RESEARCH ARTICLE

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

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Abstract

Objective: Short-course radiotherapy (25 Gy in 5 fractions) has been shown to be non-inferior to standard course radiotherapy in elderly and frail patients (60 Gy in 30 fractions). The purpose of this study was to determine the effects of temozolomide combined with short-course radiotherapy on the outcome of elderly and frail patients. **Methods:** Between January 2017 and November 2018, 90 patients (65 years old and KPS score of 50-70; 65 years old and KPS score of 80-100; and 65 years old and KPS score of 50-70) were assessed for eligibility. Nine patients were excluded because they did not meet the inclusion criteria, six patients declined to participate, and four patients were unable to complete the quality-of-life questionnaire. The remaining 71 patients were divided into two arms at random in a 1:1 ratio. Short-course radiotherapy with concurrent temozolomide and adjuvant temozolomide was given to Arm 1, while short-course radiotherapy alone was given to Arm 2. **Results:** In terms of overall survival and progression-free survival, radiotherapy with concurrent temozolomide and adjuvant temozolomide outperformed short-course radiotherapy alone. The median overall survival in arm 1 was 146 days and 121 days in arm 2 (P=0.146). The median progression-free survival in arm 1 was 109.50 days, while it was 77 days in arm 2 (P=0.028). With a median follow-up time of 6 months, the quality of life at 4 weeks and 12 weeks after treatment was not different between the two arms. **Conclusion:** We concluded that adding temozolomide to short-course radiotherapy significantly improved progression-free survival and showed an increasing trend in overall survival without compromising the quality of life.

Keywords: Glioblastoma- short course radiotherapy- temozolomide

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Introduction

Glioblastoma is the most aggressive type of glial cell brain tumor, accounting for 52% of all parenchymal brain tumors and 20% of all intracranial tumors (Kleihues et al., 2002). The median age of diagnosis for glioblastoma is 65 years, and the disease is becoming more common in the elderly (Chakrabarti, 2005). The average age of participants in most trials is 55 years, compared to the median age of diagnosis of 65 years (Laperriere et al., 2013). The median survival time for elderly patients is less than 6 months, which is attributed to comorbid conditions, less aggressive care, and unfavorable tumor biologic factors (Arvold and Reardon, 2014). When glioblastoma is first diagnosed, the standard treatment is maximal surgical resection followed by adjuvant radiotherapy (RT) with concurrent and adjuvant temozolomide (TMZ). Glioma patients treated with surgical resection alone have a 4-6 month survival rate. The combination of surgery and post-operative radiation extends survival time by up to 9-10 months (Keime-Guibert et al., 2007; Galanis and Buckner, 2000). Patients with good performance status are given 60 Gy of long-course radiotherapy over 6 weeks, along with temozolomide (Stupp et al., 2009). However, the treatment of elderly patients is still debatable. The management of elderly patients over the age of 65 is difficult work due to poor prognosis, coexisting morbidities, and the increased toxicity of radiotherapy on the aging brain (Brandes et al., 2009). Curran et al., (1993) identified older age (>50 years) as the most important prognostic factor negatively correlating with survival using recursive partitioning and amalgamation of data from 1,578 patients with malignant glioma treated in several Radiation Therapy Oncology Group (RTOG) studies. Performance status was discovered to be the next most important prognostic factor in patients over the age

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of 50. The median survival time (MST) for patients over the age of 50 with a Karnofsky Performance Status (KPS) score of 70% was 4.6 months. Unfortunately, in Curran's analysis, patients with > 50 years and KPS 70 percent made up the majority of groups IV-VI, which account for roughly three-quarters of all malignant glioma patients. Other studies have found that elderly patients with low KPS have a median survival time (MST) of less than 6 months (Walker et al., 1978). As a result, elderly and/or frail patients constitute a poor prognostic subgroup for which there is no "optimal" RT regimen.

RT dose escalation up to 60 Gy has been demonstrated in studies using a conventional, 2 Gy per fraction schedule delivered over 6 weeks. Dose escalation has demonstrated a survival advantage while maintaining acceptable toxicity. It is difficult for elderly patients to visit the clinic on a regular basis for 5-6 weeks during standard radiotherapy. As a result, it was thought that short-course radiotherapy for 1-2 weeks would improve patient compliance. Such an approach may also be advantageous in terms of travel time or cost, as well as early integration of palliative care. Newall et al., (1988) reported on 18 patients over the age of 50 who received whole-brain radiotherapy (WBRT) with 30Gy in 10 daily fractions over two weeks, with a median survival time of 44 weeks. Ten patients with KPS 70 had a 36-week median survival, while nine patients with KPS 50-70 percent had a 46-week median survival. Hernandez et al., (1990) reported on 14 hospitalized GBM patients with poor prognoses who received accelerated RT. In three weeks, a total treatment dose of 54-55Gy was administered via a combination of weekday RT (100cGy t.i.d.) and weekend RT (150-200cGy in a single fraction). The postoperative KPS ranged from 40 to 70%, with only one patient having a KPS of 90%. Four patients were over the age of 60. The average length of survival was 30.4 weeks. The authors introduced the concept of survival-treatment time ratio, which appeared to improve when the total treatment time was cut in half. It fell from one-third to one-sixth in low-risk patients. Bauman et al., (1994) used the same tumor dose and fractionation to treat 29 GBM patients over the age of 65 with 50% KPS. The average length of survival was 6 months. Kleinberg et al., (1997) described 219 patients with malignant glioma who were treated with Whole Brain RT (WBRT) (30 Gy in 10 daily fractions over 2 weeks), followed by a 2-week gap, and then a cone down boost of 21 Gy over 7 treatment days over 1.5 weeks. RTOG subgroups IV-VI had a median survival of 5.9 months and a 2-year survival rate of approximately 5%. Although it was not specifically investigated, short treatment must have been at least twice as expensive as standard RT. Konski et al., (1997) demonstrated that the shortest RT regimen produced the longest quality-adjusted survival in patients over the age of 50 with high-grade astrocytoma. In patients over the age of 50, a cost-utility analysis revealed that the shortest regimen outperformed longer and more aggressive regimens. The American Society for Radiation Oncology (ASTRO) has recently recommended hypofractionated RT (HRT) to be an appropriate treatment option for elderly and/or frail patients (Sulman et al., 2017). The recent phase III Randomized Multi-Centric trial by International Atomic Energy Agency (IAEA), showed non-inferiority of short-course RT to standard RT in elderly and/or frail patients. The median overall survival and progression-free survivals were 7.9 months and 4.2 months in the short course RT arm as compared to 6.4 months and 4.2months respectively in the standard RT arm. With a median follow-up time of 6.3 months, the quality of life between both arms at 4 weeks after treatment and 8 weeks after treatment was not different (Roa et al., 2015).

The role of concurrent and adjuvant TMZ in conjunction with RT has not been studied prospectively in patients over the age of 70. Stupp's (2005) landmark trial added concurrent and adjuvant TMZ to RT and was the first to show a convincing survival benefit with the addition of TMZ. This trial increased overall survival from 12.1 to 14.6 months. They did, however, include patients with good performance status and excluded patients over the age of 70. However, the vast majority of GBM patients are over the age of 70 or have a poor performance status. As a result, it remains unclear whether the survival advantage demonstrated in this trial also applies to the elderly and/or the critically ill. The Nordic trial compared standard fractionation without TMZ to hypofractionation (34Gy in 10 fractions) without TMZ versus TMZ alone in patients 65 and older. Survival was lower in the standard radiation group, particularly for patients over 70 years old, but this finding is complicated by the low completion rate of radiation in this group (72%), as well as the delayed time from surgery to the start of radiation (mean, 46 days) (Malmström et al., 2012). The German Cancer Society Neuro-Oncology Working Group NOA-08 trial, which included a standard fractionation arm, had a higher survival rate for elderly patients than the Nordic trial. The NOA-08 trial patients had a Karnofsky performance score of 60, started radiation sooner after surgery (mean, 30 days), had a higher completion rate (84 percent), but included cases of anaplastic astrocytoma as well as glioblastoma (although grade was not a significant prognostic factor in this trial) (Wick et al., 2012). Perry et al., (2017) discovered that combining temozolomide with short-course radiotherapy resulted in longer survival than short-course radiotherapy alone. The radiation dose given in this study was 40.05 Gy in 15 fractions over 3 weeks. According to the most recent ASTRO consensus, the addition of TMZ to HRT is safe and effective in elderly GBM patients with good KPS (Sulman et al., 2017). We intended to look into the role of temozolomide in conjunction with short-course RT (1 week) in elderly and/or frail patients.

Materials and Methods

Patients with newly diagnosed elderly and/or frail glioblastoma (65 years old and KPS score of 50-70; 65 years old and KPS score of 80-100; 65 years old and KPS score of 50-70) were eligible for this study. They were assigned to one of two groups at random. Short-course radiotherapy (25 Gy in 5 fractions over 1 week) was combined with concurrent and adjuvant temozolomide in arm 1, while short-course radiotherapy alone was used in arm 2. All patients in the trial were monitored until they died.

All patients had a pre-treatment evaluation that included a history, physical examination, baseline blood tests, and a mini-mental status. Following surgery, contrast-enhanced CT or MRI imaging was performed. Within 7 days of the start of treatment, the quality of life was assessed using the EORTC QLQ-C30 and QLQ-BN20 questionnaires.

Treatment

Patients in both arms received short-course radiotherapy, with arm 1 receiving concurrent temozolomide (75mg/m2 1 hour before RT, daily for 5 days) and adjuvant temozolomide (175mg/m^2 from Day 1 to Day 5 for 6 cycles every 4 weeks) beginning a month after RT completion.

Radiation Treatment Planning

All patients were treated with a linear accelerator with a low energy of 6MV. Depending on tumor size, location, and CT planning, the target volume was treated with a combination of the appropriate number of convergent fields. Various field configurations were acceptable as long as the dose homogeneity within the volume was greater than 10%. Each daily fraction was applied to all fields. The gross tumor volume (GTV) was defined as the total volume of the postoperative enhancing tumor and surgical cavity, or the total volume of the enhancing tumor from which a biopsy was taken. The clinical target volume was calculated by giving the GTV a 2.0 cm margin with no expansion outside of any anatomical barriers (such as the skull). The planning target volume (PTV) was created by giving the CTV a 5 mm margin in all directions. The bilateral eyes, lens, optic nerves, optic chiasma, bilateral temporal lobes, brainstem, and spinal cord were contoured. In both arms, the radiotherapy regimens included a total dose of 25 Gy delivered in 5 daily fractions over 1 week at a rate of 5 Gy per fraction. The maximum allowable difference in dose distribution within the PTV was +10. Dose-volume histograms (DVHs) were used for routine documentation. There was no instance of treatment being halted due to adverse events.

Monitoring and follow up

Patients were evaluated after RT and again four weeks later with a history, physical examination, and a mini-mental state examination. The brain was imaged for the first time three months after RT and then every three months until death. The EORTC QLQ-C30 and QLQ-BN20 questionnaires were completed four weeks after RT and then every three months thereafter.

Results

A total of 90 patients were chosen for the study, but 19 were rejected. The study enrolled a total of 71 patients. Three of these patients were still alive at the time of data analysis, while the others had died. Patients in both groups had similar baseline characteristics, with no significant differences in age, gender, race, KPS, or imaging modality (Table 1). There were 37 men and 34 women among them. The average age of diagnosis was 63. Out of 71 patients, 34 had undergone Gross Total Excision (GTE) and 37 had undergone Near-Total Excision (NTE). All of the patients were diagnosed with grade IV tumors. Temporal (25.4 percent), parietal (18.3 percent), and frontal lobes (18.3 percent) were the most commonly affected (18.3). Except for one patient, none of the patients had any prior neurological deficits. At the time of diagnosis, the majority

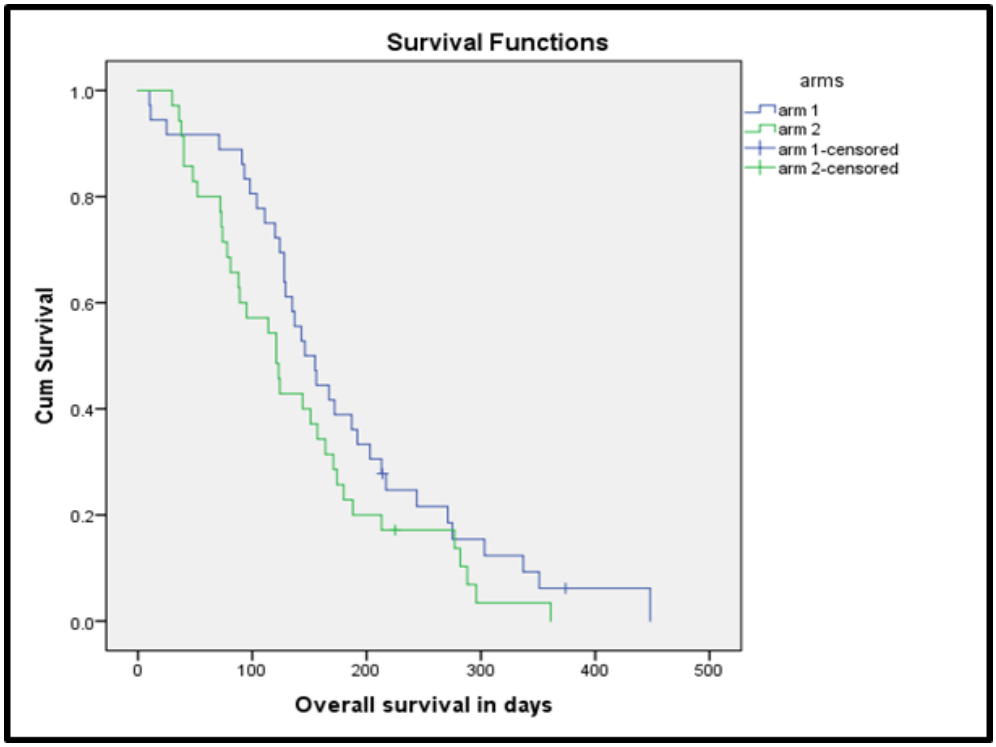

Figure 1. Comparison of Overall Survival between RT with Concurrent and Adjuvant Temozolomide (arm 1) and RT alone (arm 2)

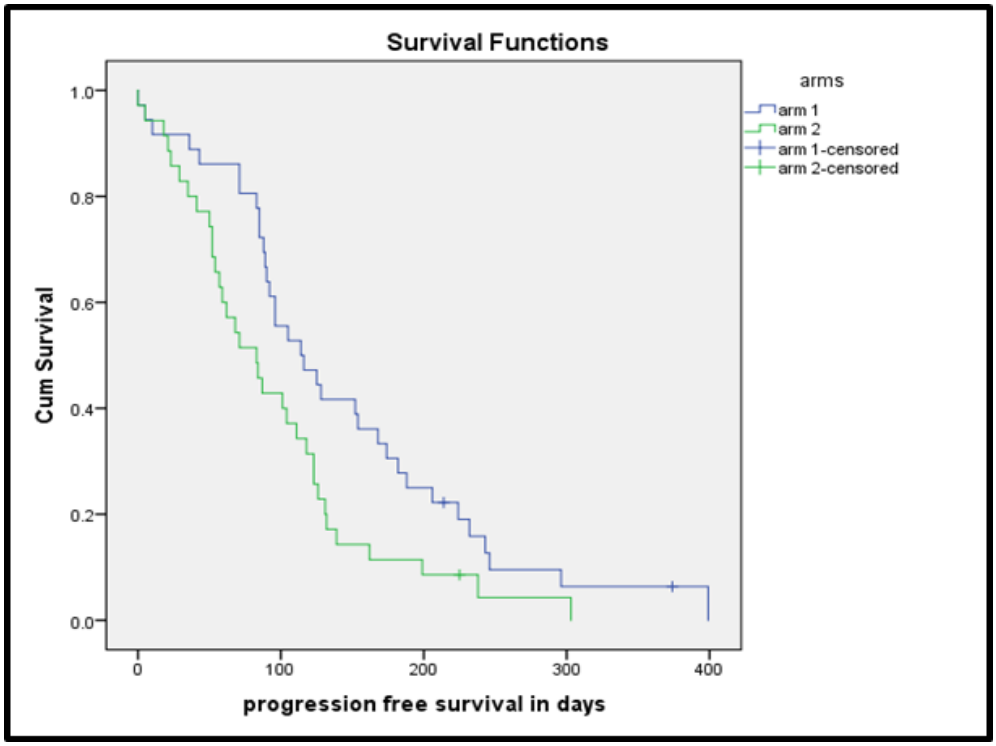

Figure 2. Comparison of Progression-Free Survival between RT with Concurrent and adjuvant Temozolomide (arm 1) and RT alone (arm 2)

of the patients were aware and oriented to time, place, and person (97.2 percent). With a p-value of 0.146, the median overall survival in arms 1 and 2 was 146 and 121 days, respectively (Figure 1). With a P-value of 0.028, the median progression-free survival in arms 1 and 2 was 109.50 days and 77 days, respectively (See Figure 2).

At baseline, one month, and three months, the global health status in arm 1 was stable, with improvement at six months and then rapid deterioration at nine months. Arm 2's overall health improved after one month and six months. It deteriorated gradually at 6 months and rapidly at 9 months.

Discussion

Glioblastoma has one of the poorest prognoses of any type of brain tumor. With an incidence rate of 3.2 newly diagnosed cases per 100,000, it is the most common malignant primary brain tumor (Kleihues et al., 2002). Glioblastoma is more common in the elderly; the median age of diagnosis is 64 years. The most powerful prognostic factor remains age. At the time of diagnosis, half of all patients are aged 64 or older, and the incidence rate in this population group is rapidly increasing (Curran et al., 1993). The median survival time for elderly patients is less than 6 months, reflecting less favorable tumor biologic factors, less aggressive treatment, and comorbid disease. Glioblastoma is classified into two types: primary and secondary. These two types develop via distinct genetic pathways, affecting patients at different ages and with varying prognoses and responses to therapy. The most common is primary glioblastoma, which affects more than 80% of patients (Walker et al., 1978). Primary glioblastoma is most common in elderly patients. Age and general health are the most important prognostic factors. Sex hormones have been implicated in the development of glioblastoma in preclinical models. However, the effect of gender on patient survival time is not fully understood. Tian et al., (2018) discovered that the 5-year cancer-specific survival (CSS) rates in the male and female groups were 6.8 and 8.3 percent, respectively (P=0.002). They concluded that gender has prognostic value in determining glioblastoma risk and advocated for additional research. The median overall survival in this study was 135 days in men and 143 days in women (P=0.315). Males and females had median progression-free survival times of 88 and 101 days, respectively (P=0.416).

For younger adult patients with favorable KPS, the standard treatment is concurrent chemo-radiation (60 Gy in 30 fractions over 6 weeks) followed by adjuvant

Characteristics	No. of patients (%) Arm 1 (n= 36) RT + TMZ	No of the Patients (%) Arm 2 (n=35) RT alone
Age, Median (Years)	63.22	61.63
Sex		
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

†, Kruskal-Wallis ANOVA; two sided P.value<0.05

temozolomide. In a subgroup analysis, however, Stupp et al., (2005) found no significant benefit for patients over the age of 65. The standard of care for elderly patients is still debatable. According to population-based studies, the median survival time for elderly patients is only 4-5 months. In a trial comparing temozolomide alone versus standard course radiotherapy (6 weeks) vs short-course radiotherapy, the Nordic clinical brain tumor study group (NCBTSG) discovered that standard course radiotherapy (6 weeks) was associated with poor outcomes in elderly patients. They recommended short-course temozolomide RT; further investigation revealed that patients with MGMT promoter methylation would benefit the most from temozolomide (Malmstrom et al., 2012). Keime-Guibert et al., (2007) demonstrated that supportive care plus RT (50 Gy in 25 fractions over 5 weeks) outperformed supportive care alone in terms of survival time. Even with standard treatment, the average survival time for elderly and frail patients is 6 months. The time required for standard course radiotherapy could account for one-third of this patient group's life expectancy. There is a need to shorten the lengthy treatment time in order to reduce the patient's hospital stay and treatment costs. Several studies have been conducted to compare standard course RT to short-course RT. Overall survival in the NOA-08 trial was 8.6 months in the temozolomide alone group and 9.6 months in the radiotherapy alone group. They included patients over the age of 65. Further investigation revealed that patients with the longest survival in the temozolomide alone group had methylated MGMT (Wick et al., 2012). The NCBTSG trial discovered that patients treated with temozolomide who had MGMT promoter methylation lived longer than those who did not (9.7 months vs 6.8 months) (Malmstrom et al., 2012). Roa et al., (2004) found no difference in survival outcomes between elderly patients who received 60 Gy in 30 fractions versus 40 Gy in 15 fractions (OS 5.1 vs 5.6 months, p=0.57). A further reduction in time was achieved in an IAEA trial that compared standard course radiotherapy (40 Gy in 15 fractions) with short-course radiotherapy (25 Gy in 5 fractions) (Roa et al., 2015). There was no difference in overall survival, progression-free survival, or quality of life between the two groups in this trial. There has yet to be a randomized trial comparing short-course radiotherapy alone to short-course radiotherapy with concurrent and adjuvant temozolomide. So, we began a trial with the hypothesis that adding temozolomide to short-course radiotherapy would improve overall survival, progression-free survival, and quality of life. The study enrolled a total of 71 patients, all of whom were elderly or frail. All patients in our study had either a near-total or a gross total excision after surgery. The extent of resection has been strongly linked to better outcomes. However, the extent of resection is frequently limited by the tumor's location. According to Byun et al., (2019), partial resection did not improve survival in patients with GBM when compared to biopsy. Furthermore, the rate of surgical complications in the partial resection group was higher than in the biopsy group. We looked at overall survival based on the extent of surgery. The median overall survival with GTE was 151 days and 129 days with NTE. Though the difference was not statistically significant, it demonstrates that survival with gross tumor resection is improving. A large retrospective study (SEER database) on 2,836 patients (age > 70 years) was conducted to determine median survival. The median survival time for patients who received both surgery and radiotherapy, surgery only, and radiotherapy only was 8 months, 3 months, and 4 months, respectively. Patients who did not receive surgery or radiotherapy had a two-month median survival (P 0.001). Adjuvant radiotherapy improved cancer-specific survival compared to surgery alone, according to the findings of this study (Scott et al., 2011). The MRC BR2 study compared standard course radiotherapy (60 Gy in 30 fractions) to a short course (45 Gy in 20 fractions) for patients with GBM. They found that a standard course resulted in a 12-month median survival and a short course resulted in a 9-month median survival (P= 0.007). The role of standard course radiotherapy as a post-surgical intervention was established in this trial. However, the outcomes for elderly and poor performance status patients treated with standard course radiotherapy remained poor (Bleehen and Stenning 1991). Minniti et al., (2012) published a phase II clinical trial in which hypofractionated radiotherapy was combined with concurrent temozolomide (40 Gy in 15 fractions) and adjuvant temozolomide in patients over the age of 70 and with KPS scores greater than 60. They discovered a 22% rate of grade III-IV toxicities associated with temozolomide uptake, with the majority (15%) being hematologic toxicity (4 percent in adjuvant temozolomide). The average length of survival was 12.4 months. At 12 and 24 months, the OS rates were 58 and 20%, respectively. A phase III clinical trial comparing hypofractionated radiotherapy with or without temozolomide in patients 65 and older was published by James et al., (2017). The median survival time for radiotherapy alone increased from 7.6 months to 9.3 months for the combined treatment (P0.001). Elderly patients are difficult to treat. Bauchet et al., (2014) discovered that various factors such as patient characteristics, study design, treatment delivery, and outcome evaluation all influence clinical outcome. The potential morbidity associated with hypofractionated radiotherapy is a risk factor for brain necrosis. Simultaneously, the radiobiological advantage of higher doses inside irradiated tumors within PTV may lead to improved overall progression-free free survival. In our study, we used log-rank with the Kaplan Meier survival estimator to conduct survival analysis on all enrolled patients. The median overall survival with temozolomide was 146 days, compared to 121 days in the short course radiotherapy arm alone (P=0.112). Though statistically insignificant, the addition of temozolomide to short-course radiotherapy increases overall survival. Short-course radiotherapy with temozolomide had a 114-day median progression-free survival compared to 83 days with short-course radiotherapy alone (P=0.024). With the addition of temozolomide, the significant improvement in progression-free survival can be translated into improved overall survival and quality of life. Taphoorn et al., (2005) discovered that patients who received both radiotherapy and temozolomide lived longer than those

who only received radiotherapy, and that longer survival was not associated with a significantly lower quality of life. This could be good news for glioblastoma patients. They used the EORTC QLQ C-30 and EORTC QLQ BN20 tools, which we also used for this study. The main challenge in analyzing quality-of-life data collected at various time points is that people with the poorest quality of life die, leaving only the healthier to live. Another problem with interpreting quality-of-life data is that not all components of the questionnaires appear to have the same effect on disease burden. According to Weitzneret al., (1997), glioblastoma patients' social functioning deteriorates, which leads to depression. Because the median overall survival in elderly and/or frail GBM patients is less than 6 months, the quality of life during this time is critical. According to Roa et al., (2015), there is no significant difference in the quality of life between patients who receive short-course radiotherapy with and without temozolomide. The two groups had similar baseline quality of life scores for symptom and function domains. Although nausea and constipation were worse during chemoradiotherapy than radiotherapy alone, changes in scores on all other symptom and function domains were comparable between the two groups. The EORTC QLQ-C30 and QLQ-BN20 quality-of-life questionnaires were used in our study to assess quality of life. The global health status in the temozolomide radiotherapy arm was stable until 3 months after treatment, then improved for 6 months before rapidly deteriorating at 9 months. The global health status improved after 1 month and 3 months of radiotherapy alone. It deteriorated gradually at 6 months and rapidly at 9 months. The rapid deterioration seen in both arms could be attributed to the disease's rapid progression. Rapid progression increases intracranial pressure, resulting in a decline in quality of life at the end of life. Both groups performed similarly in terms of physical functioning, role functioning, emotional functioning, cognitive functioning, and social functioning, with no significant differences. Symptoms in both groups were comparable from baseline to 9 months after treatment. Because survival in glioblastoma patients is very low, an acceptable quality of life should be considered. This should be a primary goal for all studies aimed at treating glioblastoma. Rather than using quality of life as the endpoint, studies should focus on a more sophisticated assessment of quality of life. As a result, studies that provide a deeper understanding of individual variables that influence subjective interpretations of quality of life are needed. These studies would shed more light on the research in this field.

Author Contribution Statement

1. First Author, Subhash Thakur; Concept design, Data Collection, Data Analysis, Manuscript Writing. 2. Second Author, Narendra Kumar; Concept design, Data Analysis, Manuscript Writing. 3. Third Author, Pravin Salunke; Manuscript Writing. 4. Fourth Author, Chirag Ahuja;Manuscript Writing. 5. Fifth Author, Renu Madan;Manuscript Writing.

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It is part of an approved student thesis. This study was approved by the ethical committee of the Post Graduate Institute of Medical Education and Research (PGIMER).

This study was registered in The Clinical Trials Registry- India, CTRI/2018/07/014931.

Conflict of interest

No conflict of interest.

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