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Retrospective Analysis of Prognostic Factors in Adult Glioblastoma Multiforme: A Single Institution Experience

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Background: Primary brain tumors represent 2% of cancers in adults. Glioblastoma Multiforme (GBM) is the most frequent among these tumors. Different prognostic factors have been identified including age, performance status, extent of surgery and genetic factors.
Aim: To analyze treatment outcome and prognostic factors in adult patients with GBM treated at a single institution.
Methods: We retrospectively collected the data of patients treated for GBM form January 2012 till December 2016. During this 5-years period, 111 patients were identified and the data of 93(84%) of them was complete and included in the analysis.
Results: Males represented 67% of patients, their median age was 52 years and the Eastern Cooperative Oncology Group (ECOG) performance status was 1, 2 and 3 in 48%, 40% and 12% respectively. Only 4.3% of patients underwent complete surgical resection, 38% underwent partial resection and 58% underwent biopsy. Post-operative treatment was radiotherapy alone in 30% of patients and chemo-radiotherapy in 70%. The median progression-free survival (PFS) and overall survival (OS) were 8 months (95% Confidence Interval: 6.678-9.322) and 10 months (95% Confidence Interval: 7.522-12.487), respectively. Longer PFS was associated with age <50 years, better baseline ECOG performance status, partial / complete excision, no corticosteroids dependence, and post-operative chemo-radiotherapy (p = 0.012, 0.001, 0.025, < 0.001 and 0.038; respectively). Similarly OS was better in association with age <50 years, better baseline ECOG performance status, partial / complete excision, no corticosteroid dependency and post-operative chemo-radiotherapy (p = 0.002, 0.032, 0.048, <0.001 and 0.024; respectively).
Conclusion: Glioblastoma Multiforme remains an aggressive disease with high mortality rate and poor outcome. Complete resection and adjuvant chemo-radiotherapy improve PFS and OS.

Keywords: Glioblastoma Multiforme, Prognosis, Egypt
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INTRODUCTION

Primary central nervous system (CNS) tumors account for 2% of all malignancies in adults. About 50% of them are gliomas. Glioblastoma multiforme (GBM) is derived from neuroepithelial cells and is the most frequent and deadly primary CNS malignancy in adults [1]. It accounts for 60-70% of gliomas in the adult population [2]. In the United States, the age-adjusted GBM incidence rate is 3.97 cases per 100,000 for males and 2.53 cases per 100,000 for females; accounting for 75% of all anaplastic gliomas in adults and 20% of primary CNS tumors [3].

Treating GBM is challenging for oncologists with a short median overall survival (OS) of only 4.2 months for patients treated with surgery alone [4]. The median survival following chemo-radiotherapy remains also poor (14.6 months) [1].

Prognostic factors for adult GBM identified by Scott et al included: age, extent of surgery (biopsy vs. complete resection) and Karnofsky performance status [5]. According to prognostic factors, adult GBM patients were classified into 4 subgroups with a median OS ranging from 2.3 months for group IV (biopsy only with poor Karnofsky performance status < 70) to 9.3 months for subgroup I (complete surgical excision and age < 75.5 years).

Maximal safe surgical resection with postoperative radiotherapy (RT) and adjuvant temozolomide or carmustine wafers after resection remains the standard of care for the treatment of adult GBM. Despite this, the survival remains poor with a median OS from 12 to 15 months and a 2-year and 3-year survival rates of 3.3% and 1.2% respectively [1].

Dexamethasone dependency during RT has been reported to be an independent poor predictor of survival in patients with high grade gliomas [6]. In one study, patients who were ‘‘steroid dependent’’ after craniotomy had a 1.9 relative death risk compared to those who were off steroids post-operatively [7]. This was also reported before from our institution by Abdel Karim et al. They found that the dependency on corticosteroids is

associated with significantly shorter OS (p<0.001) and progression-free survival (PFS) (p=0.035) [8].

In this study we aimed at evaluating the different prognostic factors in adult GBM patients treated at a single Egyptian University hospital-based oncology service.

METHODS

The current study is a retrospective analysis of adult GBM patients treated at the Clinical Oncology Department of Ain Shams University, Cairo, Egypt; in the period between January 2012 and December 2016.

The inclusion criteria included: radiological and pathological diagnosis of GBM, age >18 years and complete medical records.

The data collected included: age, gender, baseline Eastern Cooperative Oncology Group (ECOG) performance status, tumor characteristics, type of surgery, postoperative treatment and dependence on corticosteroids. Data was analyzed to determine possible prognostic factors.

During the specified time period, 111 patients were treated for GBM at our institution. The final analysis included 93 (84%) patients. Eighteen patients were excluded due to incomplete data or loss to follow up after initial diagnosis.

Data was analyzed using the Statistical Package for the Social Sciences (SPSS) version 20 (SPSS Inc., Chicago. IL). Numerical data were presented as mean and standard deviation (SD) or median and range as appropriate. Progression-free survival was calculated from the date of surgery/biopsy to the date of disease progression or death and OS from the date of surgery/biopsy to the date of death. Survival analysis was done using Kaplan-Meier method and survival correlation was assessed using log-rank test. Differences were considered significant if the p-value is <0.05.

RESULTS

The median age of patients was 52 years (range: 18-80) with a male to female ratio of 2:1. Most of the patients (88.2%) presented with a good performance status (ECOG 1-2). The mean radiological tumor size at diagnosis was 5.15 cm (±1.37) and 60% of patients had a tumor size >5 cm.

A minority (4%) of patients underwent complete resection and > 1/2 of them underwent biopsy only. All patients received postoperative radiotherapy. The radiotherapy was computerized tomography (CT)-based 3-dimensional conformal. Seventy-two percent of patients received conventional fractionation radiotherapy (60 Grays over 6 weeks) and 28% received hypo-fractionated radiotherapy (45 grays in 15 fractions over 3 weeks). Seventy percent of patients continued after radiotherapy on adjuvant temozolomide for 6 months and the remaining did not received adjuvant temozolamide due to financial problems with the Ministry of Health support program. Concomitant temozolamide with radiotherapy was not supported as well. Details of patients and tumor characteristics as well as treatment received are illustrated in table 1.

Table 1: Patients and tumor characteristics

	No.	%
Age		
< 50 years	42	45
≥ 50 years	51	55
Gender		
Female	31	33.3
Male	62	66.7
ECOG Performance status		
1	45	48
2	37	39.8
3	11	12.2
Largest tumor diameter		
< 5 cm	37	39.8
≥ 5 cm	56	60.2
Tumor Site		
Frontal	18	19
Parietal	17	18
Temporal	15	16
Occipitoparietal	15	16
Temproparietal	13	14
Frontoparietal	12	13
Brainstem	3	4
Type of surgery		
Biopsy only	53	57
Partial resection	36	38.7
Complete resection	4	4.3
Steroidal dependency		
No	30	32
Yes	63	68
Type of postoperative treatment		
Radiotherapy alone	28	30
Radiotherapy + temozolomide	65	70
Radiotherapy fractionation type		
Conventional	67	72
Hypofractionation	26	28

The median PFS for all patients was 8 months (Standard Error [SE]: 0.675; 95% CI: 6.678-9.322) and the median OS was 10 months (SE: 1.264; 95% CI: 7.522-12.487) (figures 1 and 2, respectively).

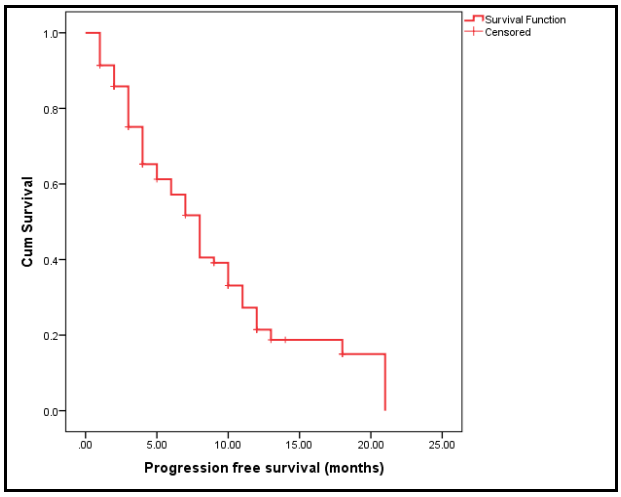

Figure 1: Kaplan-Meier progression-free survival curve for all patients

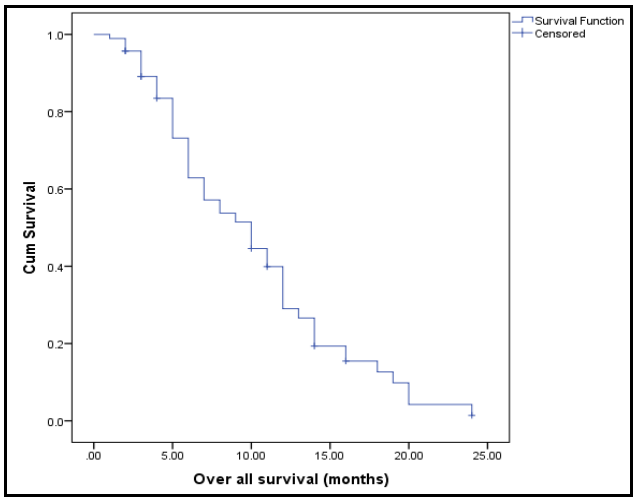

Figure 2: Kaplan-Meier overall survival curve for all patients

Tables 2 and 3 illustrate PFS and OS according to the studied variables. Progression-free survival differed significantly according to age, baseline ECOG performance status, type of surgery, adjuvant temozolomide therapy and steroidal dependency (p = 0.012, 0.001, 0.025, 0.038 and < 0.001; respectively) (figure 3). Overall survival differed significantly according to age, baseline ECOG performance status, type of surgery, steroidal dependency and adjuvant temozolomide therapy (p = 0.002, 0.032, 0.048, <0.001 and 0.024; respectively) (figure 4).

Progression-free survival and OS did not differ significantly according to gender, tumor size, site of tumor or type of radiotherapy fractionation.

DISCUSSION

In our study the median age of patients was 52 years which is younger than that reported by Caloglu et al [9] , but similar to another study from Iran. Most of the patients presented with good performance status (ECOG 1-2), similar to the results of Ahmadloo et al [10]. Eighty-six percent of patients included in their study had and an ECOG performance status score from 0 to 2.

The rate of gross total tumor resection among patients included in this study was only 4% which is much less than the 53% reported by Fekete et al [11]. This may be explained by the large mean tumor size at diagnosis in our population which was 5 cm.

In our study, younger patients (<50 years) had better OS of 12 months and PFS of 9 months when compared to older patients who had OS of 7 months and PFS of 7 months. This is similar to the findings of Li et al [12]. This is likely due to the ability of younger patients to tolerate adjuvant chemotherapy and radiotherapy after complete or partial surgical resection of the tumor.

Better baseline ECOG performance status was associated with significantly better PFS and OS in our patients, which is in concordance with the results of the results of the study conducted by Ahmadloo et al [10].

Table 2: Progression-free survival according to the studied variables

		No.	Progression free survival (months)				P value
			Median	SE	95% CI		
					Lower	Upper	
Age	< 50 yrs	42	9	1.357	6.34	11.66	0.012
	≥ 50 yrs	51	7	0.986	5.067	8.933	
Gender	Females	31	8	1.473	5.112	10.888	0.355
	Males	62	8	0.752	6.527	9.473	
Baseline ECOG performance status	1	45	10	1.413	7.231	12.769	0.001
	2	37	8	0.686	6.656	9.344	
	3	11	4	0.621	2.783	5.217	
Tumor size	< 5 cm	37	8	0.666	6.695	9.305	0.635
	≥ 5 cm	56	7	0.864	5.306	8.694	
Tumor site	Frontal	18	13	2.926	4.266	15.734	0.3
	Parietal	17	6	1.146	3.754	8.246	
	Temporal	15	10	2.443	8.211	17.789	
	Occipitoparietal	15	5	1.788	1.495	8.505	
	Temproparietal	13	5	2.271	0.549	9.451	
	Frontoparietal	12	7	1.923	3.231	10.769	
	Brainstem	3	3	1.633	0	6.201	
Type of surgery	Biopsy	53	11.45	1.275	8.954	13.952	0.025
	Partial /complete resection	30	15.31	1.030	13.295	17.332	
Steroidal dependency	No	30	13.91	1.164	11.631	16.194	<0.001
	Yes	63	5.58	0.608	4.386	6.770	
Type of postoperative treatment	Radiotherapy group	28	9	0.72	7.588	10.412	0.038
	Radiotherapy + temozolomide	65	14	1.714	10.64	17.36	
Radiotherapy protocols	Conventional	67	5	2.271	0.549	9.451	0.214
	Hypofractionation	26	7	1.923	3.231	10.769	

Table 3: Overall survival according to the studied variables

		No.	Overall Survival (months)				P value
			Median	SE	95% CI		
					Lower	Upper	
Age	< 50 yrs	42	12	0.98	10.08	13.92	0.002
	> 50 yrs	51	7	1.308	4.437	9.563	
Gender	Females	31	10	2.169	5.748	14.252	0.279
	Males	62	10	1.129	7.787	12.213	
Baseline performance status (ECOG)	1	45	11	0.753	9.524	12.476	0.032
	2	37	8	1.488	5.083	10.917	
	3	11	6	0.693	4.642	7.358	
Tumor size	< 5 cm	37	10	0.705	8.618	11.382	0.953
	> 5 cm	56	8	1.217	5.615	10.385	
Tumor site	Frontal	18	12	4.243	0.684	17.316	0.627
	Parietal	17	11	4.007	4.213	11.787	
	Temporal	15	9	1.265	9.521	14.479	
	Occipitoparietal	15	8	1.932	4.213	11.787	
	Temproparietal	13	7	0.537	5.948	8.052	
	Frontoparietal	12	8	1.932	3.146	18.854	
	Brainstem	3	5	.	.	.	
Type of surgery	Biopsy only	53	14.43	0.557	13.336	15.519	0.048
	Partial / complete resection	40	22.4	0.525	21.372	23.428	
Steroidal dependency	No	30	15	0.755	14.278	17.239	<0.001
	Yes	63	7	0.566	6.086	8.305	
Type of postoperative treatment	Radiotherapy alone	28	12	1.081	10.834	15.072	0.024
	Radiotherapy + temozolomide	65	21	1.019	19.467	23.461	
Radiotherapy protocols	Conventional	67	8	1.932	4.213	11.787	0.617
	Hypofractionation	26	9	4.243	0.684	17.316	

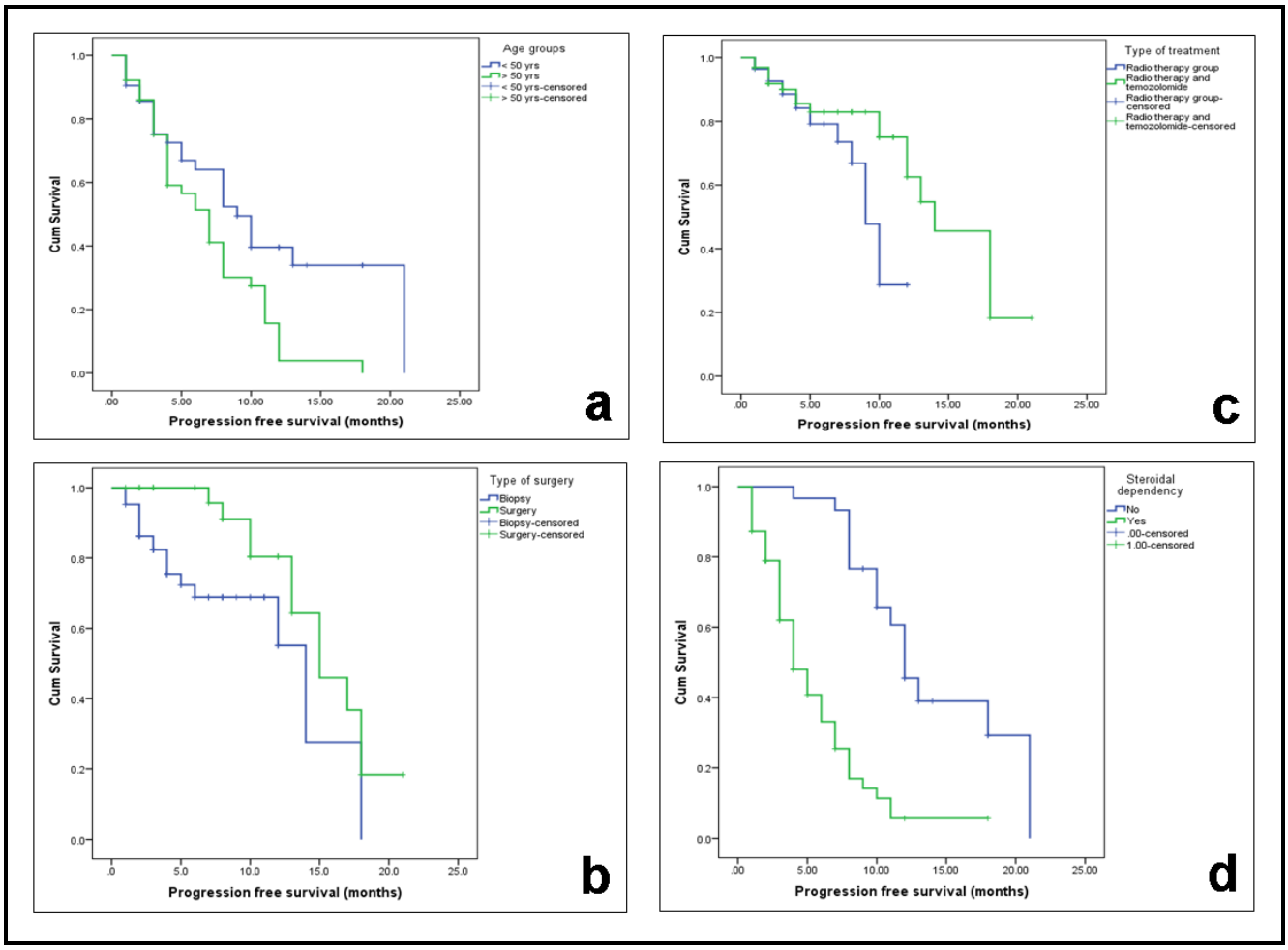

Figure 3: Kaplan-Meier progression free survival curves according to: a) age, **b)** type of surgery, **c)** type of post-operative treatment and **d)** steroidal dependency

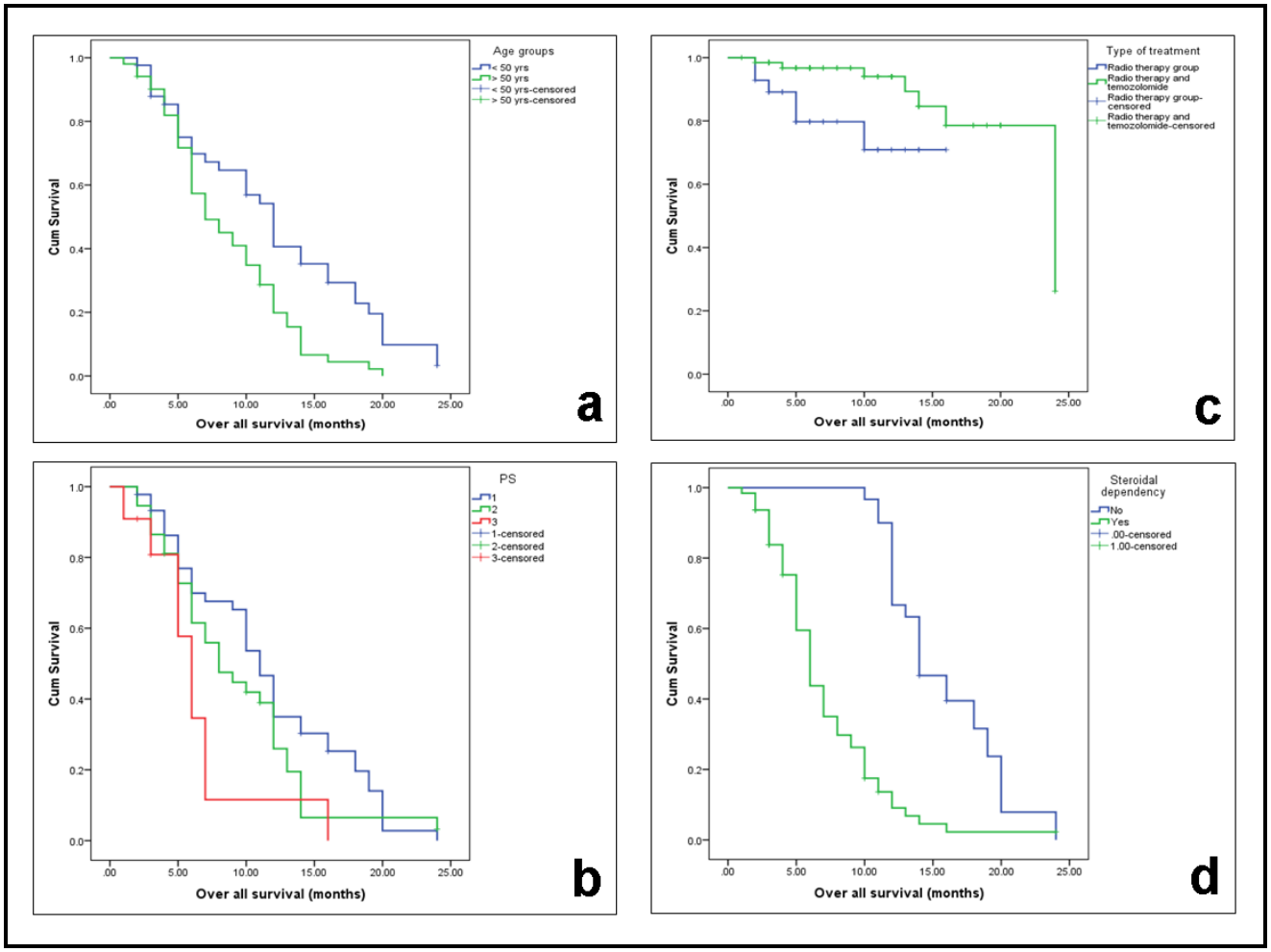

Figure 4: Kaplan-Meier progression-free survival curves according to: a) age, **b)** performance status, **c)** type of post-operative treatment and **d)** steroidal dependency

Surgical resection of malignant gliomas remains one of the most important prognostic factors. In a clinical trial, the absence of postoperative enhancing lesion by magnetic resonance imaging (MRI) significantly improved survival (median OS 17.9 vs. 12.9 months for residual disease by MRI, $p < 0.001$) [13]. This data is similar to our data where patients who underwent surgical excision had a median OS of 22 months compared to 14 months for those who underwent biopsy only.

For years, resection followed by postoperative radiotherapy was the standard for treating GBM. In late 1970s, trials began to evaluate the role of chemotherapy [14]. In the pivotal phase III European Organisation for Research and Treatment of Cancer / National Cancer Institute of Canada (EORTC-NCIC) study, the addition of temozolomide as concurrent and adjuvant treatment improved survival for GBM patients and this survival advantage was maintained after 5 years of follow up [1]. In our study, patients who received adjuvant temozolomide had significantly higher median OS of 21 months compared to 12 months for those who did not receive adjuvant chemotherapy.

Of note, in our study patients who received hypofractionation radiotherapy had median a OS of 8 months which is close to that of those who received conventional radiotherapy (9 months) and the difference was not statistically significant.

Conclusion

Glioblastooma multiforme remains an aggressive disease with low PFS and OS. Total resection and trimodality therapy provide the best approach to improve PFS and OS.

Conflict of interest

None to declare.

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