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PROGNOSTIC FACTORS AFFECTING SURVIVAL IN GLIOBLASTOMA MULTIFORME PATIENTS

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Abstract

Introduction: Glioblastoma multiforme, the most aggressive primary tumor of the central nervous system (CNS) with a poor prognosis. Despite several clinical studies conducted over many years, our capacity to significantly influence the survival outcomes for these patients remains fairly limited.

Aim of the study: To evaluate patient demographics and treatments commenced in patients with glioblastoma to study their survival rate and to investigate their prognostic factors of survival.

Methods: A retrospective analysis of newly diagnosed radiologically and/or histologically confirmed glioblastoma patients referred to our clinic at the Military Oncology Center in the period between January 2020 and December 2022. Patient demographics, treatment details, and survival data were collected. Kaplan-Meier survival curves were utilized to characterize univariate associations between age and survival. We constructed a Cox proportional hazard model that incorporated multivariate survival predictors.

Results: A total of 123 patients with a mean age at diagnosis of 55 ± 16.2 were included in this study. Overall survival was 9.8 months. Univariate analyses showed that younger age was associated with a longer survival, with a median survival of 13.2 months in patients aged less than 50 years versus 7.6 months in patients aged 50 or more. In the multivariate analysis, better survival was associated with debulking surgery vs. biopsy alone (15 vs. 8 months) (HR 0.54, 95% CI 0.41–0.70), subsequent treatment after diagnosis, standard chemoradiotherapy (16.5 months) vs. nonstandard regimens (10.3 months) vs. radiotherapy alone (5.4 months), and palliative radiotherapy (2 months).

Conclusion: The median survival rate for the patients included in the study was less than one year. Younger age, debulking surgery, and treatment with chemoradiotherapy are independently associated with longer survival.

Keywords:
Glioblastoma multiforme, Survival rate, prognosis, predictive factors

Introduction

Glioblastoma multiforme, which has an overall age-standardized incidence rate of 3.2 per 100,000 to 4.64 per 100,000 (1,2) and comprises approximately 16% of all primary brain solid tumors, is the most prevalent malignant primary brain solid tumor in adults (3,4). This tumor is the most aggressive glioma originating from cells of the astrocytic lineage and classified as a grade IV glioma according to the World Health Organization (WHO) classification (3).Despite the availability of multimodal therapy for glioblastoma, it is still challenging given

resistant tumor cells, the brain's inherent fragility, and the difficulty of most chemotherapeutic drugs passing the blood-brain barrier (5).Surgery is the cornerstone of glioblastoma treatment, followed by radiotherapy, systemic chemotherapy, and targeted therapy (6,7). The main objective of the surgical procedure is to excise the tumor to its maximum extent while minimizing damage to the healthy brain tissue that is essential for normal neurological function (8) and also associated with longer survival (9). Complete tumor eradication is difficult since glioblastoma is surrounded by migrating, infiltrating tumor cells that invade adjacent tissues (8). Studies have proven that surgical procedures, followed by theaforementioned therapy, result in limited improvement in clinical outcomes (6,7).Among all human malignancies, glioblastoma nevertheless has the lowest five-year survival rate (10) ranging from 4.7% to 10.9% in clinical trials (11,12). Previous studies reported poor survival rates, with a median survival of 6–10 months for those receiving less than standard treatment and 14.6-21.1 months for those receiving standard treatment (11,13-18).This variation in survival rate reported in the literature may be explained by several patient-related factors (such as age, sex, age of disease onset, and duration of diagnosis) (19,20), tumor factors (such as tumor size, histopathological subtypes, location of the tumor, size of necrosis, and edema surrounding the tumor) (21-23), and treatment-related factors (such as type of treatment, treatment dose, and extent of surgical excision) (12,24). Hence, it is critical to comprehend the natural history of the diseases and the factors that may impact the clinical outcome in order to determine the most suitable treatment approach.In the current study, we aimed to evaluate patient demographics and treatments commenced in a group of 123 patients with glioblastoma to study their survival rate and to investigate if there is any correlation between these factors and survival.

Material and method

We performed a retrospective analysis of newly diagnosed radiologically and/or histologically confirmed glioblastoma patients referred to our clinic at the Military Oncology Center in the period between January 2020 and December 2022. Patient demographics was retrieved from electronic medical records.Our study comprised 123 adult patients who had a confirmed diagnosis of glioblastoma, either histopathological, radiological, or both. The study excluded patients who were ineligible due to a lack of available clinical and imaging data, had a prior history of malignancies, had undergone radiotherapy, or received chemotherapy previously.

Treatment

The standard treatment consisted of radiotherapy with a total dose of 60 Gy/30 Fractions over a period of six weeks given as a once-daily fraction of 2 Gy, five days per week (Sunday through Thursday). Concomitant chemotherapy consisted of temozolomide at a dose of 75 mg per square meter of body surface area per day, given 7 days per week from the first day until the last day of radiotherapy. 4 weeks after the completion of concurrent chemoradiotherapy, patients received up to six cycles of adjuvant temozolomide, according to the standard 5-day schedule every 28 days. The sequential Temozolomide was given at a dose of 150 mg per square meter of body surface area for the first cycle and was then increased up to 200 mg starting from the second cycle if there were no hematologic side effects.

Eligible patients for the standard treatment had a WHO performance status of 2 or less and adequate hematologic, renal, and hepatic functions. Prior to radiotherapy, all patients received corticosteroids and antiepileptic medications to control symptoms.

Patients who received other than the standard dose of radiotherapy (40 Gy/15) Fr or those who did not complete the full course of concurrent or sequential Temozolomide were labeled as the non-standard chemoradiotherapy group.

Ethical consideration

Prior to data collection and analysis, ethical approval was obtained from the Ethic Review Board at Royal Medical Services. Every participant provided a written, informed, and signed consent form that comprehensively outlined the study's objectives, risks, and benefits, as well as the participant's right to withdraw from the research at any point during the study.

surveillance and follow-up

All patients had a baseline assessment, including a physical examination, magnetic resonance imaging (MRI), complete blood counts, and blood chemistry tests. Patients undergoing radiotherapy (with or without temozolomide) were to attend evaluations at the radiotherapy clinic weekly. The medical team graded treatment side effects according to the National Cancer Institute Common Toxicity Criteria, version 2.0, and managed them accordingly (25).

At the end of radiotherapy, tapering of steroids was initiated according to the patients' tolerance, and post-treatment brain MRIs were obtained 6 to 8 weeks later to assess response and as a baseline for future follow-up.
Patients subsequently underwent a comprehensive evaluation every three months, which included a brain MRI for radiologic assessment of the tumor and a thorough neurological examination.During adjuvant temozolomide therapy, patients underwent a monthly clinical evaluation and a comprehensive evaluation at the end of cycles 3 and 6.

Statistical analysis
We conducted two primary sets of analyses. We initially examined the influence of age on survival across the entire cohort of 123 individuals. We estimated median survival and utilized Kaplan-Meier survival curves to characterize univariate associations between age and survival. Second, we constructed a Cox proportional hazard model that incorporated multivariate survival predictors, such as age, type of surgery, and adjuvant treatment. We utilized a forward stepwise variable selection with an inclusion p-value of less than 0.05. We analyzed the impact of treatment on survival using Cox model analyses.

Results

Patients' characteristics
A total of 123 patients with a mean age of 55 years (ranging from 24 to 75) were included in the study.There were 78 (63.4%) males and 45 (36.6%) females. 23 (18.7%) of the patients received palliative radiotherapy and steroids without undergoing biopsy, while 100 patients underwent surgery, either for biopsy or debulking.60 patients (48.8%) had debulking surgery, and 40 (32.5%) had biopsy only. Subsequently, 44% had standard chemoradiotherapy, 21% had non-standard chemoradiotherapy, 16.3% received radical radiotherapy alone without chemotherapy treatment, and 18.7% received palliative radiotherapy.Table 1 shows patient characteristics.

Treatment details
Results showed that 18.7% of patients did not have any kind of surgery, 48.8% underwent primary debulking surgery, and 32.5% underwent a biopsy only. The median age of patients who received debulking surgery was 56 years, compared to 65 years for those who underwent biopsy only ($p < 0.001$).

Subsequent treatment details showed that 54 patients (44%) received standard adjuvant treatment consisting of CCRT (60 Gy/30 Fr concomitantly with Temozolomide), 26 patients (21%) received non-standard CCRT (40 Gy/15 Fr) or did not complete the entire course of concurrent or sequential Temozolomide, 20 (16.3%) received radiotherapy alone, and 18.7% received palliative radiotherapy (30 Gy/10 Fr). Among our patients, those who received standard therapy tended to be younger and more frequently had debulking surgery. Figure 1 shows patients treatment details

Survival rate
Overall, the median survival was 9.8 months (IQR 7.9 to 10.3 months), and the 2-year survival rate was 6.8% (95% CI: 5.6–7.3).

Factors influencing survival rate
Univariate analyses showed that advancing age was associated with a shorter survival (hazard ratio vs. age < 50: 1.70 [1.26-2.30], and for ages ≥50: 4.8 [3.5-6.5]. In multivariate analyses, debulking surgery and the type of subsequent treatment emerged as predictors of survival. Compared to biopsy only or no biopsy at all, debulking surgery was linked to better survival rates (adjusted HR 0.56 [95% CI 0.43–0.75]), with median survival rates of 15 months vs. 8 months vs. 2 months, respectively, and 24-month survival rates of 23.4% vs. 4.5% vs. 0%. The impact

of adjuvant treatment given was also evident; the median survival of patients who received standard CCRT treatment was 16.8 months, adjusted HR = 0.09 [0.06 to 0.13], while in the non-standard CCRT group (median survival 10.3 months, adjusted HR = 0.19 [95% CI 0.13 to 0.29]), when compared with radiotherapy alone (median survival 5.4 months, adjusted HR = 0.17 [95% CI 0.11 to 0.23]) and palliative radiotherapy (median survival 2.0 months), 2 year Survival rates among patients with palliative radiotherapy, radiotherapy alone, non-standard CCRT, and standard CCRT were 0%, 2%, 19%, and 38.3%, respectively. Table 2 shows the survival rate based on patients and treatment characteristics.

Tabel 1. Patients' characteristics (n=123)

Patient characteristics	**Number (%)**
Age (Mean = 55, SD = 16.2)	
< 50	47 (38.2)
≥ 50	76 (61.8)
Sex	
Male	78 (63.4)
Female	45 (36.6)
Surgery	
None	23 (18.7)
Biopsy only	40 (32.5)
Debulking	60 (48.8)
Performance Status(ECOG)	
0	18 (14.6)
1	26 (21)
2	35 (28.4)
3	22 (18)
4	22 (18)
Adjuvant treatment	
Standard CCRT	54 (44)
Non-standard CCRT	26 (21)
RT alone	20 (16.3)
Palliative RT	23 (18.7)

CCRT :Concurrent chemoradiotherapy; RT: radiotherapy

Table 2. Survival rate based on patients and treatment characteristics

Characteristic	**Total**	**Median Survival (months)**	**2- years survival(%)**
Age			
<50	47	13.2	9.3
≥50	76	7.6	3.4
Type of Surgery			
None	23	2	0
Biopsy	40	8	4.5
Debulking	60	15	23.4
Further Treatment			
Palliative XRT	23	2	0
XRT Alone	20	5.4	2
Non-standard CCRT	26	10.3	19

Standard CCRT	54	16.8	38.3
Total	123	9.8	6.8

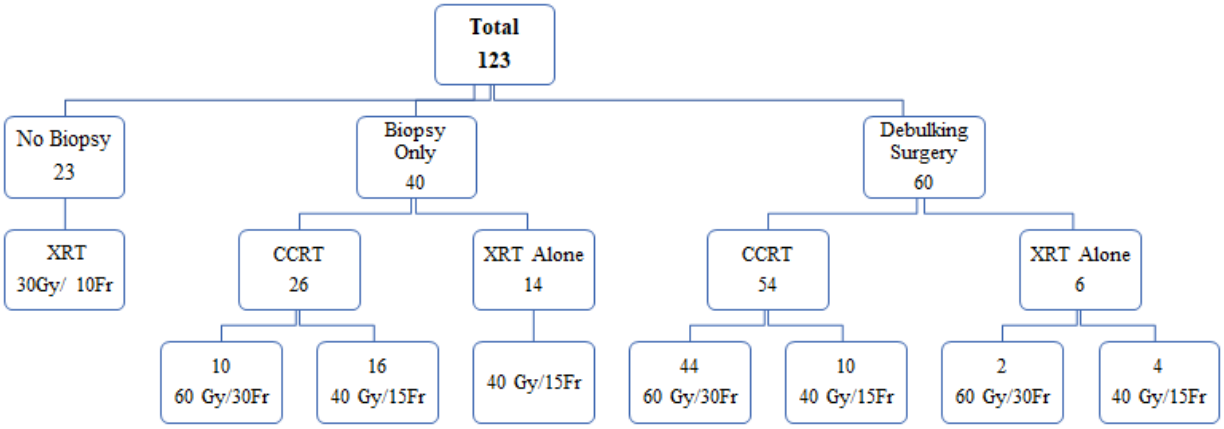

Figure 1. Patients' treatment details

Discussion

Glioblastoma multiforme, the most aggressive primary tumor of the central nervous system (CNS) with a poor prognosis, poses a significant risk to the survival and quality of life of patients (2,26).In the current study, we conducted an analysis on patient overall survival and associated prognostic factors. To the best of our knowledge, it was the first report about Jordanian glioblastoma patients' survival that included adjuvant therapy with temozolomide and radiation therapy (standard treatment) and compared them with those who received non-standard treatment.Typically, this type of brain tumor is commonly seen in patients in their sixth and seventh decades of life (5,15,21,27).In this study, the mean age of patients was 55 years, and more than half of our patients were over the age of 50.

In this study, almost two-thirds of patients were male (63.4%) and one-third were female (36.6%).Carrano et al. and Bello et al. studies demonstrated how sex influences the incidence and progression of glioblastomas. Estradiol and progesterone may have either promoting or protecting effects on glioblastomas, contrasting with the known link between testosterone and their progression (28,29).

Despite several clinical studies conducted over many years, our capacity to significantly influence the survival outcomes for these patients remains fairly limited.Our investigation showed that patient survival rates were quite poor, with a median survival of 9.8 months and a 2-year survival of 6.8%. Recent retrospective studies also reported similar findings (30,31).

In terms of the dose-response relationship with survival, patients who received standard treatment with 60 Gy showed better median survival and 2-year survival than those who received 40 Gy.Previous randomized control trials showed better dose-response in patients who received 60 Gy than those who received 45 Gy (32,33). However, a randomized controlled study by the Radiation Therapy Oncology Group (RTOG) and the Eastern Cooperative Oncology Group found that 70 Gy did not enhance survival compared to 60 Gy (34). In controlled trials, hyperfractionated regimens with higher total doses also failed to improve survival (35,36). Furthermore, compared to patients in the non-standard group who either did not receive temozolomide or did not complete the course of therapy, patients in the standard treatment group who received temozolomide exhibited higher 2-year survival.Another trial that supported this finding was a joint effort between the European Organization for Research and Treatment of Cancer and the National Cancer Institute of Canada Clinical Trials Group. In that trial, patients who received temozolomide in addition to radiation therapy had a 2.5-month improvement in overall survival, a

16% increase in 2-year survival, and an 8% improvement in 5-year survival compared to those who received radiation therapy alone (12).

This study provides further evidence of the major treatment-independent prognostic factors of age and the role of debulking surgery and adjuvant chemoradiotherapy in glioblastoma patients.Previous meta-analyses of 37 studies reported a decreased mortality rate in gross total resection and subtotal resection compared to biopsy at 1 year (RR, 0.77; 95% CI, 0.71-0.84; P <.001) and 2 years (RR, 0.94; 95% CI, 0.89-1.00; P =.04) (37).Furthermore, it has been consistently recognized in previous studies that younger age is the most significant prognostic variable affecting survival (30, 38, 39).

Study limitations

Our study is retrospective in nature, which is an important limitation. Therefore, we were unable to collect the necessary data and statistically adjust for some known prognostic indicators of survival, such as the performance status (38,40), the extent of surgical resection in the debulking group of patients (complete resection vs. partial resection) (37), and tumor molecular profile, including MGMT gene promotor methylation (41-43), that were not available at our center during that time. Furthermore, we can't exclude selection bias.

Conclusion

In this single-institution retrospective cohort review of 123 newly diagnosed patients with glioblastoma, CNS WHO grade 4, the median survival from diagnosis was 9.8 months. The median overall survival in patients who underwent debulking surgery was 15 months, compared to 8.0 months in those who had only a biopsy. Patients treated with standard therapy (radical radiotherapy with temozolomide chemotherapy) had the highest median survival of 16.9 months following surgery, compared to those who received other regimens of radiotherapy or chemotherapy. Multivariate analysis of treatment-independent variables at diagnosis identified younger age, debulking surgery, and subsequent standard adjuvant CCRT as positive prognostic factors.

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