Turk Neurosurg 33(6):1126-1131, 2023

Original Investigation

DOI: 10.5137/1019-5149.JTN.45354-23.4

Received: 26.08.2023
Accepted: 05.10.2023

Published Online: 16.10.2023

Comparative Analysis of IDH Wild-Type Multifocal and Unifocal Glioblastomas: Prognostic Factors and Survival Outcomes in Focus

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ABSTRACT

AIM: To compare the overall survival (OS), progression-free survival (PFS), and the impact of prognostic markers in unifocal and multifocal IDH wild-type glioblastomas (GBMs).

MATERIAL and METHODS: This retrospective single-institutional study involved 177 GBM patients diagnosed between 2015 and 2022. Patients with confirmed IDH wild-type GBM were selected to assess the impact of lesion focalities on prognosis. Surgical procedures included gross total resection (GTR), subtotal resection (STR) or biopsy. Radiation therapy (RT) employed the intensity-modulated (IM)RT technique, combined with concurrent temozolomide (TMZ) treatment. Survival analyses and prognostic factors were performed accordingly.

RESULTS: We examined 101 IDH wild-type glioblastoma patients, of whom 78 had unifocal and 23 had multifocal tumors. The median patient age was 60 years, comprising 37% females and 63% males. Surgical approaches included GTR (13%), STR (53%), and biopsy (34%). Positive p53 expression was seen in 65 patients. All patients received TMZ with RT. Adjuvant therapy referral was arranged for 68 patients. Progression occurred in 49% (38 unifocal, 11 multifocal cases). PFS analysis showed no significant difference between unifocal and multifocal patients. OS analysis also showed no significant difference. Univariate analysis revealed PFS factors: focalization, p53 expression, hypofractionated RT. For OS, adjuvant TMZ usage was influential. Extent of resection impacted OS-STR had 3.47-fold higher risk than GTR.

CONCLUSION: This study sheds light on the management of multifocal glioblastoma, providing insights into treatment strategies and survival outcomes. Despite challenges, optimal management approaches are crucial for improving patient prognosis and quality of life.

KEYWORDS: Glioblastoma, Multifocal GBM, Radiotherapy, Temozolamide

INTRODUCTION

Glioblastoma (GBM) stands as the most prevalent primary malignant tumor within the central nervous system (CNS) and bears an unfavorable prognosis despite contemporary treatments (11). Typically, GBMs manifest as solitary lesions; nevertheless, approximately 0.5 to 20% of all GBMs emerge as multiple lesions (M-GBM) (2).

The subset of GBMs with multiple lesions has previously been categorized into multifocal and multicentric GBMs. Multifocal GBMs exhibit a connection or distinct pathway of expansion between the foci. Conversely, multicentric tumors lack a clear link among the distinct disease foci and are frequently detected in different lobes or hemispheres of the brain, thus adopting a metastatic appearance.

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Patients who initially present with multiple foci pose a distinct challenge in terms of treatment, as evidenced by poorer outcomes (9). This is attributed not solely to the multiplicity of lesions, but also to broader dissemination, more frequent involvement of eloquent and/or deep cerebral regions, a higher likelihood of unfavorable performance status (PS), limited surgical resectability, and increased heterogeneity (1,8,11). Additionally, the management of these cases remains a point of contention in the medical literature and lacks standardization.

While obtaining a histopathological diagnosis is widely recognized as essential, the optimal surgical approach remains uncertain. Certain studies advocate for an aggressive surgical strategy involving maximal safe resection to extend survival, under the assumption that adjuvant therapies become more effective post-tumor debulking (15). In contrast, some studies emphasize the significance of biopsies, contending that extensive resection might amplify comorbidities without a concurrent survival benefit (12).

Furthermore, after biopsy or resection, the lack of established guidelines for radiotherapy and chemotherapy further complicates decision-making. Questions arise regarding the feasibility and efficacy of active oncological intervention as opposed to solely palliative care. For managing multiple lesion GBM (mGBM), Temozolomide (TMZ) continues to be the preferred choice for chemotherapy. In specific cases involving deep-seated structures, extended TMZ administration subsequent to standard therapy may be considered as a potential option (10). Given the diffuse nature of the disease and the microscopic dissemination characteristic of mGBMs, the consideration of whole-brain radiotherapy (WBRT) becomes crucial (7).

The aim of this retrospective single-institutional study is to compare the overall survival (OS), progression-free survival (PFS), and the impact of prognostic markers in unifocal and multifocal IDH wild-type glioblastomas.

MATERIAL and METHODS

A retrospective analysis was conducted on 177 patients diagnosed with glioblastoma (GBM) and treated and monitored at our clinic between 2015 and 2022. Among them, 101 patients with histopathologically confirmed IDH wild-type GBM were included to investigate the impact of unifocality (u) and multifocality (m) on prognosis.

Patient data were sourced from medical records, hospital information systems, and telephone interviews. Demographic details, including age, gender, surgical procedures, histopathological characteristics, treatment modalities, tumor focalities, follow-up information, progression data, and follow-up dates, were recorded retrospectively. The study adhered to the principles of the Declaration of Helsinki and received approval from our hospital's ethics committee (No: E1-23-4012).

The median age of the patients was 60 years (range: 25-78). Among them, 37% were female and 63% were male. The Eastern Cooperative Oncology Group (ECOG) performance status ranged from 0 to 2. Positive P53 expression was observed in 65 patients, negative in 31, and unknown in 5. Gross total resection (GTR) or subtotal resection (STR) was performed in 66% of patients, while 34% underwent biopsy alone.

Radiation therapy was administered using the IMRT technique. Gross tumor volumes are delineated based on postoperative MRI scans utilizing enhanced T1 and fluid-attenuated inversion recovery (FLAIR)/T2 sequences, 1.5 – 2 centimeters were added to form clinical target volumes (CTV). Planning target volume was generated by adding 0.3 to 0.5 centimeters to CTV. Conventional radiation therapy (CRT) (200 cGy/30 fraction) was given to 46 patients, simultaneous integrated boost radiation therapy (SIBRT) (222 cGy x 27 fraction and 185 cGy x 27 fraction) to 37 patients, and hypofractionated radiation therapy (HRT) (267cGy x 15 fraction) to 18 patients. All patients received concurrent TMZ during radiation therapy. Adjuvant therapy referral to the medical oncology clinic was made for 68 patients four weeks after completion of chemoradiotherapy. Fifteen patients did not receive adjuvant therapy due to patient preferences, and 18 had unknown adjuvant therapy status. After treatment, all patients underwent contrast-enhanced cranial magnetic resonance (MR) imaging every three months.

Statistical Analysis

Statistical analysis were performed using the Statistical Package for the Social Sciences Version 22.0 for Windows (SPSS Inc., Chicago, IL, USA) software. Categorical variables were expressed as percentages, while numerical variables were reported as median (minimum-maximum) values. Mann-Whitney U test and chi-square or Fisher's exact test were used for comparing numerical and categorical variables, respectively. Kaplan-Meier test and log-rank test were employed to analyze overall survival (OS) and progression-free survival (PFS). Univariate and multivariate Cox regression analyses were conducted for single and multiple endpoints, respectively. The significance level was set at $p<0.05$.

RESULTS

In our study, 78 out of 101 IDH wild-type patients were unifocal, and 23 were multifocal. The median follow-up duration was 12.6 months, ranging from 3.3 to 51.9 months. The median age for unifocal GBM (uGBM) patients was 61 (25-78), while for mGBM patients, it was 60 (43-76). Among the patients, 13% underwent GTR, 53% underwent STR, and 34% had only biopsy performed.

All patients received concurrent Temozolomide with radiotherapy (RT). The median RT dose was 60 Gy (30-62) for both groups (40-60). The details of the patient characteristics and administered treatments are summarized in Table I. A total of 49 (49%) patients experienced progression on follow-up magnetic resonance imaging (MRI). Among them, 38 had uGBM progression, while 11 had mGBM progression.

Regarding PFS, there was no statistically significant difference between uGBM (median 11.0 months) and mGBM (median 8.2 months) patients ($p=0.228$, Figure 1). Similarly, the OS between the two groups did not show a statistically significant

Table I: Patient Characteristics and Treatment Details

Patient characteristics	Total n (%)	Unifocal n (%)	Multifocal n (%)	p-value
Number of patients	101	78	23	
Median age(min-max)	60 (25-78)	61 (25-78)	60 (43-76)	0.514
Gender				
Female	38 (37.0)	29 (37.0)	9 (39.0)	0.865
Male	63 (63.0)	49 (63.0)	14 (61.0)	
p53				
Negative	31 (31.0)	24 (31.0)	7 (30.0)	0.449
Positive	65 (64.0)	49 (63.0)	16 (70.0)	
Unknown	5 (5.0)	5 (6.0)	0	
Adjuvant temazolamid				
Yes	68 (67.0)	54 (69.0)	14 (61.0)	0.566
No	15 (15.0)	10 (13.0)	5 (22.0)	
Unknown	18 (18.0)	14 (18.0)	4 (17.0)	
Median RT dose (min-max)	60 (30-62)	60 (30-62)	60 (40-60)	0.892
Modalite				
CRT	46 (45.0)	34 (44.0)	12 (52.0)	0.706
SIB	37 (36.0)	29 (37.0)	8 (35.0)	
HRT	18 (18.0)	15 (19.0)	3 (13.0)	
Surgery				
GTR	13 (13.0)	12 (15.0)	1 (4.0)	0.353
STR	53 (53.0)	39 (50.0)	14 (61.0)	
BX	35 (34.0)	27 (35.0)	8 (35.0)	
Recurrence				
Yes	49 (49.0)	38 (49.0)	11 (48.0)	0.952
No	28 (28.0)	22 (28.0)	6 (26.0)	
Unknown	24 (23.0)	18 (23.0)	6 (26.0)	

RT: *Radiotherapy,* ***CRT:*** *conventional radiotherapy,* ***SIB:*** *simultaneous integrated boost,* ***HRT:*** *hypofractionated radiotherapy,* ***GTR:*** *gross total resection,* ***STR:*** *subtotal resection,* ***Bx:*** *biopsy.*

difference, with median OS for uGBM at 16.5 months and for mGBM at 13.3 months (p: 0.513, Figure 2).

Univariate analysis revealed that factors influencing PFS included factors such as focalization, presence of p53 expression, and hypofractionated radiotherapy (HRT), among others. However, in the multivariate analysis, the presence of p53 expression correlated with a 67% reduction in progression risk compared to those without it (HR: 0.37, 95%CI: 0.17-0.79, p value: 0.011). Median PFS was 14.2 months for patients with HRT and 10.4 months for patients with CRT. HRT led to a statistically significant difference in PFS (HR: 0.21, 95%CI: 0.05-0.62, p value: 0.007), resulting in a 79% reduction in progression risk among HRT-treated patients (Table II).

Both univariate and multivariate analyses demonstrated that the sole factor influencing OS was the use of adjuvant Temozolomide. Median OS was 18.3 months for those with adjuvant Temozolomide versus 7.1 months for those without (p<0.001). In the multivariate analysis, another significant

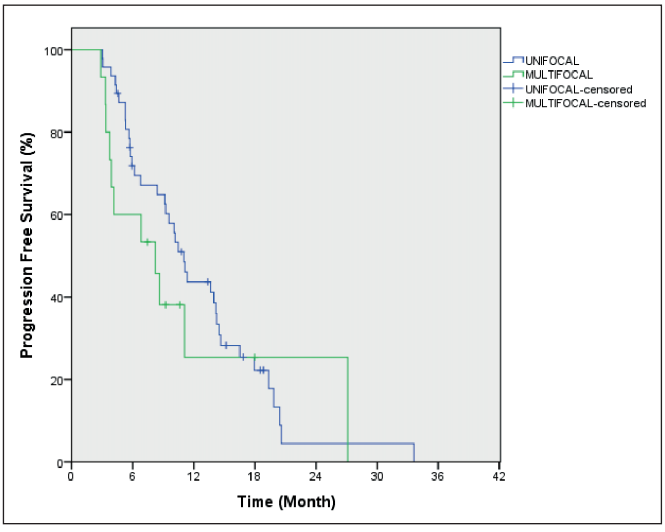

Figure 1: Progression free survival of patients with unifocal and multifocal disease. Cencored values were calculated otomatically by statistical tool (Kaplan Meier).

factor influencing OS was the extent of resection. Patients with STR had a 3.47-fold increased risk of death compared to those with GTR (HR: 3.47, 95%CI: 1.09-11.02). In the univariate analysis, patients who underwent biopsy had a 5.68-fold increased risk of death compared to those with GTR, though no statistically significant difference was observed in the multivariate analysis (Table III).

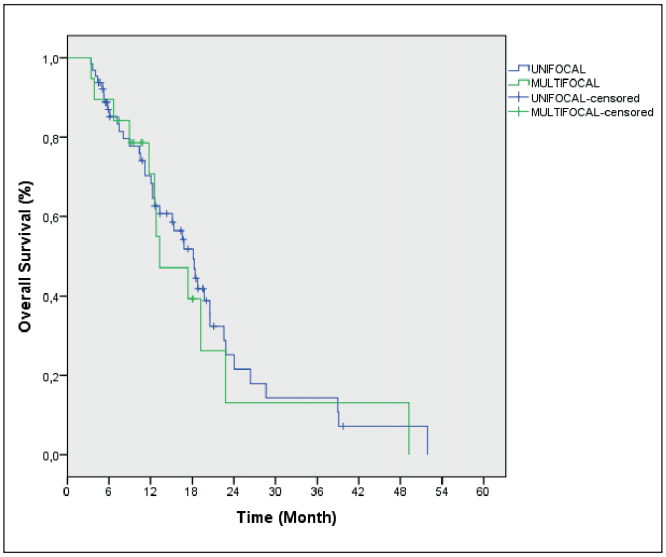

Figure 2: Overall survival of patients with unifocal and multifocal disease. Cencored values were calculated otomatically by statistical tool (Kaplan Meier).

DISCUSSION

Multifocal glioblastoma (mGBM) constitutes a subset of glioblastoma cases, ranging from 0.5% to 20% of all instances, and is frequently associated with a bleak prognosis. The most effective approach for managing these lesions remains a contentious issue due to conflicting findings in the literature. Some advocate for a conservative stance of abstaining from treatment, whereas others endorse a vigorous strategy involving maximal surgical resection followed by CRT. However, the optimal course of action is still uncertain. Surgical biopsy, nonetheless, is a crucial step for confirming the diagnosis and guiding subsequent adjuvant therapies. When addressing deep-seated lesions, stereotactic biopsy is often the preferred approach, whereas larger lesions with indications of heightened intracranial pressure (ICP) may necessitate open surgical decompression (13).

Despite the perception that mGBM has a worse prognosis compared to uGBM, some studies have not demonstrated significant differences. In our study, we investigated the impact of focal involvement on PFS and OS in 101 patients with IDH wild-type glioblastoma.

Surgical treatment for patients with multifocal lesions has gained importance (2). Guerrini et al. found in their study involving 16 mGBM patients that GTR and STR significantly improved prognosis (4). Haque et al., in a study of 45,268 patients with 17% mGBM, demonstrated the statistical significance of GTR (5). In our study, both univariate and multivariate analyses revealed a significant survival advantage of GTR compared to biopsy and STR.

Table II: Univariate and Multivariate Analyses for Progression-Free Survival (PFS)

Variables (n)	Median PFS	Univariable	p-value	Multivariable	p-value
	(mo)	HR (95% CI)		HR (95% CI)	
Age	-	0.99 (0.97-1.02)	0.912	1.03 (0.98-1.08)	0.157
Gender					
Female/Male	11.1/10.1	1.19 (0.62-2.27)	0.597	0.84 (0.35-2.02)	0.705
p53					
Negative/Positive	5.9/11.0	0.63 (0.34-1.16)	0.145	0.37 (0.16-0.81)	**0.014**
Focality					
Solitary/Multiple	11.0/8.2	1.30 (0.65-2.58)	0.444	1.63 (0.73-3.63)	0.228
Adjuvant Temozolamid					
Yes/No	10.4/3.7	1.65 (0.63-4.34)	0.303	2.60 (0.79-8.52)	0.115
Modality					
CRT/SIB	10.4/9.5	0.94 (0.49-1.80)	0.872	0.93 (0.45-1.91)	0.863
CRT/HRT	10.4/14.2	0.55 (0.23-1.33)	0.188	0.21 (0.05-0.62)	**0.007**
Surgery					
GTR/STR	14.4/11.0	1.47 (0.60-3.57)	0.392	1.54 (0.58-4.04)	0.381
GTR/BX	14.4/6.7	1.99 (0.75-5.29)	0.164	1.66 (0.56-4.95)	0.359

CRT: *Conventional radiotherapy,* ***SIB:*** *simultaneous integrated boost,* ***HRT:*** *hypofractionated radiotherapy,* ***GTR:*** *gross total resection,* ***STR:*** *subtotal resection,* ***Bx:*** *biopsy.*

Table III: Univariate and Multivariate Analyses for Overall Survival (OS)

Variables (n)	Median OS (mo)	Univariable HR (95% CI)	p-value	Multivariable HR (95% CI)	p-value
Age	-	1.02 (0.99-1.05)	0.071	1.02 (0.99-1.05)	0.142
Gender					
Female/Male	13.3/17.2	0.71 (0.40-1.23)	0.223	0.78 (0.37-1.64)	0.515
p53					
Negative/Positive	15.3/15.1	0.91 (0.49-1.71)	0.792	1.24 (0.56-2.75)	0.589
Focality					
Solitary/Multiple	16.5/13.3	1.16 (0.60-2.23)	0.652	0.78 (0.38-1.61)	0.513
Adjuvant temozolamid					
Yes/No	18.3/7.1	3.82 (1.89-7.71)	**<0.001**	4.10 (1.74-9.70)	**0.001**
Modality					
CRT/SIB	18.7/15.3	0.90 (0.50-1.62)	0.745	0.58 (0.28-1.19)	0.140
CRT/HRT	18.7/12.0	1.49 (0.78-2.86)	0.223	0.54 (0.21-1.37)	0.197
Surgery					
GTR/STR	20.5/13.6	3.80 (1.30-11.07)	**0.014**	3.47 (1.09-11.02)	**0.034**
GTR/BX	20.5/11.7	5.68 (1.75-18.37)	**0.004**	3.47 (0.91-13.23)	0.068

CRT: *Conventional radiotherapy,* ***SIB:*** *simultaneous integrated boost,* ***HRT:*** *hypofractionated radiotherapy,* ***GTR:*** *gross total resection,* ***STR:*** *subtotal resection,* ***Bx:*** *biopsy.*

Fleischman et al., in a study encompassing 20 mGBM cases, applied concurrent TMZ with radiotherapy (RT) and emphasized its suitability as a treatment option (3). The treatment of glioblastoma became standardized with the addition of concurrent chemotherapy to postoperative radiotherapy based on the Stupp trial (14). Similarly, other studies underscored the importance of concurrent RT and TMZ treatment. While Haque et al. emphasized the beneficial effect of TMZ in mGBM, a multicenter review by Li et al. concluded that adjuvant TMZ improved survival in multifocal glioblastomas (5,9). In our study, all patients received RT+TMZ, and this treatment was well-tolerated even in the 23 patients with mGBM.

Kyritsis et al. suggested a higher prevalence of p53 gene mutations in mGBMs (6). In our study, the distribution of p53 mutations was similar between both groups. Despite the heterogeneity observed in studies, our analysis revealed no significant differences in OS and PFS between uGBM and mGBM. In the pooled analysis, we found that the presence of p53 mutations significantly impacted progression-free survival, reducing the risk of progression by 67%. Patil et al. noted shorter survival in mGBM but did not provide information about RT dose or administration mode (conventional vs. hypofractionated RT) (11). Conversely, Haque et al. demonstrated the impact of hypofractionated RT on survival (5). Thus, both total RT dose and administration mode play crucial roles. In our study, both groups received the same median RT dose, and a similar percentage of patients received hypofractionated RT. Therefore, our study indicated that hypofractionated RT positively affected prognosis.

Paulsson et al. showed, in their study of 41 mGBM patients, that focal involvement did not significantly impact PFS and OS (12). Patil et al. reported a significant decrease in median survival for mGBM cases (11). Li et al. suggested in a systematic review that prognosis was worse for mGBM and that lesion number was inversely correlated with OS (9). In studies indicating decreased OS in mGBM, tumor localization, deep-seated lesions, and crossing to the contralateral hemisphere were associated factors. In our study, there was no statistically significant difference in OS and PFS between uGBM and mGBM.

Limitations of our study included the lack of tumor localization information and MGMT status assessment.

CONCLUSION

In conclusion, our retrospective study delved into the prognosis and treatment outcomes of patients with multifocal and unifocal glioblastomas. While multifocal lesions present unique challenges, our findings suggest that factors such as gross total resection and concurrent Temozolomide treatment during radiotherapy can positively impact survival. Notably, the presence of p53 mutations emerged as a significant prognostic factor. Surprisingly, our study did not reveal significant differences in survival between patients with multifocal and unifocal glioblastomas, contrasting with previous research. Hyperfractionated radiotherapy also demonstrated promise in improving prognosis. Our study underscores the complexity of managing multifocal glioblastomas and highlights the importance of tailored treatment strategies for these cases.

AUTHORSHIP CONTRIBUTION

Study conception and design: RH, IK

Data collection: RH, IK

Analysis and interpretation of results: RH, IK, IS

Draft manuscript preparation: RH, IK, IS

Critical revision of the article: RH, IK, IS, YT

Other (study supervision, fundings, materials, etc...): RH, IK, IS, YT

All authors (RH, IK, IS, YT) reviewed the results and approved the final version of the manuscript.

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