

Hypofractionated Radiation Therapy with Temozolomide for Patients with Glioblastoma Multiforme Recursive Partitioning Analyzes Class V and VI

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ABSTRACT

Objective: This study was performed to determine whether adjuvant temozolomide and 45 Gy/15 fr hypofractionated radiotherapy (RT) can be used to shorten the treatment duration in glioblastoma multiforme (GBM) patients with poor prognostic factors (Recursive Partitioning Analyzes (RPA) categories V, VI), without increasing the dose and toxicity and without risking the survival.

Methods: Patients older than 50 years, with histological diagnosis of GBM, who were in either RPA class V or VI were included in this retrospective single-arm single-center study. Patients were treated with a tumor dose of 45 Gy in 15 daily fractions in 15 treatment days in three weeks, together with concomitant temozolomide and adjuvant temozolomide.

Results: A total of 43 patients were included in this study. RT was completed as planned in full dose in all patients. No grade 3 acute toxicity due to hypofractionated RT was observed. Concomitant temozolomide was also used in all patients without dose lowering while adjuvant temozolomide as six cycles was applied in 27 patients, but in 12 of them, temozolomide dose was lowered due to hematological toxicity. Median overall survival was found as 10.5 months, and 1-year overall survival proportion was 42%. The median progression-free survival time was 8.4 months.

Conclusion: While no decrease in expected survival with hypofractionated radiotherapy and temozolomide was detected, no increase in toxicity was observed.

INTRODUCTION

High-Grade Gliomas are the most commonly encountered primary brain tumors in adults and Glioblastoma multiforme (GBM) is one of the most rapidly progressing and fatal tumor in high-grade gliomas.^[1] Surgery plus chemotherapy and radiotherapy (RT) are the gold standard treatment of GBM.^[2] Postoperative radiotherapy is usually administered with 2 Gy daily fractions in six weeks. Improvement in survival was achieved with chemotherapy added to radiotherapy; however, five-year survival is very low (9.8%).^[3,4] In these patients with short survival expectation, a shorter duration of treatment has been considered, and hypofractionated RT schedules were studied. In a randomized study reported by Poland et al. 44 patients with GBM who were treated with three split courses of hypofractionated RT to

a total dose of 50 Gy.^[5] Patients with GBM treated with hypofractionated RT regimen, had a better prognosis in comparison to the conventionally fractionated group with the two-year survival rates being 23% and 10%, respectively. In elderly GBM patients treatment with a shorter hypofractionated radiotherapy course demonstrated similar survival and palliative benefit compared to a standard 6-week course (overall survival 5.6 versus 5.1 months, $p=0.57$) in the study reported by Roa et al.^[6]

The RT schedule in Stupp study, which demonstrated the survival advantage of temozolomide addition was conventionally fractionated RT.^[3,4] Since hypofractionated radiation regimens in the above-mentioned studies had similar outcomes with conventional radiation, hypofractionated radiation was thought to be combined with temozolomide to achieve similar results in GBM patients. When the adjuvant

temozolomide is added to the short term radiotherapy (30 Gy/6 Fr), it resulted in a statistically significant survival benefit (versus hypofractionated RT) with minimal additional toxicity in elderly patients.^[7,8] Barker et al.^[9] reported that concomitant temozolomide with either conventional or hypofractionated RT significantly improved survival of poor prognostic patients with GBM. In series using concomitant and adjuvant temozolomide with hypofractionated radiotherapy regimens, treatment was well-tolerated and comparable to conventional treatment.^[10-13]

Significant survival advantage in doses over 45 Gy was reported in GBM.^[14] However, although there was an increase in toxicity, the survival advantage was not confirmed in high dose studies.^[15,16] Therefore, we aimed to have shorter overall treatment time in poor prognosis GBM patients without increasing total radiation dose with the addition of temozolomide to hypofractionated RT. Thus, this retrospective study was performed to determine whether Stupp schema^[4] of adjuvant temozolomide and 45 Gy/15 fr hypofractionated RT can be used to shorten the treatment duration in GBM patients with poor prognostic factors (Recursive Partitioning Analyzes (RPA) categories V, VI), without increasing the dose and toxicity, and without risking the survival.

MATERIALS AND METHODS

The efficacy of the concomitant application of adjuvant temozolomide with hypofractionated RT was investigated in patients with GBM in this prospective single-arm single-center study. All patients provided written informed consent, and this study was approved by the institutional ethics committee.

In patients with pathological diagnosis of GBM, the type of surgical resection was evaluated with the computed tomography (CT) or magnetic resonance imaging (MRI) and surgical epicrisis; and classified as total resection, subtotal resection or biopsy. Residual tumor after surgery was defined as gross tumor volume (GTV).

Radiotherapy was applied to the patients in two phases. In phase 1, total 30 Gy in 10 fractions to Planning Target Volume (PTV) (GTV+2.5+0.5 cm) and in phase 2, 300 cGy/fr 15 Gy in 5 fractions, a total dose of 45 Gy to PTV boost (GTV+1+0.5 cm) was applied. RT was planned with dedicated CT and three-dimensional planning systems; conformal RT was delivered with linear accelerators with photon energy of 6 MV.

The dosage of temozolomide during the procedure was in accordance with the regimen of Stupp et al.^[4] Temozolomide at a dose of 75 mg/m²/day together with RT was used per oral for 19–21 days. Four weeks after the end of RT, adjuvant temozolomide treatment began at a dose of 150–200 mg/m²/day for 1–5 days and repeated every 28 days for six cycles. Clinical evaluation was undertaken every week during RT, every month during adjuvant temozolomide treatment and repeated at the end of 3rd and 6th regimens via CT or MRI. The primary efficacy endpoint was overall

survival from the date of surgery. The secondary endpoint was progression-free survival that defined as the duration from the date of the surgical therapy to the date of radiologically detected progression; however, it should be taken into account that pseudo-progression cases could not have been excluded. It was decided that if radiological progression would have been detected in the first three months, therapy would not be terminated as long as the performance of the patient was appropriate and temozolomide was fully applied for six months. In addition, the impact of age, gender, KPS, surgery type and RPA class (Table 1) on overall survival time was investigated.

Statistical analysis

Statistical analyses were performed using Software Package for Social Sciences (SPSS). For subgroup comparisons, Chi-square test, for univariate Kaplan-Meier method and overall survival calculation Kaplan-Meier method and multivariate survival analysis Cox regression test were used. Survival comparisons were made by the Log-rank test. Toxic effects were evaluated according to Radiation Oncology/Toxicity Grading (RTOG) criteria. Level of statistical significance was $p < 0.05$.

RESULTS

A total of 43 patients were included in this study. Patient characteristics are presented in Table 2. The mean age of the patients was 62 (min-max 50–85) years; 23 (53.5%) patients were males. Surgery extent was total resection in 20 (46%), subtotal resection in 12 (28%), biopsy only in 11 (26%) patients.

RT was completed as planned in full dose in all patients (100%). The steroid was used in all patients, and it was ter-

Table 1. Radiation therapy oncology group (RTOG) recursive partitioning analyzes (RPA) categories^[17]

RPA III	Age <50, anaplastic astrocytoma and abnormal mental status Age <50, glioblastoma multiforme and KPS 90–100
RPA IV	Age <50, glioblastoma multiforme and KPS <90 Age >50, glioblastoma multiforme, KPS 70–100 partial / total resection and good neurological function
RPA V	Age ≥50, glioblastoma multiforme, KPS 70–100 and presence of neurological deficit that decreases functional capacity due to surgical resection Age ≥50, glioblastoma multiforme, KPS 70–100, minimum 54 Gy RT with biopsy only Age ≥50, KPS <70, normal mental status
RPA VI	Age ≥50, KPS <70, abnormal mental status, Age ≥50, glioblastoma multiforme, KPS 70–100, biopsy only and RT lower than 54 Gy

KPS: Karnofsky performance status; RT: Radiotherapy.

minated with dose lowering after RT. Median eight-week steroid use was needed from the initiation of RT (2–22 weeks). No grade 3 acute toxicity due to hypofractionated RT was observed. As a delayed side effect of radiation, radiation necrosis was diagnosed upon radiologic examination in two patients; however, histological confirmation was not performed. During radiochemotherapy, anemia developed in five (12%), neutropenia in eight (18%), and grade 2 thrombocytopenia in five (12%) patients.

Concomitant temozolomide was also used in all patients without dose lowering while adjuvant temozolomide as six cycles was applied in 27 patients (64%), but in 12 (28%) of them, temozolomide dose was lowered due to hematological toxicity. Adjuvant chemotherapy was terminated before planned in three (7%) patients because of grade 4 neutropenia (n=1), grade 4 thrombocytopenia (n=1) and deep vein thrombosis and thrombocytopenia (n=1). In 13 (29%) patients, chemotherapy was terminated due to progression. The median number of temozolomide cycles was noted as 5 (range=1–6).

Patients who could not complete adjuvant temozolomide treatment were evaluated according to patient characteristics. None of the patients with RPA VI were noted to complete chemotherapy while 9 of 36 patients with RPA V (25%) could not complete the planned therapy ($p<0.001$). In 13 of 24 patients (54.6%) with ≤ 70 Karnofsky Performance Status (KPS), and three of 19 patients (16.0%) with better KPS (16%), six cycles of adjuvant temozolomide could not be applied. Therefore, significantly fewer patients with low (≤ 70) KPS and RPA VI completed the treatment ($p=0.02$). The findings showed that there was

	n	%	Overall survival time	
			Median (months)	p*
Age (years)				
50–64	25	58	12.8	0.030
≥ 65	18	42	9.7	
Gender				
Female	20	46.5	10.1	0.700
Male	23	53.5	12.7	
KPS				
90–100	11	26	14.8	0.020
80	16	37	11.3	
≤ 70	16	37	7.7	
Surgery				
Total excision	20	46	10.5	0.600
Subtotal excision	12	28	9.5	
Biopsy	11	26	6.1	
RPA				
V	36	84	12.7	<0.001
VI	7	16	4.7	

KPS: Karnofsky performance status; RPA: Recursive Partitioning Analyzes.

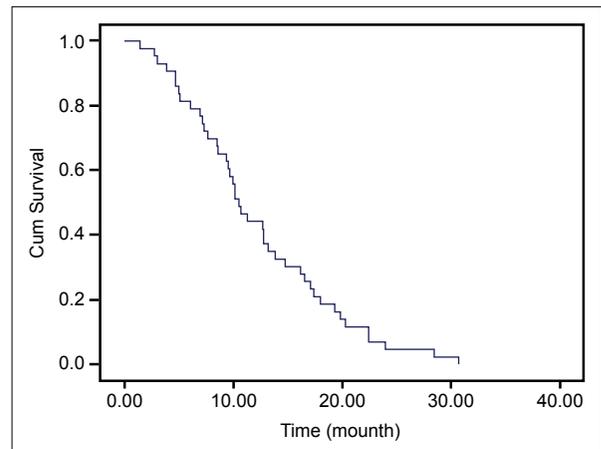


Figure 1. Overall survival.

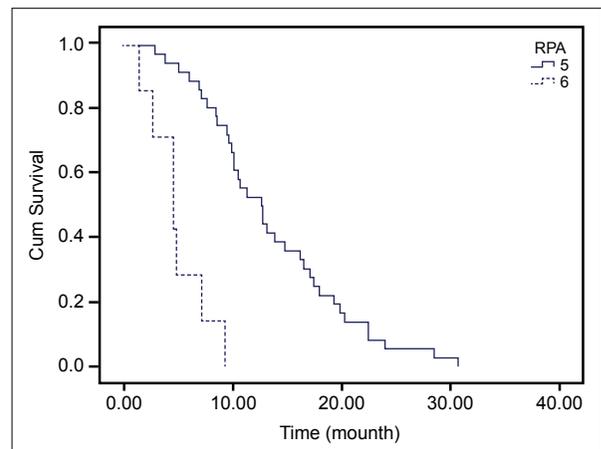


Figure 2. Survival according to RPA scoring.

no relationship between age, gender, and surgery type and treatment compliance. Median follow-up in all patients was 12 months (range= 1.5–31 months). All patients died during the analysis process.

In all patients, median survival time after the operation was found as 10.5 (range=8.8–12.3) months (Fig. 1); and 1-year overall survival proportion was 42%. The median progression-free survival time was 8.4 (range=7.6–9.2) months, and 1-year survival proportion was 26%.

Age, gender, KPS, surgery type, and RPA category were evaluated as prognostic factors affecting survival with univariate and multivariate analysis. Upon univariate analysis, overall survival time was significantly longer in younger patients ($p=0.03$), in the patients with higher KPS ($p=0.02$) and in RPA 5 patients ($p<0.001$) (Table 2; Fig. 2). Similarly, in multivariate analysis, age, KPS and RPA category were found to be among prognostic factors on survival. No effects of gender and surgery type were found on overall survival.

DISCUSSION

RTOG RPA classification system has been developed in the early 1990s and has been validated in multiple clin-

ical trials in GBM. Prognostic factors based on the RPA classification system were studied in three RTOG trials, including 1578 patients with GBM or anaplastic astrocytoma.^[17,18] Patient's age, the surgery type and performance status were reported to be the most important prognostic factors in these studies. For GBM, four groups with a median survival of 17.9, 11.1, 8.9 and 4.6 months were identified. In the study by Lin et al.,^[19] simplified model to the updated GBM database application defined three distinct classes with median survival times of 17.1, 11.2, and 7.5 months for Classes III, IV, and V+VI, respectively. GBM patients with RPA V and VI categories have limited survival expectations, and these patients may need new treatment alternatives, such as shorter duration radiotherapy for palliation in patients with poor prognosis. Hence, 45 Gy/15 fr 300 cGy/fr radiotherapy and concomitant adjuvant temozolomide treatment was tried in our study; older age (≥ 65 years), lower (< 70) KPS, RPA category 6 were determined as poor prognostic factors; and the overall survival was found to be 10.5 month that was not worse compared to previous studies in those patients.

Indeed, several studies in the last decade evaluated the effectiveness of shorter RT regimens in GBM patients with unfavorable characteristics. In historical series, 6-month survival was obtained with 30 Gy/10fr, 30 Gy/6 fr, 40 Gy/8 fr, 28 Gy/4 fr RT schemes, in patients with poor prognosis.^[20–22] Slotman et al. reported the results of a non-randomized study with 30 patients, 42Gy/14fr scheme have a median survival 11.5 months in patients with age < 50 years, KPS 80–100 and total resection and 6.5 months in patients with age > 50 years, KPS < 70 and subtotal resection.^[23] Kleinberg et al. reported eight months of survival in patients with RPA V and 51Gy /17fr RT scheme and five months of survival in RPA VI and 21 Gy/7 Fr RT scheme.^[24] Chang et al. reported that they found similar results in RPA IV-VI GBM patients treated with 50Gy/20 Fr RT as seven months median survival when compared to the results RTOG studies according to RPA scale.^[25] In all of these studies, different schemes were used and it was reported that hypofractionated RT was tolerable, provided similar survival to standard RT; and could be preferred in patients with poor prognostic factors.

Stupp et al.^[3] compared RT (60 Gy/30 fr) with RT plus temozolomide in 573 GBM patients in a randomized study and found that median survival was 12 months in RT arm and 15 months in RT plus temozolomide arm ($p < 0.001$). As a result of this study, this treatment schema became the new standard treatment approach in GBM. In our study, 10.5 months overall survival achieved with temozolomide scheme having survival advantage evidence, added to hypofractionated RT is lower than that of Stupp study. However, patients younger than 70 years and ECOG 1–2 were included in Stupp study; this difference may be considered to be depending on worse prognostic factors rather than hypofractionation.

Raymond et al.^[10] have applied 60 Gy in 20 fractions to the tumor location with IMRT concomitant boost tech-

nique and 40 Gy to the tumor periphery, together with concomitant and adjuvant chemotherapy. Overall survival of 14.4 months was found to be similar to conventional RT temozolomide studies. In RPA V-VI groups, median survival was 12.9, and disease-free survival was eight months. Weis et al.^[11] acquired 8.2 months survival with concomitant and adjuvant temozolomide with 40 Gy (2.67 Gy/fr) in 65 years and older patients and commented that it is comparable to conventional treatments and well-tolerated. Terasaki et al.^[12] achieved 15.6 months survival using temozolomide with concomitant 45Gy/15 Fr, 12 cycles of adjuvant temozolomide. There was no worsening in life quality determined by KPS and FACT-BR Subscale scores with this procedure. Chen^[13] used 60 Gy hypofractionated intensity-modulated radiotherapy (IMRT) with 3–6 Gy/fr, together with concomitant and adjuvant temozolomide treatment. Median survival of 16.2 months was obtained in KPS > 60 patients with smaller than 6 cm targets without brain stem invasion. In our study, the survival of 12.7 months in RPA five patients is similar to those studies. Survival of 4.7 months obtained in RPA VI patients was thought as there is a requirement for another treatment scheme.

In Stupp study^[3] that led temozolomide to be the standard treatment in GBM, among the 287 patients who were assigned to receive concomitant RT (60 Gy/30 Fr) plus temozolomide, 85% completed both RT and temozolomide as planned. Thirty-seven patients (13%) prematurely discontinued temozolomide because of toxic effects (in 14 patients), disease progression (in 11), or other reasons (in 12). In our study, planned therapy with 50% shorter radiochemotherapy could be applied to all patients. In Stupp study, adjuvant temozolomide was stopped due to toxicity in 8%, disease progression in 39%; thus, 47% completed six regimens. However, in our study, adjuvant temozolomide was stopped due to toxicity in 7%, and due to progression in 29%, thus 64% completed six regimen. The application of hypofractionated chemoradiotherapy scheme was better than standard chemoradiotherapy, and application of adjuvant chemotherapy was similar.

Terasaki et al.^[12] applied 30 Gy/15 Fr RT with concomitant chemotherapy to all patients similar to our study. Adjuvant chemotherapy in this study was completed as 12 cycles in 19% of the patients. Raymond et al.^[10] did not note acute toxicity except for grade 3–4 emesis in one patient of RPA V-VI group with hypofractionated RT plus concomitant and adjuvant temozolomide; late toxicity was noted in none of the patients, and 83% of the patients completed concomitant chemoradiotherapy. In the study by Weiss,^[11] of the patients ($n=24$) older than 65 years, underwent 40 Gy RT 2.6 Gy/Fr with concomitant adjuvant temozolomide, 23 completed radiochemotherapy, and 15 completed adjuvant chemotherapy. In three patients, they encountered 3-4 hematological toxicity during adjuvant chemotherapy. Chen's^[13] study was a prospective Phase I trial to systematically escalate the radiation fraction size from 3 Gy through to 6 Gy (total 60 Gy) with concurrent and adjuvant temozolomide. All (16 patients) patients

completed concurrent RT and temozolomide chemotherapy except for one patient, for unrelated to the study treatment. Similar to our study, the compliance of the patients in those hypofractionated radiochemotherapy plus chemotherapy studies was considerably favorable. The factors for our patients not completing the treatment were RPA being VI and KPS being 70 and lower. The case that none of the RPA VI patients could have completed planned therapy gave rise to the thought that choices of best supportive care, hypofractionated RT or only temozolomide should be evaluated in this group of patients.

Chen et al.^[13] detected brain necrosis in three of 16 patients after 60 Gy with 3–6 Gy/fr. One patient with vision loss had a tumor in close proximity to the optic nerve and chiasm, indicating that this treatment regimen might not be appropriate for tumors in close proximity to the optic structures. Morganti et al.^[26] carried out a dose-escalation study with hypofractionated RT with IMRT with concomitant and adjuvant temozolomide in 19 patients. None of the patients experienced dose limited toxicity. Grade 1–2 treatment-related neurologic and skin toxicity were common (11 and 19 patients, respectively). Grade >2 late neurologic toxicities were noted in none of them. The rate of freedom from late neurotoxicity at 12 and 24 months was 94.7% and 82.9%, respectively.

In the study by Floyd et al.^[27] with intensity-modulated radiation therapy (IMRT), a dose of 50 Gy was delivered in 5-Gy daily fractions within two weeks to enhancing primary disease, residual tumor, or surgical cavity. Of the 15 patients evaluated for late toxicity, three (20%) patients required reoperation for radiation necrosis. They reported that brain necrosis probability is increased with this schema. In our study, necrosis was seen in two (5%) patients radiologically, and surgery was performed to none of them. These hypofractionated schemes performed with IMRT concomitant boost technique are more conformal than our 3D RT technique. Although it might be even possible to give hypofractionated RT safely, care should be taken for these patients. For patients with a relatively better prognosis, long-term side effects of hypofractionation may become a problem and should therefore not be given.

In conclusion, the addition of temozolomide to hypofractionated RT in the selected patient group decreased the treatment duration by 50% while overall survival has not been affected in our study. Hypofractionated RT has advantages over standard RT in patients with a life expectancy of months like GBM, and this is an important concern regarding the quality of life owing to the significant time commitment required to undergo RT. This regimen offers a treatment course that is completed in three, instead of six weeks, which may be preferable in certain subsets of patients (such as RPA V-VI) when palliation is the primary treatment goal. At the same time, it has the advantage of lower-cost due to decreased RT duration over standard therapy.

Ethics Committee Approval

Approved by the local ethics committee.

Informed Consent

Retrospective study.

Peer-review

Internally peer-reviewed.

Authorship Contributions

Concept: N.I.; Design: G.Y.; Supervision: N.I.; Materials: F.T.; Data: A.A.; Analysis: N.I.; Literature search: A.A.; Writing: F.T.; Critical revision: N.I.

Conflict of Interest

None declared.

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RPA Skoru V ve VI Olan Glioblastom Hastalarında Temazolamidle Hipofraksiyone Radyoterapi

Amaç: Bu çalışma, kötü prognostik faktörlere (Recursive Partitioning Analyses -RPA- skor V, VI) sahip glioblastome multiforme (GBM) hastalarında dozu ve toksisiteyi arttırmadan ve sağkalımı azaltmadan, adjuvan temozolamid ve 45 Gy/15 fr hipofraksiyone radyoterapi (RT) rejiminin, tedavi süresini kısaltmak için kullanılıp kullanılmayacağını belirlemek için yapıldı.

Gereç ve Yöntem: Bu geriye dönük tek kollu ve tek merkezli çalışmaya; 50 yaşından büyük GBM histolojik tanı, RPA skoru V veya VI olan hastalar dahil edildi. Hastalara, üç haftada 15 fraksiyonda 45 Gy RT, eşzamanlı temozolamid ile birlikte uygulandı. Radyoterapi sonrası adjuvan temozolamid ile tedaviye devam edildi.

Bulgular: Çalışmaya toplam 43 hasta alındı. Tüm hastalar planlanan dozda RT'yi tamamladı. Hipofraksiyone RT nedeniyle grade 3 akut toksisite gözlenmedi. Eşzamanlı temozolamid bütün hastalarda doz azaltılmaksızın uygulandı. Akabinde altı kür adjuvan temozolamid alan 27 hastanın 12'sinde gelişen hematolojik toksisite nedeniyle doz azaltılmasına gidildi. Ortanca genel sağkalım 10.5 ay ve bir yıllık genel sağkalım oranı %42 idi. Ortanca progresyonsuz sağkalım süresi 8.4 aydı.

Sonuç: Hipofraksiyone radyoterapi ve eşzamanlı temozolamid ile sağkalımda bir azalma gözlenmezken, toksisitede bir artış izlenmedi.

Anahtar Sözcükler: Glioblastoma multiforme; hipofraksiyasyon; radyoterapi; temozolamid.