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ORIGINAL ARTICLE

Prognostic factors other than the performance status and age for glioblastoma multiforme: a single-institution experience

M. Caloglu[1], V. Yurut-Caloglu[1], H. Karagol[2], G. Bayir-Angin[1], F.N. Turan[3], C. Uzal[1]

[1]Department of Radiation Oncology, [2]Department of Medical Oncology, [3]Department of Biostatistics, Trakya University Hospital, Edirne, Turkey

Summary

Purpose: *To evaluate the survival of patients with glioblastoma multiforme (GBM) and analyse the prognostic factors influencing survival.*

Patients and methods: *Seventy-eight consecutive patients with GBM treated with radiotherapy (RT) and temozolomide (TMZ) (in 21 patients) between 1999 and 2006 were retrospectively analysed.*

Results: *Sixty-seven (85.5%) patients had undergone gross total or subtotal resection before RT. The median overall survival was 9.8 months, and significantly influenced by age (p=0.02), Karnofsky performance status (p=0.001), RT (p<0.0001), gender (p=0.02), concomitant TMZ (p=0.003), RT waiting time (p=0.014), and treatment time (p=0.01) in univariate analysis. In multivariate analysis, older age (p=0.03), male gender (p=0.01), absence of concomitant TMZ (p=0.008), RT dose below 60 Gy (p=0.03), RT waiting time more than 20 days (p=0.01), and treatment time more than 76 days (p=0.0072) were poor prognosticators.*

Conclusion: *This study emphasizes the importance of female gender, dose and duration of RT, and RT waiting time in patients with glioblastoma multiforme.*

Key words: chemotherapy, gender, glioblastoma multiforme, prognostic factors, radiotherapy, survival

Introduction

Glioblastoma multiforme is the most common and aggressive neoplasm of the brain in adults. These tumors account for 45-50% of all gliomas. The standard management of GBM involves cytoreduction through surgical resection, when feasible, followed by radiotherapy (RT) with or without adjuvant chemotherapy (ChT) [1]. Two large, randomized, multicenter trials confirmed that postoperative brain RT provided a significant survival advantage compared with surgery alone [2,3]. More recently, concomitant application of temozolomide (TMZ) has been shown to extend overall survival (OS) significantly, with median OS of approximately 15 months [4,5]. However, the clinical course of the disease is usually rapid and fatal, with a median survival of less than 1 year. Most patients die due to disease progression within 2 years and cure was reported in only a few cases [6].

The aim of this retrospective study was to present and discuss the clinical features and to determine progression-free survival (PFS), OS, and prognostic factors in a series of patients with primary GBM.

Patients and methods

Seventy-eight patients with newly diagnosed primary GBM who were treated at the Department of Radiation Oncology, Trakya University Hospital, from September 1999 through September 2006, were retrospectively analyzed. The local ethics committee approved the study. Adult patients over 16 years, having histologically confirmed GBM and KPS ≥60, with complete medical records including preoperative clinical evaluation, precise postoperative outcome and follow-up, and pre- and postoperative computerized tomography (CT) and/or magnetic resonance imaging (MRI) scans were evaluated.

Correspondence to: Murat Caloglu, MD. Department of Radiation Oncology, Trakya University Hospital, 22030 Edirne, Turkey. Tel: +90 284 2350 968, Fax: +90 284 2350 968, E-mail: caloglumurat@hotmail.com

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Radiotherapy

All patients received RT to limited fields once a day at 2 Gy per fraction, 5 days a week, for a total dose of 60 Gy. RT was delivered to 32 (41%) patients with a Cobalt 60 treatment unit. The remaining 46 (59%) patients were treated with 6-18 MV photons from a linear accelerator. Patients were treated with thermoplastic immobilization masks to ensure adequate immobilization during therapy and reproducibility. The treatment volumes for both the initial and the boost volumes were based on preoperative CT and/or MRI scans. For the first 46 Gy, the initial treatment volume was determined according to the volume of contrast-enhancing tumor and surrounding edema plus a 2 cm margin, or 2.5 cm margin if no surrounding edema was present. After 46 Gy, the treatment volume was reduced to include the contrast-enhancing tumor (without edema) plus a 2 cm margin to a total dose of 60 Gy.

Chemotherapy

TMZ (75 mg/m^2/d × 7 d/wk) was given for 6-7 weeks in a fasting state, 1 h before RT, and in the mornings on days without RT. Four weeks after RT, patients received adjuvant TMZ (200 mg/m^2 daily × 5, every 28 days for 6 cycles). Prophylactic antiemetics, including 5-hydroxytryptamine-3 antagonists (a single dose of ondansetron 8 mg p.o. or granisetron 1 mg p.o.), were used only when necessary during concomitant RT plus TMZ therapy, whereas they were routinely prescribed once a day before adjuvant TMZ. Anticonvulsants and corticosteroids were administered when needed.

Assessments and follow-up

During RT, patients were seen every week. Complete blood count was performed weekly during treatment, and blood chemistry was performed monthly. Neurological examinations, serum chemistry, and toxicity evaluations were performed at each adjuvant TMZ cycle. CT or MRI scans were performed before the first adjuvant treatment cycle and then every 3 months during the first 2 years. Disease progression was defined as radiological (25% or greater increase in the size of the product of the largest perpendicular diameters of contrast-enhancing tumor or any new tumor on MRI or CT), neurological, or clinical.

Statistical analyses

OS was estimated from the date of diagnosis to the date of death or the last contact date. Clinical and therapeutic factors as well as tumor characteristics were first analyzed using univariate Summary tables (absolute and relative frequencies) that were used for descriptive analysis of categorical variables. As central value, average and its 95% confidence intervals (CIs) or median and its min-max values were used for continuous variables. When appropriate, the x^2 two-tailed test was used for comparative analysis between categorical variables. Factors that seemed determinant were subsequently evaluated by Kaplan-Meier survival curves and by the log-rank test. Finally, the significant factors in univariate analysis were tested in multivariate analysis using the Cox regression method. A two-sided 5% significance level was used for the comparisons of the groups. Statistica version 7 program was used for statistical analysis.

Results

Patient demographics and baseline disease characteristics are listed in Table 1. Twenty-nine (37%) of the patients were female. Median age was 53 years (range 16-78). Thirty-seven (47%) patients were ≤53 years old. Forty-two (54%) patients had KPS score of ≥80. Macroscopic gross total resection was performed in 48 (61.5%) patients; 19 (24.3%) patients underwent subtotal resections, and the remaining 11 (14.2%) underwent only biopsy before initiation of RT. The tumor was ≥4 cm in 56 (72%) patients. A preoperative history of seizures was present in 13 (27%) patients. Nine (11%) patients had multicentric tumor. In 24 (31%) patients the tumor was located in the frontal lobe and in 21 (27%) patients in more than one lobe. The most frequently involved site was the frontal lobe (57%) in females; however, multilobar involvement was seen predominantly in males (37%).

The median duration of follow-up was 8 months (range 0-28). The median time from diagnosis to the start of RT was 25 days (range 11-78). Median RT dose was 60 Gy (range 6-66). The median RT time was 42 days (range 8-69). Seventy-five (96%) patients received the planned RT (at least 42 Gy). Three patients died with disease progression while undergoing RT. Sixty-nine (88%) patients completed their RT within the prescribed 6 weeks. In one patient, the duration of RT was 69 days due to acute toxicity. The median overall treatment time, from diagnosis to the end of RT, was 76 days (range 29-150).

Twenty-one (27%) patients were treated with concomitant RT plus TMZ. Sixteen of them were females. More females than males received the concomitant treatment (57% of females vs. 10% of males;

Table 1. Patient, tumor and treatment characteristics

Characteristic	*No. of patients (%)*
Gender	
Male	49 (63)
Female	29 (37)
Age (years)	
≤53	37 (47)
>53	41 (53)
KPS	
<80	36 (46)
≥80	42 (54)
Tumor localization	
Frontal lobe	24 (31)
Multilobar	21 (27)
Temporal lobe	13 (17)
Parietal lobe	9 (12)
Cerebellum	6 (8)
Thalamus	5 (6)
Multicentric tumor	
Absent	69 (89)
Present	9 (11)
Tumor size (cm)	
≤4	22 (28)
>4	56 (72)
Operation type	
Total	48 (62)
Subtotal	19 (24)
Biopsy only	11 (14)
Preoperative seizure history	
Present	13 (27)
Absent	65 (73)
RT plus TMZ	
Received	21 (27)
Not received	57 (73)
RT dose (Gy)	
<60	8 (10)
≥60	70 (90)
RT waiting time (days)	
≤20	37 (47)
>20	41 (54)
RT time (days)	
<45	16 (21)
≥45	62 (79)
Treatment time (days)*	
<76	61 (78)
≥76	17 (22)

RT: radiotherapy, KPS: Karnofsky performance status, TMZ: temozolomide
*includes the time period from diagnosis to the RT completion

p<0.0001). Fifty-seven (73%) patients received RT alone. TMZ was discontinued in 3 patients because of acute toxicity during RT (2 patients with infection and 1 with grade 3 thrombocytopenia after 3 weeks).

By the time of analysis, 65 (83%) patients had died. Median OS for all patients was 9.8 months (range 3.2-29.6). It was 22.8 months (CI 95%: 8.5-37.1) for 21 patients who received TMZ and 7.6 months (95% CI: 5.1-10) in patients who were not given TMZ (p=0.008). Median PFS was 5.7 months for whole cohort (95% CI: 4.8-6.7). During follow-up, recraniotomy was performed in 4 (5%) patients. Only in one patient, intracranial and spinal seeding metastases developed 17 months after diagnosis. Four (5%) patients received second-line RT and 8 received ChT for local disease progression. Thirty-eight (40%) patients were treated symptomatically with dexamethasone (2 × 8 mg/day) after disease progression.

Univariate and multivariate analysis

In univariate analysis the following variables were found significantly favorable for OS (Table 2): age ≤53 years (p = 0.02), KPS ≥80 (p =0.001), external RT ≥60 Gy (p< 0.0001), female gender (p = 0.02), concomitant ChT (p = 0.003), RT waiting time ≤20 days (p = 0.014), overall treatment time <76 days (p = 0.01). Parameters without statistical significance included tumor size ≤4 cm vs. > 4 cm (p=0.5); total vs. subtotal resection (p = 0.2); unilobar vs. multilobar invasion (p =0.1), preoperative seizure history present vs. no such history (p=0.6), and RT duration ≤45 days vs. >45 days (p = 0.8). On the other hand, external RT ≥60 Gy (p< 0.0001), and concomitant ChT (p = 0.044) were positive prognostic factors for PFS.

Regression analysis was carried out for factors identified as significant in univariate analysis. Older age (p=0.03) (Figure 1), male gender (p=0.01) (Figure 2), RT waiting time ≥20 days (p=0.01) (Figure 3), absence of concomitant ChT (p=0.008) (Figure 4), RT dose <60 Gy (p=0.03) (Figure 5), and overall treatment time ≥76 days (p=0.0072) (Figure 6) were independent poor prognostic factors for OS (Table 2). For PFS only external RT ≥60 Gy was an independent prognosticator (p< 0.0001).

Discussion

GBM is characterized by the World Health Organization as an astrocytic tumor with nuclear atypia, mitosis, endothelial proliferation or necrosis. It is the most common malignant tumor of the central nervous system in adults, representing 50% of all gliomas and 20% of all operated intracranial solid lesions [6]. The standard therapeutic approach for patients with this highly malignant primary brain tumor is still neurosurgical debulking followed by localized radiation to the cranium up to 60 Gy. After this conventional treatment, median OS ranges between 9 to 12 months [7]. The demographic characteristics of our group and median survival were comparable to those reported in previous studies of patients with GBM. While Baxendine-Jones

Table 2. Univariate and multivariate analysis of prognostic factors for overall survival

Prognostic factor	*No. of patients*	*Median survival (months)*	*Univariate analysis p-value*	*Multivariate Cox regression analysis p-value*
KPS				
<80	36	6.6	0.001	0.5
≥80	42	10.6		
Age (years)				
<53	37	9.9	0.02	0.03
≥53	41	8.4		
Gender				
Male	49	8	0.02	0.01
Female	29	10.7		
RT waiting time (days)				
<20	40	11.2	0.014	0.01
≥20	38	7.4		
RT plus TMZ				
Received	21	22.8	0.003	0.008
Not received	57	7.6		
RT dose (Gy)				
<60	8	1.2	<0.0001	0.03
≥60	70	9.9		
Treatment time (days)*				
<76	61	12.17	0.01	0.0072
≥76	17	8.53		

RT: radiotherapy, KPS: Karnofsky performance status, TMZ: temozolomide
*includes the time period from diagnosis to the RT completion

et al. reported 53 years as median age at the time of diagnosis, Bouvier-Labit et al. reported it as 56 years [8,9]. In addition, gender distribution was also close to Baxendine-Jones' study in which 65% of patients were male and 35% female [8].

The outcome is almost always fatal; cure has only been reported in a few cases. Many predictive and prognostic factors have been considered, however, at present, only young age and good performance status are commonly regarded to offer longer survival. A high KPS has often been associated with a favorable outcome in many trials [10-13]. However, in the current study, although KPS had a prognostic effect in univariate analysis, this effect was not confirmed in multivariate analysis. There

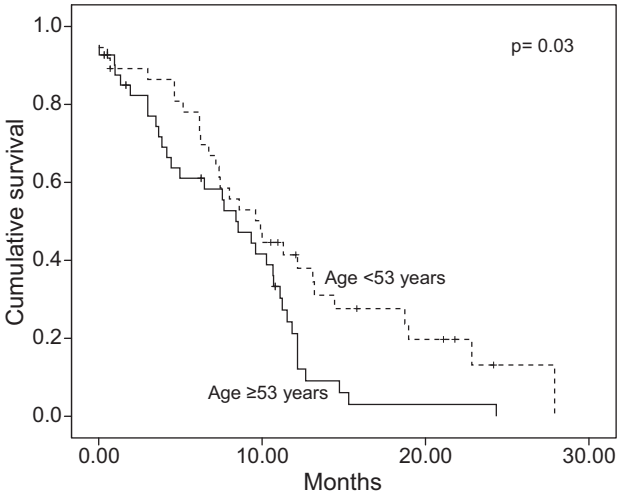

Figure 1. Overall survival according to age.

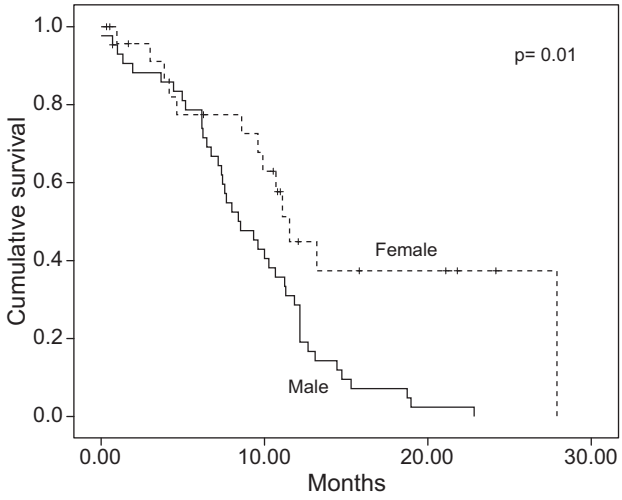

Figure 2. Overall survival according to gender.

are limited data stating that KPS is not significant factor for survival. In the study of Mineo et al., KPS was not found as important prognosticator [6]. The authors claimed that this discrepancy could be related to the use of different scales in evaluating clinical performance. In another randomized trial KPS was significant for survival but was not predictive of response to ChT [14]. Because the evaluation of patients' performance is a subjective process which depends on who is doing it, there might be some underestimations in scoring of KPS in our study, causing a discrepancy with the previous studies.

Young age is the other important prognosticator for GBM. Simpson et al. reported that patients younger than 40 years had the best survival rates [15]. Multivariate analysis in our study showed that age ≤53 was an independent factor for survival.

The significance of the extent of surgery and postoperative tumor size still remains unclear, particularly as they are related to survival. Several studies demonstrated that postoperative tumor size was correlated with longer survival, whereas others did not [7,16,17]. Although the effect of total vs. subtotal resections on survival is still a matter of debate, there is consensus that the tumor should be removed as much as possible without causing any significant neurological deficit [18-20]. It is also stated that frontal lobe localization is a better prognostic factor for survival than temporal and parietal lobe lesions [15]. It has been speculated that frontal tumor locations offer the chance of more surgical accessibility and total tumor removal. In addition, Gehan and Walker stated that patients with parietal lobe tumors had a worse survival [21]. However,

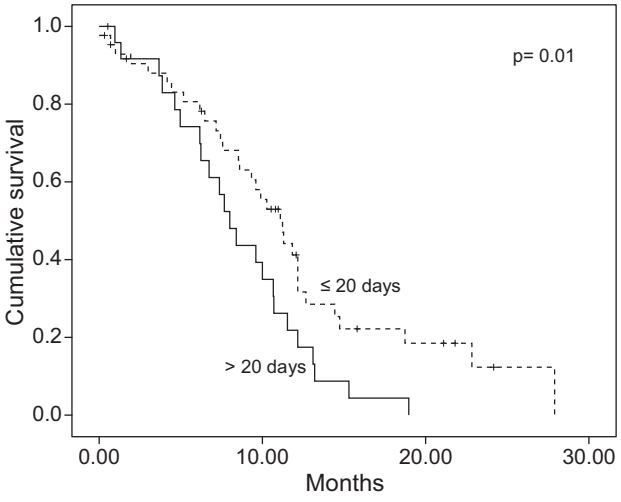

Figure 3. Overall survival according to RT-waiting time.

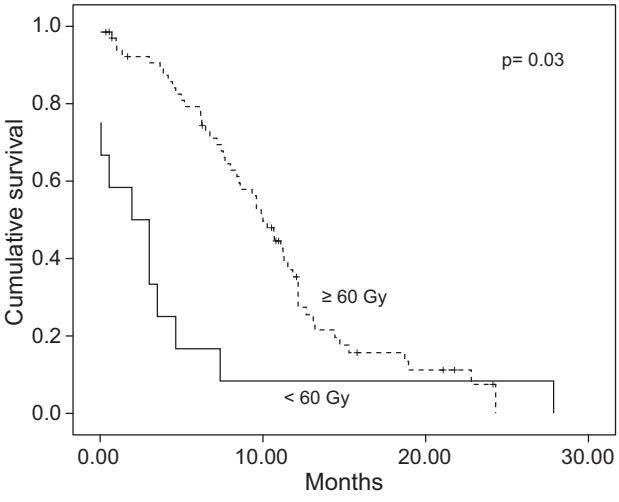

Figure 5. Overall survival according to radiotherapy dose.

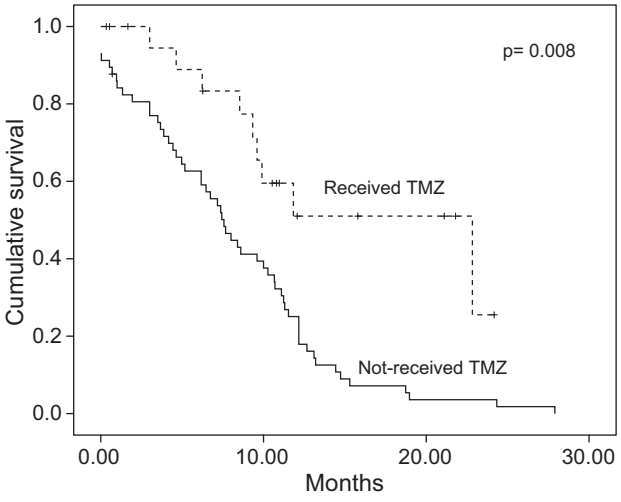

Figure 4. Overall survival according to concomitant temozolomide (TMZ).

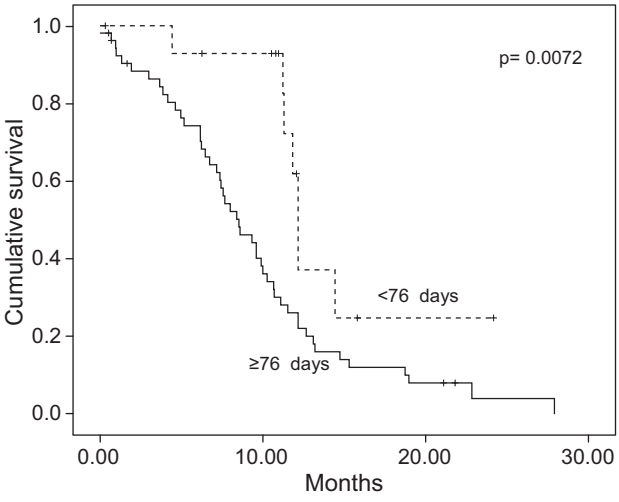

Figure 6. Overall survival according to treatment time.

tumor size, tumor location, and the extent of surgery did not show prognostic importance for survival in our study. The presence of seizures is one of the other controversial prognostic factors [22,23]. We also did not find any significance of it for survival. However, seizures may be a symptom for early diagnosis, which probably results in total removal of the tumor.

The effect of RT on gliomas is best documented in GBM. However, in patients with low performance status, >50 years, or tumor irresectability, the prognosis is poor and applying RT for either adjuvant or definitive settings may not be sufficient to improve the overall outcome. Four randomized trials reported doubling of survival from 4-5 months without, to 8-10 months with postoperative irradiation [3,12,24,25]. The optimal irradiation dose is widely discussed [26,27]. In an RTOG randomized trial, no significant difference was found between the total doses of 60 and 70 Gy (1.8-2 Gy/fraction) [26]. While the administration <60 Gy has been associated with poorer outcome, higher radiation doses using standard fractionation resulted in only an increased risk of radiation injury [28]. In the presented study, irradiation dose <60 Gy was also significant negative prognostic factor for survival. Furthermore, receiving a dose <60 Gy may reflect poor performance or rapid clinical deterioration of the patient.

Another controversial issue is the effect of the waiting time to start RT. Burnet's data suggested a mean tumor doubling time of 24 days, so that a delay to start RT would be expected to have an adverse effect. Considering patients by treatment intent, median survival decreased as delay increased, and almost no patient survived long enough after a 70-day delay [29]. Do et al. found longer waiting times for RT to be a significant negative predictor of OS - the risk of death increased by 2% for each day of waiting [30]. Similarly in our study, RT waiting time longer than 40 days was a negative factor that independently affected survival. Thus prompt initiation of therapy might be a reasonable approach for GBM.

Additionally, in the current study it was found that overall treatment time is an independent prognostic factor for outcome. This time is consisted of treatment waiting time and RT duration. Interestingly, while waiting time and overall treatment time were found to be independent factors, the RT time wasn't significant neither in univariate nor in multivariate analysis. Meanwhile, it is well known that GBM undergoes molecular changes during RT that lead to accelerated proliferation that diminishes the effectiveness of prolonged fractionated irradiation [31]. In addition, the effects of prolongation of RT time due to unplanned interruptions have been also investigated for different tumor sites including head and neck cancers, lung cancer, cervical carcinoma, anal canal cancer, bladder carcinoma, prostate carcinoma, and breast carcinoma [32]. So far there has been no data emphasizing these effects, particularly for GBM. In conclusion, the unfavorable effect of overall treatment time in the present study could be attributed to accelerated proliferation of the GBM.

Gender was not included in several analyses as a prognostic factor; when it was, it invariably did not impact the treatment outcome [15,18]. Coons et al. found that female gender was a poor prognostic variable for survival [33]. Similarly Reavey-Cantwell et al. stated that females had a decreased length of survival in univariate analysis, a factor which remained a marginal risk factor in multivariate analysis [34]. On the contrary, female gender was an independent favorable prognostic variable for survival in our retrospective study, maybe attributable to the fact that most of the female patients were treated with RT plus TMZ. In addition, although it was not an independent favorable prognostic factor in the present study, frontal localization of the tumor had a statistically significant predominance in females. It might be speculated that these tumor and treatment-related variables in female gender cause a better survival.

TMZ seems to be an effective agent in the treatment of malignant gliomas, offering a favorable safety profile compared with nitrosoureas. A number of studies have demonstrated the radiosensitizing properties of TMZ *in vitro* and *in vivo* [35,36]. A phase II study by Stupp et al. demonstrated that concomitant RT plus continuous daily TMZ followed by adjuvant TMZ is well-tolerated and improves survival in patients with newly diagnosed GBM [37]. A recently completed phase III study by the European Organization for Research and Treatment of Cancer (EORTC) has confirmed this data [4]. The results of our study also support the benefit of the combination of RT and TMZ in patients with GBM.

Conclusion

To date, only 2 clinical parameters are regarded as widely accepted indicators of prolonged survival, which are high performance status and younger age at the time of diagnosis [29]. Additionally, the role of concomitant TMZ has also been emphasized in several studies [4]. The present retrospective single-institution study emphasizes the importance of female gender, dose and duration of RT, and RT waiting time. Although our results are based on a relatively small patient series, they may provide some helpful information for daily practice.

Further studies are needed to assess the possible impact of these prognostic factors on survival.

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