Late Radiation Outcomes of Patients with Newly Diagnosed Glioblastoma Treated with Accelerated Hyperfractionated Radiotherapy and Temozolomide

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OBJECTIVE
This study aimed to evaluate the late radiation outcomes in patients with glioblastoma who were treated with accelerated hyperfractionated radiotherapy (AHRT) and concurrent plus adjuvant temozolomide (TMZ).

METHODS
Between 2006 and 2007, 32 consecutive patients with glioblastoma were treated with AHRT and TMZ. The total dose of 66 Gy was administered in 33 fractions within 6 weeks. In phase I, PTV1 received 40 Gy (2 Gy per fraction, five times per week). In phase II, 26 Gy was delivered to PTV2 by adding a second daily fraction at intervals of 8 hours once every 3 days. All patients received chemotherapy according to the Stupp protocol. Toxicities were evaluated based on the CTCAE v3.0.

RESULTS
The median follow-up period was 18 months. A total of 28 patients completed the planned radiotherapy schedule, and 20 patients received six cycles of adjuvant TMZ. Median overall survival (OS) and progression-free survival (PFS) were 17 and 10 months, respectively. In univariate analysis, age, performance status, and RPA classes III–IV were found significant for OS. Multivariate analysis showed that six cycles of TMZ administration affected both OS and PFS. Late grade-4 central nervous system (CNS) toxicities were observed in five patients.

CONCLUSION
It was observed that it is both feasible and effective to administer AHRT with TMZ in a selected group of patients. It provides better short-term survival advantage than the standard treatment regimen.

Keywords: Accelerated hyperfractionation; glioblastoma; radiotherapy; temozolomide.
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Introduction

In adults, glioblastoma (GB) is the most common malignant glial tumor. It has a median survival period of 12–18 months.[1,2] Radiotherapy (RT) plays an important role in the treatment of GB.[2,3] Walker et al. have shown that postoperative RT doubled the survival as compared to that of supportive treatment.[4] After six randomized studies, postoperative RT was accepted as the standard component of treatment.[3-8] Many studies have investigated the role of chemotherapy; however, the effect in the majority of these trials

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was limited.[9] In 2005, the European Organization for Research and Treatment of Cancer (EORTC) and National Cancer Institute of Canada intergroup trial demonstrated the improvement in survival with RT plus concurrent and adjuvant temozolomide (TMZ). Thus, for the first time, the benefit of systemic chemotherapy in GB was proved with a phase III study.[10]

The standard treatment for patients with newly diagnosed GB is wide surgical resection followed by postoperative RT and concurrent plus adjuvant chemotherapy. Despite the advancements in treatment modalities, the prognosis is still poor, and the five-year survival rate is below 10%.[11] Efforts are being made to improve the results in GB with the developments in modern RT techniques after TMZ. Because of improved functional imaging methods and innovations in the RT techniques, better results can be obtained by raising the dose. Recently, different fractionation schemes and higher doses with intensity modulated radiation therapy (IMRT) or stereotactic radiosurgery (SRS) have been investigated.[12-20]

In this study, the late radiation results in patients with newly diagnosed GB who were treated with accelerated hyperfractionated RT and concurrent plus adjuvant TMZ were evaluated.

Materials and Methods

This was a prospective observational clinical study. It was approved by the ethics committee of Istanbul University, Istanbul Medical Faculty. Written informed consent was obtained from each patient before their participation.

Patient Selection

Between 2006 and 2007, 32 patients with newly diagnosed GB were enrolled in the study. Inclusion criteria for the patients were as follows: (a) histologically confirmed GB (WHO grade IV); (b) age between 18 and 70 years; (c) total or subtotal resection; (d) Karnofsky performance status (KPS) score ≥70%; and (e) normal hematologic, renal, and hepatic parameters. Patients who had received prior RT to the brain and with recurrent disease or concurrent other malignancy were excluded.

Treatment Characteristics

All of the patients underwent surgery; 29 of them had (90.6%) gross total resection, and 3 (9.4%) of them had subtotal resection. RT started within 6 weeks after the surgical resection in 81% of the patients. During simulation and treatment, patient immobilization was provided with an individualized thermoplastic mask. The computed tomography simulation was made in the supine position with a 0.5-cm thick slice. Initial clinical target volume 1 (CTV1) included the contrast-enhancing lesion and surrounding edema on the preoperative MRI with a 15-mm margin. Then the field was reduced, and the volume of boost (CTV2) was defined as the area of contrast-enhancing lesion plus a 15-mm margin. Planning target volumes were created by adding 5-mm margins to CTVs. Treatment plans were planned using the Three-Dimensional Conformal Radiotherapy Technique (3-D CRT). According to tumor location, radiation was delivered from three or four fields with 6–18 MV linear accelerators. The total dose of 66 Gy was administered in 33 fractions over 6 weeks. In the first phase of treatment, PTV1 received 40 Gy (2 Gy per fraction a day, five times a week). In phase II, the total dose was increased to 26 Gy by adding a second daily fraction at intervals of 8 hours once every 3 days.

All patients received concurrent TMZ 75 mg/m2 daily during RT. One month after completion of RT, according to the Stupp protocol, adjuvant TMZ was administered 150–200 mg/m2 daily for 5 days every 28 days.

Follow-Up

During chemoradiotherapy, patients were followed up for weekly blood count, and they were evaluated for acute toxicities. In addition, during adjuvant TMZ period, monthly follow-ups with blood tests and serum chemistries were conducted. A neurologic examination was also performed at each visit. Later on, follow-ups were conducted every 3 months for the first 2 years and every 6 months thereafter. A contrast-enhanced cranial MRI was performed 1 month after the end of RT and every 3 months thereafter. If radiation necrosis was suspected in patients, perfusion MRI or MR spectroscopy was performed. Disease progression is defined radiologically (a 25% or greater increase in the largest vertical diameter of a contrast-enhancing tumor on MRI, or a new lesion). In case of progression, each patient was re-evaluated for second-line treatment options such as surgery, RT, or chemotherapy. Treatment-related toxicities were graded according to the Common Terminology Criteria for Negative Events (CTCAE) 3.0.[21]

Statistical Analysis

Overall survival (OS) time was calculated from the date of diagnosis (biopsy or surgical resection) to the date of death from any cause. Progression-free survival (PFS) time was calculated from the date of diagnosis to the date of progression of the disease or to the time

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at which new lesions appeared. Survival analyses were performed according to the intention-to-treat principle. The Kaplan–Meier method was used to calculate the OS and PFS rates. In univariate analysis, the log-rank test was used to compare survival according to different prognostic factors. A multivariate Cox regression analysis was used to determine prognostic factors affecting OS and PFS. For the statistical analysis, SPSS version 20 for Windows (IBM Corp., Armonk, NY) was used. The p-value <0.05 was accepted to be significant.

Results

Patient Characteristics

There were 18 male (56.3%) and 14 female (43.8%) patients. The median age was 56 years (range: 26–70 years). On pre-treatment assessment, median KPS

Table 1 Clinical and tumor characteristics of all patients

Characteristics	Number (%)
Age (year), Median(range)	56 (26-70)
≤50	11 (34)
>50	21 (66)
Gender	
Female	14 (43.8)
Male	18 (56.3)
Karnofsky Performance status (%)	
Median (range)	90 (70-100)
RPA classes	
III	9 (28)
IV	2 (6)
V	21 (66)
Tumor location	
Frontal lobe	12 (37.5)
Temporal lobe	8 (25)
Parietal lobe	8 (25)
Others	4 (12.5)
Resection	
Gross Total	29 (90.6)
Subtotal	3 (9.4)
Concomitant TMZ	
Yes	30 (93.7)
No	2 (6.3)
Adjuvant TMZ	
6 cycles	20 (62.5)
5 cycles	2 (6.2)
4 cycles	3 (9.3)
3 cycles	1 (3.1)
None	6 (18.75)

Abbreviations: RPA: Recursive partitioning analysis; TMZ: Temozolomide

score was 90%. The most common tumor localization was the frontal lobe (37.5%). The patient characteristics are listed in Table 1.

Of the 32 patients, 28 (87.5%) completed the planned 66 Gy of RT dose. TMZ at 75 mg/m2/day was started concomitant with RT in all patients, but treatment was discontinued due to toxicities in two patients. Six cycles of adjuvant TMZ was completed in 20 patients (62.5%). Six patients did not receive the adjuvant chemotherapy. One patient refused the treatment, one patient discontinued treatment due to grade IV pancytopenia, one patient died of pneumonia during RT, and three patients died due to disease progression at the end of RT.

Survival Outcomes and Prognostic Factors

The median follow-up period was 18 months (range: 2–98 months). At the time of the analysis, all of the patients who participated in the study were dead. Only two patients lived longer than 5 years (96 and 98 months). The median OS time was 17 months. The OS rates from 1 to 5 years were 75%, 28.1%, 12.5%, 9.4%, and 6.3%, respectively (Fig. 1).

Distant metastasis or leptomeningeal disease was not observed in any patient. However, a local failure developed in all patients during follow-up. Salvage chemotherapy was given to 12 patients. Nine of them received TMZ, and the remaining three had fotemustine. Ten patients had best supportive care, five patients underwent re-operation, and one patient re-irradiated with stereotactic radiosurgery. The median PFS time was 10 months. The PFS rates at 1 and 2 year were 35.5% and 6.5%, respectively (Fig. 2).

In univariate analyses, the age (≤50 years) (p=0.011), RPA classes III-IV (p=0.011), KPS ≥90 (p=0.013), and

Fig. 1. Overall survival for all patients.

Fig. 2. Progression free survival for all patients.
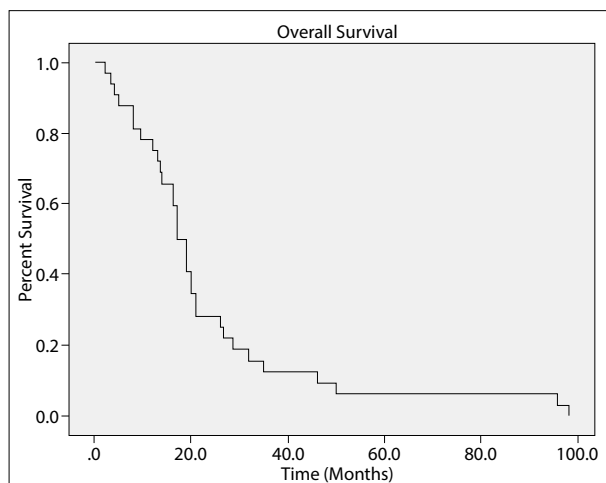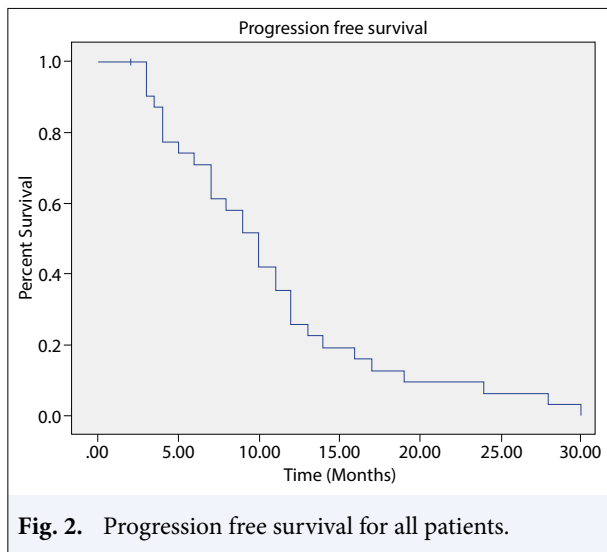
use of six cycles of adjuvant TMZ (p<0.0001) were found as significant prognostic factors for OS. The PFS rate was significantly higher in patients who received six cycles of adjuvant TMZ compared to that in patients who received less than six cycles (11 vs. 4 months, p<0.001) (Table 2).

In multivariate analysis, only the use of adjuvant six cycles of TMZ was found to be the most important

prognostic factor for both the OS (p=0.003) and PFS (p=0.005) (Table 3).

Acute and Late Toxicity

The most commonly developed acute side effect during chemoradiotherapy was hematologic toxicity. Grade-4 toxicity was observed in eight patients. Six patients had grade-4 lymphopenia, one patient had grade-4 leukopenia, and one patient had grade-4 thrombocytopenia. Furthermore, fatigue was observed as the most common non-hematologic toxicity (Table 4). Pneumonia developed in one patient. During the adjuvant TMZ period, moderate nausea and vomiting, as well as grade 2–3 lymphopenia and thrombocytopenia developed. Deep vein thrombosis was observed in two patients, and pulmonary embolism was observed in two patients.

As a late toxicity, radiation necrosis was detected in 12 (42.8%) patients after median 12.5 months from RT. Radiation necrosis was diagnosed with radiological imaging in ten patients and with biopsy in two patients. However, most of the patients were asymptomatic, only one patient had grade-3 necrosis, and the other had grade-4 necrosis. In addition, other late grade 3–4 central nervous system (CNS) toxicities included visual loss in two patients, somnolence in one patient, cognitive disturbance in one patient, and memory impair-

Table 2   Analysis of potential predictive factors affecting overall survival (OS) and progression-free survival (PFS) in univariate analysis

Variables	N	OS rates (%)			PFS rates (%)		
		2-years	5-years	p	1- year	2- years	p
Age							
≤50	11	45.5	18.2	0.011	36.4	9.1	0.224
>50	21	19	0		30	5.5	
Gender							
Female	14	28.6	0	0.518	38.5	7.4	0.997
Male	18	27.8	11.1		27.8	5.6	
RPA class							
III-IV	11	45.5	18.2	0.011	36.4	9.1	0.224
V	21	19	0		30	5	
KPS (%)							
≥90	18	38.9	11.1	0.013	44.4	5.6	0.352
<90	14	14.3	0		23.1	7.7	
Surgery – RT interval							
< 6 weeks	25	28	4	0.379	37.5	8.3	0.607
≥ 6 weeks	7	28.6	0		28.6	0	
Adjuvant TMZ							
Less than six cycles	12	0	0	<0.0001	9.1	0	<0.0001
Six cycles	20	45	10		50	10	

Abbreviations: N: Number of patients; RPA: Recursive partitioning analysis; KPS: Karnofsky performance status; RT: Radiotherapy; TMZ: Temozolomide

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Table 3 Analysis of potential predictive factors affecting overall survival and disease-free survival in multivariate analysis

Variables	HR	OS 95% CI	p	HR	PFS 95%	p
Age (≤50 vs. >50)	0.59	0.225-1.575	0.296	0.884	0.350-2.236	0.795
RPA classes (III-IV.vs.V)	0.95	0.242-1.576	0.344	1.5	0.264-9.375	0.654
KPS (%) (≥90 vs. <90)	0.459	0.203-1.037	0.061	1.378	0.632-3.002	0.420
Adjuvant TMZ (6 cycles vs. < 6 cycles)	0.235	0.090-0.614	0.003	0.065	1.527-10.240	0.005

Abbreviations: RPA: Recursive partitioning analysis; KPS: Karnofsky performance status; TMZ: Temozolomide

Table 4 Acute toxicity

Toxicity	1	Grade 2	3	4
Hematologic				
Anemia	2	1	0	0
Thrombocytopenia	1	1	1	1
Leukopenia	2	1	1	1
Lymphopenia	6	2	3	6
Gastrointestinal				
Nausea	5	2	0	0
Vomiting	3	1	0	0
Hepatotoxicity				
AST	1	0	0	0
ALT	5	0	0	0
Others				
Fatigue	12	5	0	0
Dermatitis	18	2	0	0

Table 5 Late toxicities according to CTCAE v 3.0

Toxicity	No. of patients (%)	Grade 1	2	3	4	5
Radiation necrosis	12 (42.8)	6	4	1	1	0
Cognitive disturbance	19 (67.8)	6	12	0	1	0
Memory impairment	12 (42.8)	7	4	1	0	0
Somnolence	7 (25)	0	6	0	1	0
Retinopathy	2 (7.1)	0	0	0	2	0

ment in one patient (Table 5). Grade-5 CNS toxicity did not develop in any patient.

Discussion

Although GB is treated with a multimodal approach, it still has the worst prognosis among malignant glial tumors.[1-3,11] Surgical resection is one of the primary treatment modalities, and the extent of surgical intervention is an important prognostic factor for survival. [22-24] However, maximal safe resection is not always possible due to the performance status of the patient and the tumor localization. Furthermore, even if the tumor is removed by extensive resection, the neoplastic cells may remain in the adjacent normal tissues due to the infiltrative nature of the tumor, and they may repopulate. Therefore, RT is needed to eradicate residual cells. As compared to chemotherapy after surgery or surgery alone, randomized trials have shown that adjuvant RT is more effective on survival [1,3] The Brain Tumor Study Group (BTSG) 69-01 showed that median OS was 3.5 months in patients receiving only supportive care after surgery, whereas the median survival was extended to 9 months in patients who received postoperative RT.[4]

GB is a highly radio-resistant tumor. In the preclinical studies, it has been reported that high doses (≥80 Gy) are required to eliminate malignant glial cells.[25] Moreover, early clinical trials have shown a relationship between dose and survival. Walker et al. reported that the median survival improved from 13.5 weeks to 42 weeks when the radiation dose was increased from 45 Gy to 60 Gy.[26] In addition, Reni et al. found that doses above 60 Gy were associated with increased survival.[27]

The current standard dose used in GB treatment is 60 Gy. However, in follow-ups, the most common problem is still a local failure, and most of the recurrences develop within the high-dose area.[28,29] The

administered dose is probably insufficient. To date, a number of dose-escalation trials have been conducted to improve the local control using different techniques such as altered fractionation, stereotactic radiosurgery, brachytherapy, or IMRT.[12,15-20,30-35]

Increasing the treatment dose by altered fractionation has been used for a long time in rapidly growing tumors. The aim is to exploit radiobiological advantages. In this way, the total radiation dose is increased without prolonging the duration of the treatment and without excessive late toxicity. Thus, repopulation is prevented. For this reason, hyperfractionation was frequently used in the early dose-escalation trials. However, most of these studies have failed, and no survival advantage has been demonstrated compared to standard conventional fractionation.[35-38] Unlike, Fitzek et al. reported that median survival was prolonged to 20 months in patients receiving 90 cobalt Gy equivalent doses with accelerated fractionated proton/photon therapy.[39]

Most of the above-mentioned studies have been performed before the TMZ period. In 2005, Stupp et al. showed a remarkable improvement in survival with the addition of TMZ in GB treatment, and they opened a new era.[10] After the use of TMZ with RT became standard in GB management, RT dose-escalation studies have been accelerated again to improve survival further.[13,16-18,32,33,40,41]

Kaul et al. compared 64 patients who underwent accelerated hyperfractionated RT with 67 patients who underwent conventional RT, and they found no significant difference between the two groups.[40] Similarly, Badiyan et al. failed to show improvement in survival rate in patients who received high-dose RT with TMZ compared to those who received the standard-dose RT.[41] On the other hand, Massaccessi et al. performed a dose-escalation study by using the simultaneous integral boost (SIB) IMRT technique, and they reported that 70 Gy delivered in 25 fractions with TMZ was well tolerated.[16] In addition, a study in Japan reported that the median survival was extended to 21.6 months in patients treated with hyperfractionated concomitant boost proton RT of 96.6 GyE in 56 fractions.[42]

In this study, the total radiation dose was increased to 66 Gy with accelerated hyperfractionation. The 1-year and 2-year OS rates were found as 75% and 28.1%, respectively. In addition, the median OS time was 17 months, and the median PFS time was 10 months. Whereas, in the Stupp's trial, the 1-year and 2-year OS rates were reported as 61.1% and 26.5%, re-

spectively. There was a median 2.5-month survival advantage according to this trial. But the 5-year survival rates are similar.

In this study, it was observed that patients with good performance status and younger age (≤50 years) have a higher survival rate. These findings are consistent with the prognostic factors mentioned in previous trials. Also, the RPA model, which was defined as a prognostic factor by Curran et al., showed well correlation with survival rates in our study.[43] Patients with RPA class III–IV had 5-month survival advantage over those with RPA class V (p=0.036). Furthermore, in multivariate analysis, the use of six cycles of adjuvant TMZ was found to be independent prognostic factors for both OS and PFS.

In several AHRT trials, it has been reported that the duration of treatment can be safely shortened with acceptable acute and late toxicities.[39,44,45] However, late toxicities related to radiation in this study were found to be slightly higher than those in the literature. The use of 3-D CRT and the volume of the normal tissue exposed to radiation are larger because CTV1 contains peritumoral edema. As a matter of fact, currently the target volume has been reduced in the EORTC protocol, and the incidences of toxicities have decreased with the widespread use of IMRT.[46,47]

On the other hand, radio-necrosis is regarded as a favorable event in terms of survival by some researchers. A correlation between radio-necrosis and improved outcomes has been shown in some series. [39,48-50] For example, Peca et al. reported that a median OS was 32 months in patients with radio-necrosis, whereas it was 10 months in patients with tumor progression.[50] However, there was no significant relationship between radio-necrosis and survival in our series (p=0.2).

There are some limitations in this study. First, the number of patients investigated was small, and they were retrospectively assessed. Secondly, since the study was conducted about 10 years ago, the MGMT methylation status of the patients was unknown. Thirdly, while dose-intensification studies of today are conducted with modern RT techniques such as IMRT, 3-D CRT was used in our study at that time. However, the positive aspect of the study is that all patients were followed up to death, and long-term results were presented.

Conclusion

In conclusion, RT is one of the most important treatment modalities in high-grade gliomas after resection.

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Our results show that accelerated hyperfractionated RT and TMZ are feasible, and they improve survival in a selected group of patients. However, it causes a slight increase in late neurotoxicity. In future, it may be possible to achieve the desired results in studies performed using advanced RT and functional imaging techniques, with the combination of new targeted agents.

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