ORIGINAL ARTICLE

Study to Determine the Significant Prognostic Factors Related with Better Clinical Outcome in Glioblastoma Multiforme Patients

FAHRI ERYILMAZ[1], MUHAMMAD ASIF RAZA[2]
[1]*Department of Neurosurgery, Ministry of Health Hitit University Corum Erol Olcok Training and Research Hospital, Corum, Turkey*
[2]*Assistant Professor, Department of Neurosurgery, Jinnah Hospital Lahore*
Correspondence to: Fahri Eryilmaz, Email: drfahrier@hotmail.com

ABSTRACT

Aim: In adults glioblastoma multiforme (GBM) is the deadly and utmost communal brain tumor. GBM has poor prognosis and the median general endurance hardly surpasses one-year. In this study, we retrospectively assessed the demographic and clinical characteristics of patients with GBM and to recognize significant prognostic factors that may be associated with better results in our population.

Material and Methods: The clinicopathological, treatment parameters (ie, chemotherapy, radiotherapy and the surgical resection extent) and demographic parameters were attained from medical records. SPSS version 23.0 was applied for all statistical analyzes. The overall survival and median progression-free survival was 14.1 and 10 months; correspondingly.

Results: In the subjects with the longest overall survival group, a tumor was found in the frontotemporal area, and then in the frontal area. In a univariate analysis, age, co-administration of adjuvant temozolomide (TMZ) and chemoradiotherapy were prognosticators of both overall survival (OS) and progression-free survival (PFS). Though, in multivariate analysis, radiotherapy and age were important determinants of endurance. Subjects who received the cyber-knife after relapse had a lengthier operating system.

Conclusion: The patients were retrospectively assessed with GBM in the facility, and the outcomes confirmed formerly testified factors influencing GBM endurance.

Keywords: glioblastoma multiforme; prognosis; overall survival; chemotherapy; radiotherapy; surgical resection

INTRODUCTION

In adults, GBM is the most prevalent malignant brain tumor. With an overall survival time of 12 months, the prognosis remains low, considering advancements in healthcare[1-2]. The safest surgical method is primary tumor resection accompanied by a mixture of radiotherapy treatment and supplementary TMZ is the quality of care[3-4]. In recent years, improvements in surgical and radiotherapy methods, and the incorporation of chemotherapy to treatment, have exhibited enhanced survival and improved local control[5]. But even, the disease nearly often returns, and recovery in the long run is very low. In the event of a relapse, treatment modalities are minimal[6-7]. Anti-angiogenic treatment, immunotherapy, selective molecular therapy, gene therapy and adjuvant radiotherapy are modern methods and are being tested in many clinical trials[8]. For GBM, histopathological conditions are essential factors. Such are the prognostic variables like tumor location, the extent of surgery and Karnofsky Performance Status[9-10]. In this study, in order to recognize significant prognostic variables that could be correlated with patient results in this group, we retrospectively examined the demographic and clinical topographies of patients with GBM in the hospital.

MATERIAL AND METHODS

This retrospective study was held in the Department of Neurosurgery, Jinnah Hospital Lahore for 2 years duration from April 2018 to April 2020, the study included patients diagnosed patients of GBM. A total of 109 patients were selected for this analysis. The local ethics committee has approved the study. Medical records were used to collect demographic, clinical-pathological and therapeutic criteria (i.e., radiotherapy, chemotherapy and degree of surgical resection). Patient death data are collected from the hospital record.

The period between primary surgery and death or progressive disease has been described as PFS. The period from diagnosis to death or last observation of living patients has been described as OS. SPSS 23.0 [SPSS Inc.; Chicago, IL, USA] was applied for data analysis andfor the estimation of OS and PFS for OS; Kaplan-Meier curves were used. For univariate analyses; Log-rank test was applied. To assess individual variables for OS, multivariate linear regression analysis was applied. A “p” value below 0.05 has been found to be statistically important.

RESULTS

109 patients diagnosed with GBM were involved in the study: 65 (59.6 percent) men and 44 (40.3 percent) women. The patients' mean age was 58 years and the mean diameter of the tumor was 40 mm. Characteristics of the tumor and care are illustrated in Table-1.

During treatment, the bulk of patients got combined chemoradiotherapy. Afterwards, most of the patients received chemotherapy (Table-2).

The patients underwent 1st, 2nd and 3rd line treatment after a relapse. The most appropriate first-line care regimen following disease development was cyber-knife stereotaxic radiotherapy. Any of the patients underwent second-line chemotherapy with bevacizumab and irinotecan. Due to the weak general health status of the patient, only a few patients might undergo tertiary therapy. There was a median follow-up duration of 12 months (4-7 months). There was a median PFS of 10 months. By gender, place, and form of surgery, PFS did not vary statistically. As compared to radiotherapy alone, concomitant chemoradiotherapy resulted in longer PFS. There was a longer PFS in patients who got supplementary TMZ than in those who did not obtain TMZ. In the whole sample population, average survival was 14.2 months; in women, 12.6 months; and in males, 15.5 months (p: 0.4).

Table-1: Tumor and Treatment Characteristics

Tumor site	Temporal	31 (28.4%)
	Parietal	17 (15.6%)
	Frontal	16 (14.7%)
	Frontoparietal	13 (11.9%)
	Parietooccipital	11 (10.1%)
	Frontotemporal	8 (7.3%)
	Occipital	5 (4.6%)
	Other	8 (7.3%)
Primary/secondary	Primary	96 (88.1%)
	Secondary	8 (7.3%)

	Unknown	5 (4.6%)
Hemisphere	Right	44 (40.4%)
	Left	56 (51.4%)
	Midline	6 (5.5%)
	Unknown	3 (2.8%)
Operation type	Total	56 (51.4%)
	Subtotal	38 (34.9%)
	Biopsy	9 (8.3%)
	Unknown	6 (5.5%)
Adjuvant treatment	Chemoradiotherapy	91 (83.5%)
	Radiotherapy	8 (7.3%)
	No treatment	6 (5.5
	Unknown	4 (3.7%)
TMZ	Yes	74 (67.9%)
	No	17 (15.6%)
	Unknown	18 (16.5%)

Table-2: Treatments in Recurrence

First line		49
	Cyber-knife	23 (46.9%)
	Operation	17 (34.7%)
	Irınotecanplus bevacizumab	6 (12.2%)
	TMZ	3 (6.1%)
Second line		21
	Irınotecanplusbevacizumab	11 (52.4%)
	Cyber-knife	6 (28.6%)
	TMZ	4 (19.0%)
	Chemoradiotherapy	1 (4.8%)
Third line		11
	Cyber-knife	5 (45.5%)
	Irınotecanplus bevacizumab	3 (27.3%)
	TMZ	3 (27.3%)

Table-3 Univariate and Multivariate Analysis for PFS

Characteristic		Univariate			Multivariate		
		OR	CI	p-value	OR	CI	p-value
Age	<65	2.3	1.4-3.7	0.003	2.2	1.3-3.7	0.007
	>65						
Gender	Women	1.4	0.9-2.2	0.323	1	0.6-1.6	0.623
	Men						
Surgery	Biopsy	1.2	0.9-1.5	0.652	1.2	0.9-1.5	0.751
	Subtotal						
	Total						
Radiotherapy	Concurrent	4.6	1.6-13.3	0.007	4.2	1.3-14.1	0.033
	Alone						
TMZ	Yes	2	1.5-2.7	0.0002	1.9	1.4-2.7	0.002
	No						
Side	Right	1.2	0.8-1.9	0.648	1	0.6-1.6	0.766
	Left						

Table-4: Univariate and Multivariate Analysis for OS

Characteristic		Univariate			Multivariate		
		OR	CI	p-value	OR	CI	p-value
Age	<65	1.9	1.1-2.9	0.054	1.6	1.0-2.7	0.122
	>65						
Gender	Women	1.3	0.8-2.1	0.499	1.1	0.7-1.7	0.876
	Men						
Surgery	Biopsy	1.2	0.8-1.4	0.676	1.1	0.9-1.5	0.852
	Subtotal						
	Total						
Radiotherapy	Concurrent	10.8	3.5-33.2	0.0002	29.9	6.7-137.3	0.0002
	Alone						
TMZ	Yes	1.3	1.0-1.7	0.218	1.3	1.0-1.7	0.352
	No						
Side	Right	1.3	0.8-2.0	0.566	1	0.7-1.6	0.75
	Left						
Cyber-knife	Yes	2.6	1.6-4.4	0.002	2.5	1.5-4.3	0.004
	No						
Irınotecan plus bevacizumab	Yes	0.6	0.4-1.1	0.062	0.7	0.4-1.3	0.23
	No						

Patients with secondary tumors (low-grade diffuse astrocytoma or development of anaplastic astrocytoma) lived longer than patients with main glioma, but there was no statistically meaningful gap (13.3 months vs 23.9 months, p:0.25). Based on the site of the tumor, average survival differed. A tumor was located in the frontotemporal area (20.6 months) and then the frontal region (18.0 months) in the community of patients with the longest average survival. The average survival of the left and right tumors was comparable (p<0.19). One-dimensional and multivariate analyses indicated that there was a longer OS in patients who got cyber-knife following relapse. Age, co-administration of chemoradiotherapy, and adjuvant TMZ were all PFS and OS predictors in a univariate study. However, age and concomitant radiotherapy were major determinants of survival in a multivariate study (Table-3 and Table-4).

DISCUSSION

We analyzed the clinical features of GBM patients in this report. Clinicopathological variables correlated with treatment results are tumor position, age, combined radiotherapy, the usage of adjuvant TMZ and a cyber-knife to manage relapses[10-11]. The OS and PFS median were 14.1 and 10 months, correspondingly, in our sample group. The observations are in accordance with earlier studies. Better PFS are shown in patients who underwent combined therapy; this is in line with recent research suggesting that better outcomes are achieved by adding chemotherapy at the same time[12-14]. Stupp et al. testified OS of 14.6 months in GBM patients having 56 years median age managed with radiotherapy plus adjuvant and concomitant TMZ. In this analysis, the 58 years was the median age and the 16.9 months was the OS compared with the work of Stupp[15-16]. Frontotemporal and frontal neoplasms have the longest average survival in our study. Three successive Radiation Oncology Community (RTOG) clinical trials testing the impact of localization on clinical results have found that frontal lobe tumor patients have a longer survival period than temporal or parietal tumor patients (11.4, 9.1 and 9.6 months)[17].

For the management of recurrent tumors, emergency re-irradiation has long been prescribed. Although the beneficial impact of cyber-knife in the GBM recurrence is contested, retrospective results suggest improved tumor regulation[18-19]. As a therapeutic choice, recent studies have looked at radiosurgery and fractionated stereotaxic radiosurgery for recurrent glioma patients. Single-center, observational trials have shown that stereotaxic radiosurgery is well accepted and findings of effectiveness appear positive. Retrospective analyses have shown that the annual OS concentrations vary from 16% to 44% for relapsing GBM treated with fSRT/SRS. Greenspoon et al and Larson et al, respectively exhibited the median overall survival was 9 and 9.5 months, respectively in 2 prospective trials. In a radiotherapy oncology clinic, our patients obtained basic care and were supervised primarily by oncologists and radiotherapists. Many patients who received oncological radiotherapy during the first relapse and radiotherapists preferred care with cyber-knife during the first relapse[20-21]. During primary care, patients are typically referred to the oncology clinic regardless of a relapse. As a consequence, on the first relapse, most underwent cyber knife treatment, and on the second relapse, chemotherapy. In our research, average survival was longer for patients who received cyber-knife for tumor recurrence than for those who did not undergo this therapy[22]. There are certain drawbacks to this report. As a consequence of the retrospective aspect of the sample, some knowledge was lacking, however while we attempted to monitor possible confounding variables using multivariate regression, the randomized controlled trial did control factors that could impact the outcome. As a consequence of personal interests and perceptions, post-relapse therapy was heterogeneous[23-24]. In addition, the standard requirements for an answer remained vague and the so-called success was not systemic.

CONCLUSION

While this was a retrospective review of patients in one hospital, previously documented factors impacting the survival of GBM were confirmed in the findings. Future studies assessing the function of the cyber scalpel in the treatment of GBM would be funded.

REFERENCES

1. Lämmer F, Delbridge C, Würstle S, Neff F, Meyer B, Schlegel J, Kessel KA, Schmid TE, Schilling D, Combs SE. Cytosolic Hsp70 as a biomarker to predict clinical outcome in patients with glioblastoma. PloS one. 2019 Aug 20;14(8):e0221502.
2. Kim I, Jang BS. Abstract B168: A Radiosensitivity gene signature and PD-L1 status predict clinical outcome of patients with glioblastoma multiforme in The Cancer Genome Atlas Dataset.
3. Jang BS, Kim IA. A Radiosensitivity Gene Signature and PD-L1 Status Predict Clinical Outcome of Patients with Glioblastoma Multiforme in The Cancer Genome Atlas Dataset. Cancer Research and Treatment: Official Journal of Korean Cancer Association. 2020 Apr;52(2):530.
4. Liu Q, Qi C, Li G, Su W. Prediction of the Outcome for Patients with Glioblastoma with lncRNA Expression Profiles. BioMed Research International. 2019 Dec 23;2019.
5. Antonopoulos M, Van Gool SW, Dionysiou D, Graf N, Stamatakos G. Immune phenotype correlates with survival in patients with GBM treated with standard temozolomide-based therapy and immunotherapy. Anticancer Research. 2019 Apr 1;39(4):2043-51.
6. Werlenius K, Fekete B, Blomstrand M, Carén H, Jakola AS, Rydenhag B, Smits A. Patterns of care and clinical outcome in assumed glioblastoma without tissue diagnosis: A population-based study of 131 consecutive patients. PloS one. 2020 Feb 13;15(2):e0228480.
7. Sippl C, Ketter R, Braun L, Teping F, Schoeneberger L, Kim YJ, List M, Nakhoda A, Wemmert S, Oertel J, Urbschat S. miRNA-26a expression influences the therapy response to carmustine wafer implantation in patients with glioblastoma multiforme. Acta neurochirurgica. 2019 Nov 1;161(11):2299-309.
8. Petrelli F, De Stefani A, Ghidini A, Bruschieri L, Riboldi V, Dottorini L, Iaculli A, Zaniboni A, Trevisan F. Steroids use and survival in patients with glioblastoma multiforme: a pooled analysis. Journal of Neurology. 2020 Jan 30:1-8.
9. Potharaju M, Mathavan A, Mangaleswaran B, Ghosh S, John R. Delay in adjuvant chemoradiation impacts survival outcome in glioblastoma multiforme patients. Acta Oncologica. 2020 Mar 3;59(3):320-3.
10. Navone SE, Guarnaccia L, Locatelli M, Rampini P, Caroli M, La Verde N, Gaudino C, Bettinardi N, Riboni L, Marfia G, Campanella R. Significance and prognostic value of the coagulation profile in patients with glioblastoma: implications for personalized therapy. World neurosurgery. 2019 Jan 1;121:e621-9.
11. Li H, He Y, Huang L, Luo H, Zhu X. The nomogram model predicting overall survival and guiding clinical decision in patients with glioblastoma based on the SEER database. Frontiers in Oncology. 2020 Jun 26;10:1051.
12. Bark JM, Kulasinghe A, Chua B, Day BW, Punyadeera C. Circulating biomarkers in patients with glioblastoma. British journal of cancer. 2020 Feb;122(3):295-305.
13. Alimohammadi E, Bagheri SR, Sadeghsalehi A, Rizevandi P, Rezaie Z, Abdi A. Prognostic factors in patients with glioblastoma multiforme: focus on the pathologic variants. Acta NeurologicaBelgica. 2019 Jun 20:1-0.
14. Peeken JC, Goldberg T, Pyka T, Bernhofer M, Wiestler B, Kessel KA, Tafti PD, Nüsslin F, Braun AE, Zimmer C, Rost B. Combining multimodal imaging and treatment features improves machine learning-based prognostic assessment in patients with glioblastoma multiforme. Cancer medicine. 2019 Jan;8(1):128-36.
15. Ryu JY, Min KL, Chang MJ. Effect of anti-epileptic drugs on the survival of patients with glioblastoma multiforme: A retrospective, single-center study. PloS one. 2019 Dec 2;14(12):e0225599.
16. Tan AC, Ashley DM, López GY, Malinzak M, Friedman HS, Khasraw M. Management of glioblastoma: State of the art and future directions. CA: A Cancer Journal for Clinicians. 2020 Jun 1.
17. Zuo S, Zhang X, Wang L. A RNA sequencing-based six-gene signature for survival prediction in patients with glioblastoma. Scientific reports. 2019 Feb 22;9(1):1-0.
18. Seliger C, Genbrugge E, Gorlia T, Chinot O, Stupp R, Nabors B, Weller M, Hau P, EORTC Brain Tumor Group. Use of metformin and outcome of patients with newly diagnosed glioblastoma: Pooled analysis. International Journal of Cancer. 2020 Feb 1;146(3):803-9.
19. Nassiri F, Taslimi S, Wang JZ, Badhiwala JH, Dalcourt T, Ijad N, Pirouzmand N, Almenawer S, Stupp R, Zadeh G. Determining the Optimal Adjuvant Therapy for Improving Survival in Elderly Patients with Glioblastoma: A Systematic Review and Network Meta-analysis. Clinical Cancer Research. 2020 Jun 1;26(11):2664-72.
20. Brenner, A., Friger, M., Geffen, D.B., Kaisman-Elbaz, T. and Lavrenkov, K., 2019. The Prognostic Value of the Pretreatment Neutrophil/Lymphocyte Ratio in Patients with Glioblastoma Multiforme Brain Tumors: A Retrospective Cohort Study of Patients Treated with Combined Modality Surgery, Radiation Therapy, and Temozolomide Chemotherapy. Oncology, 97(5), pp.255-263.
21. Wu S, Yang W, Zhang H, Ren Y, Fang Z, Yuan C, Yao Z. The prognostic landscape of tumor-infiltrating immune cells and immune checkpoints in glioblastoma. Technology in Cancer Research & Treatment. 2019 Aug 24;18:1533033819869949.
22. Alimohammadi E, Bagheri SR, Taheri S, Dayani M, Abdi A. The impact of extended adjuvant temozolomide in newly diagnosed glioblastoma multiforme: a meta-analysis and systematic review. Oncology Reviews. 2020 Feb 18;14(1).
23. Norden AD, Korytowsky B, You M, Kim Le T, Dastani H, Bobiak S, Singh P. A real-world claims analysis of costs and patterns of care in treated patients with glioblastoma multiforme in the United States. Journal of managed care & specialty pharmacy. 2019 Apr;25(4):428-36.
24. Cunha ML, Maldaun MV. Metastasis from glioblastoma multiforme: a meta-analysis. Revista da Associação Médica Brasileira. 2019 Mar;65(3):424-33.