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Treatment Strategies for Glioblastoma Multiforme: A Single Center Experience

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ABSTRACT Objective: The patient data, along with the diagnoses of glioblastoma multiforme (GBM), the treatments administered, and the clinical outcomes of these treatments, were assessed to inform future therapeutic strategies. **Material and Methods:** The records of 123 patients diagnosed with GBM, treated at the medical oncology outpatient department of the Atatürk Training and Research Hospital of İzmir Kâtip Çelebi University, Faculty of Medicine between 2007 and 2020, were collected and analyzed. **Results:** The study found that adjuvant chemoradiotherapy enhanced overall survival (OS). Re-operation and stereotactic radiosurgery offered a survival benefit in patients with recurrent disease, whereas re-irradiation did not. For patients with relapsed disease, re-administration of temozolomide proved beneficial for those with progression-free survival (PFS) over 15 months, and the combination of bevacizumab plus irinotecan (BEV/IRI) was chosen for patients with PFS under 15 months. Patients who underwent second-line chemotherapy exhibited significantly higher OS compared to those who did not. Additionally, patients treated with bevacizumab as a second-line therapy showed significantly greater OS than those who had not received bevacizumab. Regarding PFS and OS, the study's real-life data surpassed that reported in existing literature. **Conclusion:** Given the high mortality and recurrence rates associated with GBM, the development of new treatment modalities is imperative. Treatment strategies should include combination therapies and should be complemented by supportive care when necessary, always adhering to the principle of "first, do no harm."

Keywords: Glioblastoma; chemoradiotherapy; chemotherapy, adjuvant; chemotherapy, adjuvant; radiosurgery

Glioblastoma multiforme (GBM) is an aggressive malignancy of the central nervous system (CNS) that is more prevalent in males, presenting with a median survival time of 15 months and a median age of diagnosis at 64 years.[1] GBM stands as the most common primary malignant CNS tumor, with fewer than 10% of patients living beyond 2 years after diagnosis. Long-term survivors often experience neurological disorders, cognitive deficits, and a decline in social functions.[2] Several clinical prognostic factors have been identified that are associated with a more favorable outcome, such as younger age at diagnosis, cerebellar tumor location, high-performance status, and complete tumor resection.[1] Furthermore, molecular studies have been beneficial for predicting prognosis and treatment response. Mutations in IDH1/2 are indicative of a favorable prognosis, while methylation of the O^6-methylguanine-DNA methyltrans-

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ferase (MGMT) promoter suggests sensitivity to alkylating agents.[3] However, in developing countries, where comprehensive molecular studies are not feasible for every patient, research has turned towards identifying more accessible and cost-effective biochemical markers.

As for treatment, the established standard of care for GBM includes maximal safe resection, followed by 6 weeks of concurrent radiotherapy (RT) and temozolomide (TMZ), and then 6 months of adjuvant TMZ.[4] Despite aggressive initial treatment, around 90% of GBM cases recur within 2 years, with no consensus on the standard of care for recurrent GBM.[5] Second surgery and re-irradiation are considered local therapeutic options in cases of recurrent GBM.[6] The treatment modalities for GBM can also be combined. There is limited evidence suggesting that re-surgery, with or without re-irradiation and chemotherapy (CT) may be appropriate for some individuals.[7] Additionally, stereotactic radiosurgery (SRS), known for its precise and conformal delivery of high radiation doses, is another option for treating local recurrences.[8] Indeed, SRS has been demonstrated to improve survival in patients with local recurrence and to possess a more favorable safety profile compared to repeated surgical resection.[8] Furthermore, systemic therapies can be employed in this situation, either alone or in combination.[7] The single agents bevacizumab (anti-vascular endothelial growth factor receptor monoclonal antibody), bevacizumab plus irinotecan (BEV/IRI), chemotherapeutic agents such as lomustine and fotemustine, CT combinations such as procarbazine, lomustine, vincristine (PCV), and regorafenib (oral multikinase inhibitor) are among the treatments used.[7] However, despite multimodal treatment approaches, this cancer type is still virtually always deadly.[9,10]

Despite recent improvements in understanding the biology of this disease and multimodal methods for treatment, novel therapeutic alternatives are clearly needed for GBM, which has a low survival rate. In this study, the aim was to evaluate the demographic data of patients who were subsequently diagnosed with GBM, the treatments received, and the clinical outcomes of these treatments, and to determine the contribution to the patients receiving the treatments available in the country.

MATERIAL AND METHODS

This study received approval from the Clinical Research Ethics Committee of İzmir Kâtip Çelebi University, Faculty of Medicine, Atatürk Training and Research Hospital (date: June 15, 2023, no: 0294). It was carried out in accordance with the Declaration of Helsinki and principles of good clinical practice. The demographic details of 123 patients, monitored at the Faculty of Medicine, Atatürk Training and Research Hospital of İzmir Kâtip Çelebi University from 2007 to 2020, with fully accessible data, were initially evaluated. Of them, two patients were later excluded because the survival was more than 10 years, which contradicted the inclusion criterion, and the diagnosis was suspected, so a pathology revision was planned. The patients who declined to participate in the study were also excluded. Only patients with an ECOG performance status (PS) of 0-1 at diagnosis were considered for inclusion.

The evaluation of the patients included age, gender, surgical history, adjuvant treatments received, whether adjuvant therapy comprised solely of RT or included CT following chemoradiotherapy (CRT), recurrence management via re-operation, and the application of SRS. Progression-free survival (PFS) was determined as the duration from the start of treatment to the initial progression or relapse, while overall survival (OS) was calculated from the time of diagnosis until death. Furthermore, aspects such as the treatments administered at primary, secondary, and tertiary care levels, the response durations to these treatments, and the management of patients who exhibited progression during treatment, including their transition to alternative therapeutic options, were meticulously examined.

STATISTICAL ANALYSIS

IBM SPSS Statistics for Windows, version 25.0 (IBM Corp., Armonk, NY, USA), was used for statistical analysis. The Kolmogorov-Smirnov test was used to examine the conformity of the variables to a normal distribution. Descriptive statistics are presented as the mean±standard deviation for normally distributed continuous variables and frequency (percentage) for categorical variables. Survival times

were calculated with the Kaplan-Meier method. Between-group comparisons of survival times were performed with the log-rank test. Cox regression analyses were performed to determine the significant factors independently associated with mortality and progression. Variables were analyzed with univariate Cox regression analysis, and statistically significant variables were included in the multivariate Cox regression analysis. One-way analysis of variance was used for comparisons involving more than two groups. The homogeneity of variance was evaluated with Levene's test. When there was a significant difference among the groups, the Bonferroni correction, a post hoc test, was used for comparison. p values less than 0.05 were considered to indicate statistical significance.

RESULTS

The study included 120 patients (52 females and 68 males), with a mean age of 54.72±12.31 (range 17-80). Upon examining the demographic data, it was observed that the largest group within the general population was aged between 50-70, accounting for 56.1%, and GBM was more prevalent in males. Subtotal resection was performed on 69 (57.50%) patients, and total resection on 48 (40.00%) patients. Thirty-seven (30.83%) patients underwent re-operation. Fifteen (12.50%) patients received adjuvant radiotherapy, and 100 (83.33%) patients underwent adjuvant CRT. Six (5.00%) patients received re-irradiation, and 12 (10.00%) patients underwent SRS.

Sixty-four (53.33%) patients received first-line CT, with 53 (44.17%) receiving BEV/IRI and 11 (9.17%) receiving TMZ. All patients who received first-line and second-line CT had an ECOG PS of 0-1. Twenty-one (17.50%) patients received second-line CT, six (5.00%) of whom included bevacizumab. Progression was detected in 116 (96.67%) patients, and 113 (94.17%) cases resulted in death (Table 1).

The mean OS was 25.96 months [95% confidence interval (CI): 21.61-30.32], and the median OS was 19.00 months (95% CI: 16.18-21.82). OS was significantly lower in older patients (>65) compared to younger ones (p=0.014). Patients who underwent re-operation had a significantly higher OS compared to those who did not (p=0.001). Patients who received adjuvant CRT had a significantly higher OS than those who received no adjuvant therapy (p<0.001), while no significant differences in OS were observed between the adjuvant RT group and other groups (Figure 1). Patients who underwent stereotactic surgery had a significantly higher OS compared to others (p=0.011). Patients receiving BEV/IRI treatment had a significantly higher OS than those who did not receive first-line CT, and those receiving TMZ treatment had a significantly higher OS compared to other patients (p<0.001). When evaluating first-line CT in patients with high PFS (>15 months), no significant differences were found be-

TABLE 1: Summary of demographics and treatment procedures.

Age	54.72±12.31
Sex	
Female	52 (43.33%)
Male	68 (56.67%)
Operation	
No operation	3 (2.50%)
Subtotal resection	69 (57.50%)
Total resection	48 (40.00%)
Reoperation	37 (30.83%)
Adjuvant treatment	
No adjuvant treatment	5 (4.17%)
Radiotherapy	15 (12.50%)
Chemoradiotherapy	100 (83.33%)
Re-irradiation	6 (5.00%)
Stereotactic radiosurgery	12 (10.00%)
Chemotherapy, 1st line	
No chemotherapy	56 (46.67%)
BEV/IRI	53 (44.17%)
TMZ	11 (9.17%)
Chemotherapy, 2nd line	
No chemotherapy	99 (82.50%)
Bevacizumab	1 (0.83%)
BEV/IRI	5 (4.17%)
Carboplatin	2 (1.67%)
Etoposide	1 (0.83%)
Carbo/Etop	1 (0.83%)
Fotemustine	11 (9.17%)
Progression	116 (96.67%)
Exitus	113 (94.17%)

Descriptive statistics were presented by using mean±standard deviation for normally distributed continuous variables and frequency (percentage) for categorical variables; BEV/IRI: Bevacizumab plus irinotecan; TMZ: Temozolomide.

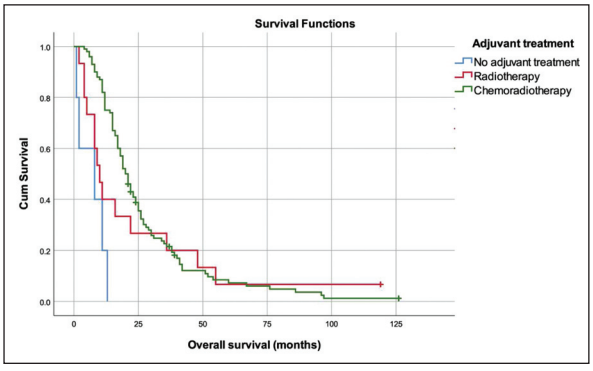

FIGURE 1: Overall survival plot with regard to adjuvant treatment.

tween CT groups. Patients who received second-line CT had a significantly higher OS than those who did not (p=0.004). Patients receiving bevacizumab as second-line treatment had a significantly higher OS than those who never received bevacizumab (p=0.007). Patients with high PFS (>15 months) had a significantly higher OS than others (p<0.001). No significant differences were observed in OS based on sex, type of operation, and re-irradiation groups (Table 2).

Multivariable Cox regression analysis revealed that adjuvant CRT, first-line CT, and PFS were independently associated with mortality risk. Patients who received adjuvant CRT exhibited a 4.219-fold lower risk of death compared to those who did not receive any adjuvant therapy [hazard ratio (HR): 0.237, 95% CI: 0.088-0.635, p=0.004]. Patients treated with BEV/IRI as first-line CT had a 2.433-fold lower risk of death than those who did not receive first-line CT (HR: 0.411, 95% CI: 0.260-0.651, p<0.001), and those treated with TMZ as first-line CT had a 3.745-fold lower risk of death compared to those who did not receive first-line CT (HR: 0.267, 95% CI: 0.121-0.589, p=0.001). Patients with higher PFS (>15 months) had a 6.849-fold lower risk of death than other patients (HR: 0.146, 95% CI: 0.079-0.267, p<0.001) (Table 3).

The mean PFS was 14.71 months (95% CI: 11.91-17.52), and the median PFS was 10.00 months (95% CI: 8.39-11.61). PFS was significantly higher in patients who received adjuvant CRT compared to those who did not receive any adjuvant therapy (p=0.038), while no significant differences were observed in PFS between the adjuvant RT group and other groups. No significant differences in PFS were found based on age, sex, and type of operation (Table 4).

Cox regression analysis indicated that adjuvant CRT was the only factor associated with PFS. Patients who received adjuvant CRT had a 2.907-fold lower risk of progression than those who did not receive any adjuvant therapy (HR: 0.344, 95% CI: 0.138-0.858) (Table 5).

DISCUSSION

In recent years, the association of molecular outcomes with clinical outcomes has underscored the importance of isocitrate dehydrogenase (IDH) as a predictive marker, now incorporated into the diagnostic criteria for brain tumors, indicating favorable prognostic and CT response.[11] Moreover, MGMT status has been identified as a predictive marker for a better therapeutic response.[11] The differentiation between IDH-mutant and IDH-wild type GBMs, as stipulated by the 2016 WHO classification, was not feasible for all patients, as the inclusion of patient data from 2007 onward meant that these molecular evaluations were not routinely conducted in earlier periods. Data on MGMT promoter methylation were similarly inadequate. Of the twenty-one patients assessed for IDH mutation, only one exhibited an IDH-1 mutation. Therefore, making comparisons based on mutation status was not possible. The patient with the IDH-1 mutation, a 32-year-old woman, had an OS of 15 months. Following adjuvant treatment after her initial surgery, she underwent a second surgery and succumbed to disease progression three months later while receiving first-line BEV/IRI therapy.

GBM was predominantly observed in men aged 50-70 years, aligning with existing literature.[1] The observed OS rates exceeded the anticipated 10-12 months reported in the literature.[12] Study participants were individuals presenting to the radiation oncology or medical oncology clinic for initial evaluation post-diagnosis. Patients with the poorest survival, who died during the diagnostic process or shortly after surgery, were excluded from the study, potentially in-

TABLE 2: Overall survival (months) with Kaplan-Meier method and comparisons of groups with Log rank test.

	Exitus, n (%)	Mean (95% CI)	Median (95% CI)	p value
All patients	113 (94.17)	25.96 (21.61-30.32)	19.00 (16.18-21.82)	N/A
Age				
≤65	90 (94.74)	27.84 (22.94-32.75)	21.00 (17.84-24.16)	0.014
>65	23 (92.00)	20.10 (10.37-29.83)	11.00 (9.08-12.92)	
Sex				
Female	49 (94.23)	28.56 (20.36-36.75)	18.00 (13.29-22.71)	0.462
Male	64 (94.12)	23.40 (19.66-27.14)	19.00 (15.64-22.36)	
Operation				
No operation	3 (100.00)	43.67 (11.49-75.84)	52.00 (0.00-116.01)	0.520
Subtotal resection	69 (97.10)	24.43 (19.73-29.13)	19.00 (15.52-22.48)	
Total resection	48 (89.58)	27.45 (18.78-36.12)	19.00 (14.48-23.52)	
Reoperation				
No	79 (95.18)	21.09 (16.59-25.58)	15.00 (12.02-17.98)	0.001
Yes	34 (91.89)	36.46 (27.81-45.11)	25.00 (16.95-33.06)	
Adjuvant treatment				
No adjuvant treatment	5 (100.00)	7.00 (2.32-11.68)	8.00 (0.00-20.88)a	<0.001
Radiotherapy	14 (93.33)	23.80 (8.61-38.99)	10.00 (6.21-13.79)ab	
Chemoradiotherapy	94 (94.00)	27.07 (22.57-31.56)	20.00 (17.21-22.79)b	
Re-irradiation				
No	107 (93.86)	24.91 (20.52-29.30)	18.00 (15.21-20.79)	0.115
Yes	6 (100.00)	45.17 (22.54-67.80)	27.00 (0.00-65.41)	
Stereotactic radiosurgery				
No	101 (93.52)	23.90 (19.32-28.47)	17.00 (14.28-19.72)	0.011
Yes	12 (100.00)	45.08 (32.14-58.02)	42.00 (40.33-43.67)	
Chemotherapy, 1st line				
No chemotherapy	52 (92.86)	17.42 (12.17-22.67)	12.00 (8.95-15.05)a	<0.001
BEV/IRI	51 (96.23)	29.14 (22.93-35.36)	22.00 (17.55-26.45)b	
TMZ	10 (90.91)	52.27 (36.40-68.14)	42.00 (31.21-52.79)c	
Chemotherapy, 1st line(1)				
No chemotherapy	11 (73.33)	35.90 (17.69-54.12)	25.00 (20.62-29.38)	0.051
BEV/IRI	11 (91.67)	58.92 (43.40-74.43)	51.00 (34.03-67.97)	
TMZ	8 (88.89)	57.00 (39.27-74.73)	48.00 (30.47-65.53)	
Chemotherapy, 2nd line				
No	93 (93.94)	22.80 (18.36-27.24)	17.00 (14.71-19.29)	0.004
Yes	20 (95.24)	40.29 (29.33-51.25)	31.00 (19.04-42.96)	
Bevacizumab treatment(2)				
No	57 (93.44)	19.50 (14.73-24.27)	15.00 (10.23-19.77)	0.007
Only 2nd line	5 (83.33)	58.33 (31.45-85.22)	38.00 (16.40-59.60)	
PFS				
≤15 months	83 (98.81)	15.92 (13.99-17.85)	15.00 (12.77-17.23)	<0.001
>15 months	30 (83.33)	49.66 (39.41-59.91)	41.00 (37.07-44.93)	

(1) Only patients with PFS>15 months were included in the analysis; (2) Patients who received BEV/IRI in the first-line treatment were excluded from the analysis; Letters denote pairwise comparison results, if two groups have same letter that means there is no significant difference between them; CI: Confidence interval; BEV/IRI: Bevacizumab plus irinotecan; TMZ: Temozolomide; PFS: Progression-free survival.

fluencing the survival results positively due to their absence.

Furthermore, it was noted that 117 patients underwent surgical intervention, while 3 were diagnosed via brain biopsy. Surgery was the primary treatment option for eligible patients, reflecting the literature's assertion that surgery enhances survival in GBM patients.[13] The lack of a discernible survival

TABLE 3: HRs for mortality, Cox regression analysis results.

	Univariable HR (95% CI)	Multivariable HR (95% CI)
Age, >65	1.760 (1.107-2.797)	1.150 (0.704-1.878)
Sex, Male	1.152 (0.784-1.693)	
Operation(2)		
Subtotal resection	1.897 (0.591-6.092)	
Total resection	1.751 (0.538-5.696)	
Reoperation	0.516 (0.343-0.777)	0.710 (0.455-1.109)
Adjuvant treatment(3)		
Radiotherapy	0.182 (0.062-0.531)	0.405 (0.138-1.190)
Chemoradiotherapy	0.152 (0.059-0.392)	0.237 (0.088-0.635)
Re-irradiation	0.524 (0.228-1.204)	
Stereotactic radiosurgery	0.465 (0.252-0.857)	0.992 (0.507-1.942)
Chemotherapy, 1st line(4)		
BEV/IRI	0.481 (0.323-0.717)	0.411 (0.260-0.651)
TMZ	0.225 (0.112-0.455)	0.267 (0.121-0.589)
Chemotherapy, 2nd line	0.501 (0.307-0.816)	0.782 (0.426-1.435)
Progression-free survival >15 months	0.137 (0.077-0.244)	0.146 (0.079-0.267)

(2) Reference category is "No operation"; (3) Reference category is "No adjuvant treatment"; (4) Reference category is "No chemotherapy"; HR: Hazard ratio;
CI: Confidence interval; BEV/IRI: Bevacizumab plus irinotecan; TMZ: Temozolomide.

benefit from surgery among the study patients was ascribed to the limited number of patients, particularly those not undergoing surgery.

The data from this study reveal that adjuvant therapy following surgery, the re-administration of surgery in patients who relapse, and the use of SRS in isolated relapses offer an OS benefit.[5,14,15] The findings indicate that utilizing SBRT significantly improves OS. Regarding disease progression, SBRT proved to be more effective than re-irradiation. In this research, the application of surgery at the time of relapse significantly enhanced OS, despite conflicting evidence in existing literature.[16] Research has identified that only approximately 20 to 30 percent of patients with recurrent glioblastoma qualify for a second surgery.[16] It is believed that the appropriate patients were selected for this study, as the incidence of surgery at relapse aligns with recommendations in the literature. Nevertheless, while re-surgery may offer symptomatic relief for patients, its impact on PFS and OS remains to be confirmed. This study is significant for demonstrating the OS benefit of re-surgery. In line with the literature, it is concluded that surgery should be reserved for specific groups of patients.[17,18]

In our study, 64 (53.33%) patients received first-line CT. The patients were evaluated for performance at the beginning of the study. When progression occurred after surgery and adjuvant treatments, first-line treatments were planned. Treatment was not planned for patients with worsening performance status. Treatment was not planned for 2 patients who refused treatment, even though their ECOG

TABLE 4: Progression-free survival (months) with Kaplan-Meier method and comparisons of groups with Log rank test.

	Progression, n (%)	Mean (95% CI)	Median (95% CI)	p value
All patients	116 (96.67)	14.71 (11.91-17.52)	10.00 (8.39-11.61)	N/A
Age				
≤65	92 (96.84)	15.53 (12.42-18.63)	11.00 (8.96-13.04)	0.053
>65	24 (96.00)	12.32 (5.55-19.09)	8.00 (7.24-8.76)	
Sex				
Female	51 (98.08)	14.67 (9.97-19.37)	10.00 (7.99-12.01)	0.828
Male	65 (95.59)	14.54 (11.41-17.66)	10.00 (7.98-12.02)	
Operation				
No operation	3 (100.00)	29.33 (0.00-62.31)	26.00 (0.00-64.41)	0.450
Subtotal resection	67 (97.10)	14.11 (10.38-17.83)	10.00 (8.65-11.36)	
Total resection	46 (95.83)	14.50 (10.42-18.58)	8.00 (6.30-9.70)	
Adjuvant treatment				
No adjuvant treatment	5 (100.00)	5.80 (2.11-9.49)	7.00 (0.00-17.74)[a]	0.038
Radiotherapy	15 (100.00)	12.53 (6.75-18.31)	8.00 (7.07-8.93)[ab]	
Chemoradiotherapy	96 (96.00)	15.59 (12.29-18.88)	10.00 (8.49-11.51)[b]	

CI: Confidence interval; Letters denote pairwise comparison results, if two groups have same letter that means there is no significant difference between them.

TABLE 5: Hazard ratios for progression, Cox regression analysis results.

	Univariable HR (95% CI)
Age, >65	1.536 (0.972-2.426)
Sex, Male	0.961 (0.663-1.394)
Operation(2)	
Subtotal resection	2.044 (0.630-6.637)
Total resection	1.932 (0.591-6.315)
Adjuvant treatment(3)	
Radiotherapy	0.416 (0.149-1.159)
Chemoradiotherapy	0.344 (0.138-0.858)

(2) Reference category is "No operation"; (3) Reference category is "No adjuvant treatment". Multivariable analysis was not performed due to only one variable was found to be significant; HR: Hazard ratio; CI: Confidence interval.

performance score ranged from 0-1. All patients who received first-line treatment had an ECOG performance score ranging from 0-1. However, whether the prolonged survival of patients receiving first-line treatment is due to performance or treatment is controversial, and this is one of the limitations of this study. Although the ECOG performance score ranged from 0-1, comparisons could not be made due to the small number of patients who did not receive treatment.

The findings suggest that for patients experiencing progression after completing adjuvant CT following adjuvant CRT, re-administration of TMZ is a feasible option for those with a PFS>15 months. Conversely, in patients with early progression and a short PFS, clinicians tend to prefer the combination of BEV/IRI over TMZ. The effectiveness of BEV/IRI and TMZ was found to be similar in patients with a PFS of over 15 months. Therefore, for this group, both retrying TMZ and switching to BEV/IRI are considered viable treatment strategies without a clear superiority of one over the other.

Due to the selection of TMZ for only one patient in the group with a PFS of 15 months or less, a direct comparison could not be conducted. The suboptimal survival outcomes observed in 39 patients who received BEV/IRI may be attributed to potentially aggressive molecular features, contributing to their early progression. Furthermore, the anticipated poor prognosis in this cohort was also reflected in their diminished performance status, affecting the feasibility of treatment planning compared to patients with a PFS of more than 15 months (74% vs. 88%).

For patients who had not previously received bevacizumab as a second-line treatment, employing bevacizumab or the BEV/IRI combination offered benefits over alternative therapies. These findings underscore the role of bevacizumab in the treatment of GBM beyond the initial treatment phase, highlighting the effectiveness of subsequent treatments when chosen judiciously for appropriate patients and agents.

LIMITATIONS OF THE STUDY

In addition to the small number of patients, the limitations of the study were that the patients could not be analyzed according to IDH mutation status or MGMT promoter methylation status. Another limitation of the study was that only patients with good performance scores received first- and second-line treatments, which created bias in the results.Additionally, in the 2nd series, treatment was given to patients with an ECOG PS of 0-1. A limitation of the present study is that CT did not increase survival in the first or second series, as the majority of the patients did not receive first- or second-line treatment due to their low performance status.

Another limitation was the composition of the patient cohort, which was a selected group referred to radiation oncology and medical oncology outpatient clinics. Additionally, access to advanced diagnostic methods and treatments was restricted due to socioeconomic factors and the retrospective design of the study.

CONCLUSION

Despite these limitations, the findings demonstrated that while the OS rates observed were superior to those reported in existing literature, the need for novel treatment approaches for GBM remains urgent, given the high rates of mortality and relapse. Integrated treatment approaches combining surgery, RT, CT, bevacizumab, and targeted therapies are recommended.

Furthermore, re-surgery and SBRT should be considered for suitable patients. Supportive care should also be provided as needed, with an emphasis on prioritizing patient safety and adhering to the principle of "first, do no harm."

Source of Finance

During this study, no financial or spiritual support was received neither from any pharmaceutical company that has a direct connection with the research subject, nor from a company that provides or produces medical instruments and materials which may negatively affect the evaluation process of this study.

Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

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