Original Article

Comparative outcomes of short-term and long-term fractionation with temozolomide in older glioblastoma patients: Single-center experience

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ABSTRACT

Background: The main goal of our study is to comparatively evaluate outcomes of hypofractionation and long-term fractionation with temozolomide (TMZ) in glioblastoma patients older than 65 years.

Methods: Eighty patients with glioblastoma meeting the eligibility criteria of >65 years of age, the Karnofsky performance score (KPS) >60, no previous radiotherapy (RT) to the brain referred to our department between October 2009 and October 2016 for adjuvant chemoradiotherapy after surgery were studied. The first group of patients received a dose of 6000 cGy in 30 fractions and the second group was delivered 4000 cGy in 15 fractions All patients used TMZ concomitantly with RT. We used the paired *t*-test and the Wilcoxon signed-rank test with Statistical Package for the Social Sciences, version 15.0 (SPSS, Inc., Chicago, IL, USA) software for statistical analysis.

Results: Forty-six patients were men (57.5%), and 34 patients (42.5%) were woman. Median age was 68 years (range 66–87). Median KPS was 75 (range 60–100). Median follow-up time was 12 months (range 6–30). Median overall survival was 15.2 months and 14.3 months for patients with hypofractionation and conventional fractionation, respectively, with no statistical significance ($P = 0.13$).

Conclusion: Hypofractionation should be recommended to the elderly glioblastoma patients older than 65 years because of the short treatment time, reduced acute adverse effects of both TMZ and RT compared to long-term fractionation.

KEY WORDS: Glioblastoma, hypofractionation, older

INTRODUCTION

Hypofractionation with temozolomide has been widely used in glioblastoma patients since it was approved by decision making studies. We intended to compare short-term and long-term radiotherapy (RT) with temozolomide (TMZ) in older glioblastoma patients. Glioblastoma, anaplastic astrocytoma and anaplastic oligodendroglioma are malignant, rapidly progressive brain tumors in adults. The most common malignant primary brain tumor is Grade 4 glioblastoma according to the World Health Organization (WHO) Classification. 0–6-methyl guanine DNA methyl transferase (MGMT) status affects outcomes of treatment with TMZ in glioblastoma. Isocitrate dehydrogenase mutation and the codeletion of 1p and 19q status divide gliomas to the subgroups.

High-grade gliomas are treated with a combined-modality approach including postoperative chemoradiation therapy and adjuvant long-term chemotherapy following surgery. Involved field RT plus margin is the standard treatment approach for adjuvant RT in patients with high-grade gliomas. Limiting the RT field is based on the fact that high-grade glioma recurrences occur after within two centimeters of the original tumor site in 80%–90% of cases.

Conventional 60 Gy RT dose is usually delivered to the residual tumor or tumor bed plus a margin.

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Target volume is determined by T2-weighted magnetic resonance imaging (MRI) abnormality within a 1.0–2.0-cm margin. When T1 contrast-enhancement volume is used for planning, T2-defined tumor and a margin of 2.0–2.5 cm is usually used to define the target volume.

Patients who are managed with doses of 50–60 Gy had a longer median survival compared to others who received lower doses. 60 Gy in 2-Gy fractions is the standard target dose for glioblastoma. Dose escalation above 60 Gy with different fractionation regimens has not been shown to gain further benefit. Dose escalation to the contrast-enhancing volume is the subject of ongoing trial.

Nowadays, computed tomography (CT)-based treatment planning with novel software is used to create treatment plans for intensity modulated radiotherapy (IMRT). Fusion of planning CT and MRI may assist in definition of RT target volumes.[1] 6 Mv photon is the most commonly used beam energy.

More than half of the patients with glioblastoma are 65 years of age or older. Older age and poor performance status affect prognosis with shorter survival. The dismal prognosis of older adults in this group has led to uncertainty for optimal treatment. Comorbid disease, polypharmacy, social and economic status guide treatment decisions in older glioblastoma patients.

While hypofractionated radiation therapy plus TMZ has been increasingly used in older patients, a 6-week radiation regimen is typically used in younger adults. 40 Gy in 15 fractions delivered in 3 weeks has been increasingly popular as an alternative fractionation.

Older patients may not tolerate the 60 Gy long course-radiation. The optimal fractionation and total dose still remain uncertain in older patients. Standard course radiation therapy have lower normal tissue toxicity rates for late effects, however, the median survival of glioblastoma patients is <12 months.

Short course RT has similar efficacy with lower short-term toxicity compared to long-term course. Hypofractionated regimens seem to be appropriate for older patients with a poor functional status. The aim of our study is to comparatively evaluate outcomes of hypofractionation and long-term fractionation with TMZ in glioblastoma patients older than 65 years.

We intended to compare the two groups with older age and glioblastoma received either short-course or long-course chemoradiotherapy. The basic rationale of our study was to evaluate dose-dependent results in limited age group.

METHODS

Eighty patients with glioblastoma meeting the eligibility criteria of >65 years of age, Karnofsky performance score (KPS) >60, no previous RT to the brain referred to our department between October 2009 and October 2016 for adjuvant chemoradiotherapy after surgery were studied. This study is a retrospective trial comparing two groups including short course and long-term RT with TMZ. Informed consents of all patients were collected from their files before the research and the study was performed in compliance with the Declaration of Helsinki principles.

CT images were acquired for each patient with proper procedure. All patients were immobilized in supine position with both arms on the side, using a thermoplastic head mask. Three radiopaque markers were used to assist in target definition. After positioning and immobilization were completed, scans were acquired at CT-simulator (GE Lightspeed RT, GE Healthcare, Chalfont St. Giles, UK) to use for treatment planning. Both scans were acquired with 0.25 cm slice thickness. The acquired images were sent to the contouring workstation through network. Magnetic resonance scans of the patients acquired 1–2 days before planning CT images were fused with the planning CT scans. Advantage sim MD simulation and localization software (advantage sim MD, GE, UK) was used for contouring treatment volumes and critical organs. Gross tumor volume (GTV), clinical target volume (CTV), planning target volume (PTV), body, eyes, optic nerves, eyeballs, chiasm, and brainstem were delineated on both scans. GTV was delineated only the tumor and edema in T2-scans, CTV was GTV plus 2 cm. and PTV was CTV plus 0.5 cm. PrecisePLAN (Elekta, UK) Treatment Planning System was used in generating the three-dimensional conformal RT plans for each patient. Beam organizations, wedges, and the beam angles were applied in all plans of the patients. Multileaf collimators were used to shape treatment fields when necessary. The CTV coverage was between 90% and 110% of the prescribed dose. Dose-volume histograms were generated for all delineated structures. The treatment was delivered using a linear accelerator (Synergy, Elekta, UK) allowing on-line set-up verification under image guidance with kilo-voltage cone beam CT (X-ray volumetric imaging, Elekta, UK) mounted on the LINAC gantry. Follow-up visits were scheduled for every patient routinely at 3-month intervals.

Eighty patients with glioblastoma undergoing surgery referred to our department for adjuvant chemoradiotherapy between October 2009 and October 2016 were compared in terms of the fractionation schedules of hypofractionation and conventional fractionation. Two groups were generated. First group consisted of 42 patients receiving 6000 cGy in 30 fractions with daily 200 cGy. Second group included 38 patients who received 4000 cGy in 15 fractions with daily 266 cGy. All patients in both the groups used 75 mg per square meter of body-surface area per day TMZ with RT 7 days per week and six cycles consisting of 150–200 mg/m^2 for 5 days during each 28-day cycle after chemoradiotherapy as an adjuvant treatment. Age, KPS, overall survival (OS), progression-free survival were noted and

analyzed between these two groups. Patients were followed up at 3 months' intervals.

Statistical analysis

In descriptive statistics, mean and standard deviation was used for normally distributed variables which were analyzed using the paired *t*-test, and median (minimum–maximum) was used for nonnormally distributed variables which were analyzed using the Wilcoxon signed-rank test. Hazard ratio (HR) and confidence interval (CI) were determined. Statistical Package for the Social Sciences, version 15.0 (SPSS, Inc., Chicago, IL, USA) software was used for analysis and the level of significance was set at $P < 0.05$.

RESULTS

Eighty patients older than 65 years received RT for glioblastoma between October 2009 and October 2016. Thirty-eight patients were managed with hypofractionated RT in 40 Gy and other 42 patients were treated with conventional RT in 60 Gy. All patients in groups were received TMZ. Both groups used 75 mg per square meter of body-surface area per day TMZ with RT 7 days per week and six cycles consisting of 150–200 mg/m^2 for 5 days during each 28-day cycle after chemoradiotherapy as an adjuvant treatment. Out of the total 80 patients, 46 patients were men (57.5%), and 34 patients (42.5%) were women. The median age was 68 years (range 66–87). Median KPS was 75 (range 60–100). Median follow-up time was 12 months (range 6–30). Forty six patients had received 60 Gy in 2 Gy fractional dose RT with concurrent and adjuvant TMZ according to Stupp protocol at primary diagnosis of glioblastoma. Other groups of 34 patients were delivered 40 Gy in 2.66 Gy per fraction with TMZ. The type of surgery at primary diagnosis included total resection in 24 patients (30%), subtotal resection in 40 patients (50%), and biopsy in 16 patients (20%). Tumor localization was in the frontal lobe in 14 patients (17.5%), in the parietal lobe in 22 patients (27.5%), in the temporal lobe in 24 patients (30%) and in the occipital lobe in 20 patients (25%). Pathological review confirmed the diagnosis of glioblastoma in 100% of patients. Median OS was 15.2 months and 14.3 months for patients with hypofractionation and conventional fractionation, respectively, with no statistical significance ($P = 0.13$). HR was 1 for two groups with 95% CI. There was no interruptions due the toxicity for the entire group. Sex, extent of surgery at primary diagnosis and lesion location were not associated with OS. All patients continued adjuvant TMZ for 6 months. Adverse events were analyzed during concomitant and adjuvant period of chemoradiotherapy. Entire group were followed weekly within the chemoradiotherapy period and monthly in the adjuvant period. Three patients in hypofractionation group had hematological toxicity but six patients in conventional group suffered from hematological toxicities. Out of these three patients in first group, two patients had grade 3 thromocytopenia, one patient had Grade 1 anemia. Out of these six patients in second group, four patients had Grade 3 thrombocytopenia, two patients had Grade 2 anemia. No infections or thromboembolic events were seen in the study groups. Patient characteristics are listed in Table 1.

DISCUSSION

Chemoradiation and long-term chemotherapy following maximal surgical resection has been standard for glioblastoma patients. Overall treatment time and biological effective dose are the problems for this aggressive disease with dismal prognosis. Hypofractionated accelerated RT reduces total treatment interval and increase also biological effective dose finally. 60 Gy in 20 fractions over 4 weeks and 60 Gy in 30 fractions over 6 weeks were compared for OS by Mallick *et al*. The advantages of hypofractionated treatment are dose escalation and decreasing overall treatment time.[2] The optimal treatment time and scheme has not still been established. Matsuda *et al*. analyzed 45 Gy in 15 fractions with TMZ followed by bevacizumab as a salvage treatment in glioblastoma patients older than 75 years old. Results are found to be safe and effective with hypofractionated RT.[3]

34 Gy in 10 fractions combined with TMZ was analyzed in literature for the outcomes and tolerability. Ten patients were enrolled in this hypofractionated scheme and tolerability was better for this elderly group of patients.[4] Increased cell death and reducing tumor cell population are the advantages of short term treatment in glioblastoma. High dose RT also brings radionecrosis which may be radiographically defined. Retrospective studies are more than prospective ones about this issue. Gerasimov *et al*. advised hypofractionation as a safe and feasible option for elderly.[5] Radiation necrosis, neuroendocrine dysfunction, neurocognitive decline are the long-term effects of hypofractionation. Intensity-modulated RT and proton therapy improve conformality and normal tissue protection.[6]

There are limited data about optimal treatment of elderly glioblastoma patients. When the best supportive care was the only treatment for glioblastoma after surgery for elderly patients in past, NORDIC and NOA-08 studies recommended RT or hypofractionated RT with TMZ to this group of patients and this scheme started to be used by clinicians. Hypofractionation should be the optimal treatment but conventional 60 Gy was not advised by some reviewers

Table 1: Patient characteristics

	Long-term	Short-term
Sex (%)		
Woman	20 (25)	14 (17.5)
Man	22 (27.5)	24 (30)
Age (years) (mean)	66	71
KPS (mean)	74 (60-90)	79 (65-95)
Extent of surgery (%)		
Biopsy	8 (10)	8 (10)
Subtotal resection	24 (30)	16 (20)
Total resection	14 (17.5)	10 (12.5)
OS (months)	14.3	15.2

KPS= Karnofsky performance score, OS= Overall survival

in literature.[7] Haque *et al*. analysed 5126 glioblastoma patients for the outcomes of hypofractionation and conventional fractionation. Only 126 of all were managed with hypofractionation and the other 5000 patients were delivered conventional treatment. Conventional fractionation improved OS compared to hypofractionation but the different number of two groups may have reached the conflicting results. The use of hypofractionation has been increasing in recent years.[8] 267 newly diagnosed glioblastoma patients were enrolled in comparative analysis for hypofractionation and conventional schedule. 60 Gy in 15 fractions and 60 Gy in 30 fractions with chemotherapy were compared. No statistical significance was defined in this study which resulted with comparable outcomes of both groups.[9] Only hypofractionation resulted in shorter survival time compared to combined treatment of chemoradiotherapy. Optimal surgery and adjuvant chemoradiotherapy with hypofractionation potentially improved outcomes in elderly glioblastoma patients irrespective of MGMT status.[10] Hypofractionated RT with 40 Gy, conventional RT with 60 Gy, chemotherapy and best supportive care were comparatively analyzed in an article by Bingham *et al*. Hypofractionation was also better than best supportive care and had similar results with conventional fractionation.[11] Chemotherapy and hypofractionation combination had better OS regardless of older or younger than 65 years compared to single hypofractionation. This study enrolled the patients with glioblastoma in National Cancer Database diagnosed between 2005 and 2012.[12]

The elderly glioblastoma is defined as patient older than or equal to 65 years and worsening prognosis with increasing age. 40 Gy in 15 fractions with TMZ is suitable and effective adjuvant therapy for this group. Older patients with glioblastoma have not been recommended management due to the comorbid issues and toxicity of treatment, however, reviews in literature show that more aggressive resection and hypofractionation with TMZ improve survival.[13] The factors influencing treatment outcomes of glioblastoma are Karnofsky Performance Status, MGMT methylation status and aggressive surgical resection.[14] Concomitant hypofractionated RT and TMZ with simultaneous integrated boost therapy was analyzed in 24 glioblastoma patients by Scoccianti *et al*. This novel approach may be suitable and logical treatment approach for patients with good prognosis.[15] Hypofractionation with TMZ was compared to only hypofractionation in an article by de Moraes and Laperriere. The results of this study associated with OS and prognosis seem to be improving with combined treatment.[16] Accelerated hypofractionation was delivered with 6 Gy in 6 fractions to contrast-enhancing tumor plus 5 mm and 4 Gy in 6 fractions to fluid-attenuated inversion recovery plus 2 cm. This scheme reduced total treatment time to 6 days in 2 weeks. Tolerability of this acceleration, OS, progression-free survival was similar to the historical outcomes with decreased steroid usage.[17] While advanced age and poor performance status are the major concerns for glioblastoma, there is a tendency for investigations about novel medical approaches and hypofractionation schemes.[18]

In an article by Harris *et al*., patients with glioblastoma older than 80 years and between 74 and 80 years old were compared for survival outcomes. Elderly glioblastoma do not have a worse prognosis as it was supposed by the current data. Selected elderly patients should deliver extended surgery and adjuvant chemoradiotherapy combination.[19] Although treatment associated toxicities are increased with chemoradiotherapy in elderly glioblastoma patients compared to only hypofractionation, moderate improved survival results are better with combination therapy.[20] Chemoradiotherapy following extended surgery seems to be better than only external beam radiotherapy with it is survival advantage. Hypofractionation usage has been increasing over conventional fractionation in elderly glioblastoma population by the radiation oncologists worldwide.[21] OS was compared between patients newly diagnosed older than 65 years and younger than 65 years. Elderly patients had shorter OS compared to younger patients before surgery and adjuvant chemoradiotherapy combination because of the older treatment methods including only supportive care, radiotherapy or TMZ.[22] The American Society of Clinical Oncology and American Society for Radiation Oncology guidelines recommend focal reirradiation through stereotactic radiosurgery (SRS) or fractionated stereotactic radiotherapy after local relapse.[23] Hypofractionated radiotherapy with TMZ was delivered between 35 and 42 Gy in 10 fractions by Uto *et al*. No Grade 3 nonhematological adverse effect was seen while only one patient in this group experienced Grade 4 neutropenia.[24] Standard conventional fractionation with 60 Gy in 30 fractions and hypofractionation with 40 Gy in 15 fractions were comparatively analyzed by Wang *et al*. in elderly glioblastoma. Outcomes showed that OS rates were similar between two groups.[25] Another study from Greece was about hypofractionation of 45.5 Gy in 13 fractions for 14 elderly glioblastoma patients. This study recommended hypofractional dose as an alternative to 2.66 Gy daily dose in 15 fractions.[26] Hypofractionation studies for high grade glioma patients is presented in Table 2.

Our study has similar results with current literature for the elderly glioblastoma patients. The advantages of our study are to have patients more than 65 years old with glioblastoma in this study interval and the experience of our center about this WHO Grade 4 tumor. The limitations of our study enroll single center experience and the limited number of study population.

Median OS was increased from nearly 12–14 months with this Stupp's scheme.[27] 40 Gy in 2.66 Gy is as effective as 60 Gy in 2 Gy for elderly glioblastoma with decreased radiotherapy time and similar OS.[28] Recurrent glioblastoma lesions should be treated with re-excision, bevacizumab, IMRT or SRS according to the patient's KPS, tumor and edema size, location and the treating physician's choice.[29]

Table 2: Hypofractionation studies for high grade glioma patients with older age

Author	Year	Number of patients	Grade (glioma)	Dose (fractions)	Median survival (months)
Thomas	1994	38	Grade 3-4	30 Gy/6	6
Jeremic	1999	44	Grade 4	45 Gy/15	9
Roa	2004	100	Grade 4	60 Gy/30	5.1
				40 Gy/15	5.6
Malmstrom	2012	342	Grade 4	60 Gy	6
				34 Gy	7.5
Minniti	2012	71	Grade 4	40 Gy/15	12.4
Minniti	2013	65	Grade 4	40 Gy/15	12.4

CONCLUSION

Hypofractionation should be recommended to the elderly glioblastoma patients older than 65 years because of the short treatment time, reduced acute adverse effects of both TMZ and RT compared to long term fractionation.

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Conflicts of interest

There are no conflicts of interest.

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