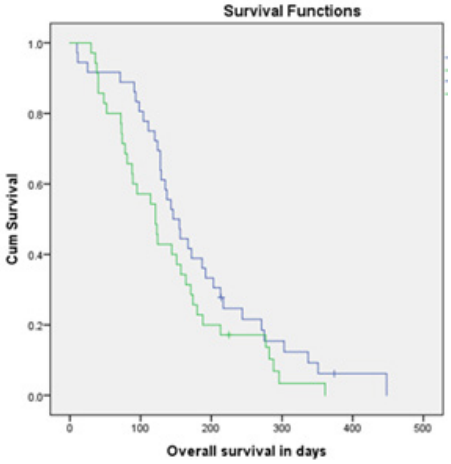

Figure 2: The median overall survival in arm 1 was 146 days whereas median overall survival. **Note:** (⌐¬) arm 1,(¬⌐) arm 2, (⊣—) arm 1-censored, (⊣—) arm 2-censored.

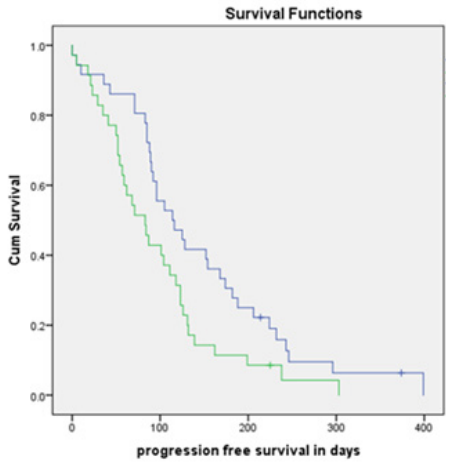

Figure 3: The median progression free survival in arm 1 and arm 2 were 109.50 days and 77 days respectively with P value of 0.028 (statistically significant). **Note:** (⌐¬) arm 1,(¬⌐) arm 2, (⊣—) arm 1-censored, (⊣—) arm -2 censored.

DISCUSSION

The incidence of glioblastoma is higher in the elderly population; the median age of diagnosis is 64 years. Age remains the most powerful prognostic factor among Glioblastoma (GBM) patients. Half of all patients with GBM are aged 64 years or older at the time of diagnosis, and the incidence rate of GBM in patients aged over 65 years is increasing rapidly. Median survival for elderly GBM patients is less than 6 months and reflects less favourable tumour biologic factors, receipt of less aggressive care, and co morbid disease. There are two types of glioblastoma-primary and secondary types. These two types evolve through different genetic pathways, affecting patients at different ages and differing in prognosis and response to therapy. Primary GBM occurs most frequently in elderly patients. The most important prognostic factor for GBM patients are age and general condition. Preclinical models have suggested a role for sex hormones in the development of Glioblastoma Multiform (GBM). However, the impact of gender on the survival time of patients with GBM has not been fully understood. In the study by it was found that the 5-year Cancer Specific Survival (CSS) rates in male and female group were 6.8% and 8.3% respectively (P=0.002). They concluded gender has prognostic value for determining GBM risk and advocated for further investigation. In our study the median overall survival in males and females was 135 days and 143 days (P=0.315). The median PFS in males and females was 88 days and 101 days (P=0.416).

The standard of care for elderly GBM patients remains controversial and undefined. As per Stupp et al. the standard treatment for younger adult patients with favorable KPS, consists of concurrent chemo radiation followed by adjuvant TMZ. But this study showed no significant benefit for patients aged over 65 years in a subgroup analysis from the trial, but this analysis was not prespecifie. The standard of care for elderly GBM patients remains controversial. Among elderly patients, median survival is markedly reduced at only 4-5 months, according to population-based studies [11]. In a trial by Nordic Clinical Brain Tumour Study Group (NCBTSG), where they compared Temozolomide alone vs. Standard Course Radiotherapy (6 weeks) *vs* hypofractionated Radiotherapy in elderly GBM patients (age>60 years), they found that standard course radiotherapy was associated with poorer outcomes in elderly patients (age>70 years). They advised for both temozolomide and hypofractionated radiotherapy. On further analysis, they concluded patients with MGMT promoter methylation would benefit most from temozolomide [12].

The survival of elderly and frail patients with even standard treatment is 6 months. Due to their poor prognosis, the time taken for standard course radiotherapy could constitute a third of the life expectancy for this patient group [13]. So, there is need to curtail the lengthy treatment time in order to reduce the hospital stay of the patient and curtail the treatment cost. At the same time, it decreased hospital stay duration, which provides patients to spend more time at home with family members. There are different studies which have compared standard course Radiotherapy with short course radiotherapy [14]. In NOA-08 trial, Overall survival in temozolomide alone group and radiotherapy alone group was 8.6 months and 9.6 months respectively. They included patients of more than 65 years. On further analysis, they found patients with longest survival were methylated MGMT in temozolomide alone group. NCBTSG trial found that patients treated with temozolo-

mide who had MGMT promoter methylation survived longer than those without MGMT promotor methylation (9.7 months *vs* 6.8 months). Demonstrated no difference in the survival results in elderly patients receiving 60 Gy/30# vs. 40 Gy/15# (O.S 5.1 months' vs. 5.6 months, p=0.57) [15].

Further shortening of time was done in trial by IAEA, which compared standard course radiotherapy (40 Gy/15#) with short course radiotherapy (25 Gy/5#). This trial showed no difference in overall survival, progression free survival and quality of life between patients receiving standard course radiotherapy and short course radiotherapy. No randomized trial has been conducted yet comparing short course radiotherapy alone with short course radiotherapy plus concurrent and adjuvant temozolomide [16]. So, we started a trial with hypothesis that temozolomide added to short course radiotherapy can improve the overall survival, progression free survival without compromising quality of life. We had a total of 71 patients enrolled in the study; all patients were either elderly or frail. All patients included in our study were post-operative either near total excision or gross total excision. The extent of resection has been greatly associated with better outcome. But the location of the tumour often limits the extent of resection. Study by concluded that Partial resection failed to improve survival compared with biopsy for patients with GBM. Moreover, the surgical complication rate in the partial resection group was greater than that in the biopsy group. We analyzed the overall survival according to the extent of surgery. The median overall survival was 151 days with GTE and 129 days with NTE. Though the difference was not statistically significant, it showed the increasing trend of survival with gross tumour resection [17].

A large retrospective study (SEER database) was done of 2836 patients (age>70 years) for median survival. It was analyzed that the median survival for patients who underwent surgery and Radiotherapy, who underwent surgery only and who received radiotherapy only was 8 months, 3 months and 4 months respectively. Those patients who received neither surgery nor radiotherapy had median survival of 2 months only (P<0.001). This study concluded that adjuvant radiotherapy improved cancer specific survival compared to surgery alone. The Study by MRC BR2, compared standard course radiotherapy (60 Gy/30F) with 45 Gy/20F for GBM patients. They showed median survival of 12 months with 60 Gy/30F and 9 months with 45 Gy/20F, (P=0.007). This trial established the role of standard course radiotherapy post-surgical intervention. However, the outcomes remained poor for elderly and poor KPS patients treated with standard course radiotherapy.

A phase II clinical trial published by. Tested HFRT+TMZ (40 Gy, 15 fractions) and adjuvant TMZ in patients aged over 70 years and with a KPS score >60. They reported a 22% rate of grade III-IV toxicities linked to TMZ uptake, the majority (15%) constituting hematologic toxicity (4% in adjuvant TMZ). The median survival was 12.4 months. OS rates at 12 and 24 months were 58% and 20%, respectively published a phase III clinical trial comparing HFRT ± TMZ in patients of 65 years of age or older. The median survival time increased from 7.6 months for radiotherapy alone to 9.3 months for the combined treatment (P<0.001). Elderly patients with GBM are challenging to treat. Study by showed different factors like patient characteristics, study design, treatment delivery and evaluation of outcomes all influence clinical outcomes. The potential morbidity with hypo fractionated RT is the hotspot which could lead to brain necrosis. At the same time, radiobiological advantage of higher doses inside irradiated tumour within PTV could lead to improved overall and progression free survival [18].

CONCLUSION

In our study, Survival analysis for all enrolled patients were done using log rank test with Kaplan Meier survival estimator. The median overall survival in short course radiotherapy with temozolomide was 146 days compared to 121 days in short course radiotherapy arm alone (P=0.112). Though statistically insignificant, there is increasing trend of overall survival with addition of temozolomide to short course radiotherapy. The median progression free survival in short course radiotherapy with temozolomide was 114 days compared to 83 days with short course radiotherapy alone (P=0.024). The significant improve in progression free survival with addition of temozolomide can replicate into improved overall survival and improved quality of life. In conclusion, addition of temozolomide to hypofractionated radiotherapy (25 Gy in 5 fractions) appears to be feasible treatment option for elderly or frail patients.

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