Treatment Outcome and Prognostic factors of Glioblastoma Multiforme

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Abstract:

Background and Aim: Background and aim: This is a retrospective study of Egyptian patients with glioblastoma multiforme who had undergone biopsy and or surgical resection and radiation to identify clinical, pathological, radiological and to asses treatment outcome (overall survival OS and progression free survival PFS).

Patients and methods: two hundreds & ten patients with glioblastoma multiforme data was collected and recorded in a personal database from paper and electronic medical records and variables were analyzed.

Results: The median overall survival time was 9 months, while the median time to progression was 6 months. Multivariate analysis revealed that ECOG PS, absence of adjuvant temozolamide, tumor site, were statistically significant independent predictors for overall survival OS and progression free survival PFS. Hazard ratios & confidence intervals of OS were 1.72 (1.16-2.56), 1.94 (1.41-2.67), 1.43 (1.05-1.94) respectively, while for PFS, Hazard ratios & confidence intervals were 2.1 (1.5-2.9), 1.4 (1.05-1.9), and 1.44 (0.98-2.13), respectively.

Conclusion: Glioblastoma multiforme still an aggressive disease with short PFS and OS. Good performance status, TMZ chemotherapy and tumor location were significant prognostic factors.

Keywords: Glioblastoma multiforme, prognostic factors, overall survival, progression free survival.

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Introduction:

Glioblastoma multiforme (GBM) is the most aggressive and common variety of primary astrocytoma. It is responsible for 57 percent of all gliomas and 48 percent of all primary central nervous system tumors [1].

The incidence rate is 3.2 per 100,000 people on average when adjusted for age [2]. GBMs are common in the brain, but they can also be discovered in the brain stem, cerebellum, and spinal cord. The four lobes of the brain account for 61% of all primary gliomas: frontal (25%) temporal (20%), parietal (13%), and occipital (3%) [3].

Primary brain tumors account for about 1-2 percent of all human neoplasms in Egypt, with high-grade gliomas being the most common kind [4].

Following initial diagnosis, typical treatment includes surgery with maximum possible excision, postoperative fractionated external beam radiation, and concurrent and adjuvant temozolamide [5].

Despite the variety of modern therapies against GBM, it is still a deadly disease with extremely poor prognosis [6]. From the time of diagnosis, patients usually have a median survival time of 14 to 15 months [7].

Several factors, clinically (age, performance status), treatment (quality of surgery, radiation, chemotherapy), and tumor features (volume, site, primary or secondary) have all been researched to see how they affect outcomes. Young age, a good ECOG performance status at the initial diagnosis, radiation, and tumor resection degree have all been proposed as significant prognostic variables for GBM cases [8].

Aim of work

To asses treatment outcome (OS and PFS) of Egyptian patients with glioblastoma multiforme who had undergone biopsy and or surgical resection and radiation and presented to Clinical Oncology & Nuclear Medicine Department at MUH between January 2012 to December 2017.

To identify clinical, pathological, radiological and treatment factors that influence treatment outcome.

Patients and Methods:

Patients:

240 glioblastoma multiforme patients were registered in Clinical Oncology and Nuclear Medicine Department - Mansoura University in the period between January 2012 and December 2017, missed files in 13 patients forced us to exclude them from our study, 10 patients were not eligible for our study eligibility criteria, and 7 patients did not complete their treatment course, so they were also excluded. As a result, 210 Patients with radiologically and pathologically confirmed glioblastoma multiforme treated at our department were included in this retrospective analysis.

Inclusion criteria:

1. Age > 18 y old.
2. Radiologically and pathologically confirmed GBM.
3. Patients who had undergone biopsy or surgical resection and received PORT.

Exclusion criteria:

Patients with secondary GBM (ptn known to be low grade glioma and ended their treatment before and presented with high grade glioma).

Ethical considerations:

The Medical Research Ethics Committee at Mansoura University's Faculty of Medicine approved the study protocol.

Methods:

- This study is a retrospective study and all the informations were collected and recorded in a personal database from paper and electronic medical records.
- Variables analyzed were age, sex, ECOG PS, clinical history delay (The time in months between onset of the first clinical symptoms and diagnosis of glioblastoma), symptoms, tumor location, tumor size, extent of tumor resection (total, subtotal and biopsy), treatment (radiotherapy and chemotherapy) & dose of radiotherapy.
- After collection of clinical, radiological, pathological and treatment data, we divided the patients on the basis of each variable into subgroups to determine their impact on PFS (defined as the interval between date of surgery and radiographic progression) and OS (defined as the period from pathological diagnosis to death or last follow up).

Statistical analysis

IBM-SPSS software (IBM Corp., 2019) was used to enter and analyze data. Armonk, NY: IBM Corp., IBM SPSS Statistics for Windows, Version 26.0.

Qualitative data was expressed as a percentage and as a frequency. The Shapiro-Wilk test was used to check for normality in quantitative data, with $p>0.050$ indicating that the data was normally distributed. Boxplots were examined for the presence of significant outliers (extreme values). If the data was regularly distributed, the mean and standard deviation (SD) were used; otherwise, the median and interquartile range (IQR) were used. The Log rank test was used to examine the survival distributions of two or more groups of a between-subjects factor for equality. A regression model is the Cox proportional-hazards model that was used to investigate the association between the survival time of patients and one or more predictor variables. Survival analysis is expressed by The Kaplan-Meier survival curves. p value ≤ 0.050, is considered statistically significant.

Results:

Glioblastoma multiforme patients attended to Clinical Oncology and Nuclear medicine Department Mansoura university hospital during the period from January 2012 to December 2017 were enrolled in this retrospective study.

240 glioblastoma multiforme patients were registered in our department during this period. This our retrospective study include210 eligible patients with radiologically and pathologically proven glioblastoma multiforme treated at our department.

Following surgery (Total resection for 10 patients, subtotal resection for 111 patients or just biopsy for 89 patients), All patients received 3D Conformal radiotherapy using Elekta linear accelerator. Nine patients received hypofractionated radiotherapy (30 GY/10 tt for 6 patients and 45GY/15ttt for 3 patients). All other patients (201) received conventional radiotherapy. Fourty two patients received radiotherapy alone (39 patients received 60 GY / 30 ttt over 6 weeks, and 3 patients received only 54 GY/ 27 ttt). Sixty patients received radiotherapy with concurrent Temozolamide (TMZ) at daily dose 75 mg/m2 (6 patients did not complete their radiotherapy course, 4 patients received 56 GY/ 28 ttt and 2 patients received only 54 GY/ 27 ttt). Concurrent chemoradiotherapy followed by adjuvant Temozolamide at a dose of 150 to 200 mg/m2 for 5 days of a 28-day cycle, for 6 cycles was received by 108 patients. 5 patients did not complete their radiotherapy dose (3 patients received 56 GY/28ttt, and 2 patients received only 54 GY/27 ttt).

Table 1 shows that there were 134 male patients (63.8%), and 76 female patients (36.2%). Their median age was 54 years, ranging from 18 to 72 years.

Neurologic deficit (hemiplegia-weakness- tremors – dysarthria-aphasia-amnesia & short memory-fascial palsy) was the predominant presentation in 100 patients (47.6%) followed by increased ICT (headache, vomiting, blurred vision) in 64 patients (30.5%).

The median duration of complaints in months was 2 months, ranging from 0.5 to 12 months.

89 (42.4%) patients were with ECOG PS 2 followed by ECOG PS 1 in about 40.5% of all patients.

48.1% of the tumors were located in more than one site of cerebral hemispheres while 20.5 % were located in parietal region.

The median diameter of tumor size was 5cm (1.5-10).

42.4% of glioblastoma multiforme patients underwent biopsy while 52.9 % underwent subtotal surgical resection. Total resection was performed in only 10 patients (4.8%).

187 (89%) patients were treated with radical radiotherapy dose 60 Gy while 14 (6.7%) of patients were received radiotherapy dose less than 60 Gy. Nine patients received hypofractionated radiotherapy.

168 (80%) patients treated with concurrent temozolomide chemotherapy.

108 patients (51.4%) received chemoradiotherapy plus adjuvant chemotherapy while 60 (28.6%) patients received chemoradiotherapy alone.

The median follow up period was 14 months.

Table 2 reports a statistically significant higher median PFS in age <54 years vs ≥ 54 years (8 vs. 5), ECOG PS <3 (1-2) vs 3 (7 vs. 3), those who received adjuvant treatment vs. those who did not receive adjuvant treatment (8 vs. 4), and frontal or parietal sites vs. other sites (8 vs. 6). Patients who underwent total resection have higher median PFS as compared to those who underwent subtotal resection or only biopsy, however the difference was not statistically significant.

Table 3 shows the results of cox regression to predict tumor progression. Of the predictor variables, absence of adjuvant temozolamide, tumor site other than frontal or parietal and ECOG PS were statistically significant independent predictors of tumor progression. Hazard ratios were 2.1 (1.5-2.9), 1.4 (1.05-1.9) and 1.44 (0.98-2.13), respectively.

Table 4 shows a statistically significantly higher OS in age <54 years vs. ≥ 54 years (12 vs 7), ECOG < 3 (1-2) vs. 3 (10 vs 5), those who received adjuvant treatment vs. those who did not receive adjuvant treatment (12 vs 5).

Table 5 shows that ECOG PS, absence of adjuvant temozolamide, tumor site other than frontal or parietal, were statistically significant independent predictors of overall survival. Hazard ratios & confidence interval were 1.72 (1.16-2.56), 1.94 (1.41-2.67), 1.43 (1.05-1.94), respectively.

Survival analysis in all patients (210 patients):
Progression free survival (PFS)

For the 210 cases, the median time to progression was 6 months, figure1.

Prognostic factors affecting PFS:

The PFS was significantly affected by patient age, ECOG PS and adjuvant treatment, figures (2,3,4).

Overall survival (OS):

For the 210 cases, the median overall survival time was 9 months. This was illustrated in figure 5.

Prognostic factors affecting OS:

The median overall survival was significantly affected by patient age, ECOG PS and adjuvant treatment, figures (6,7,8).

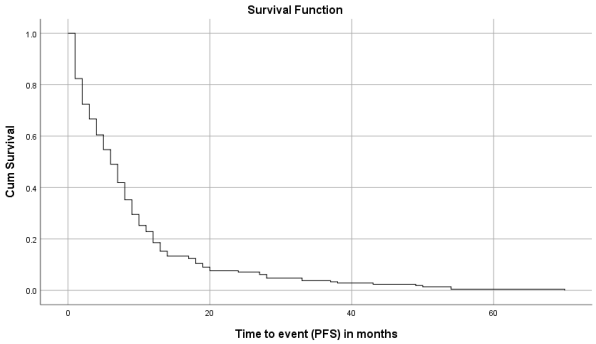

Figure :1 PFS in GBM patients

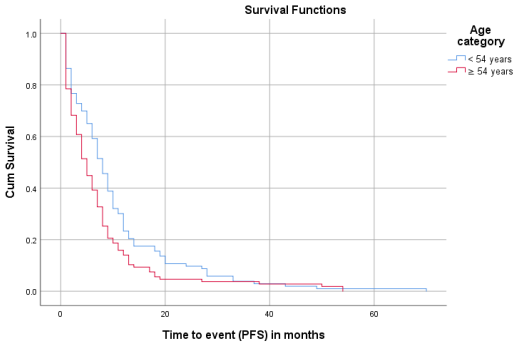

Figure 2: Effect of age on PFS

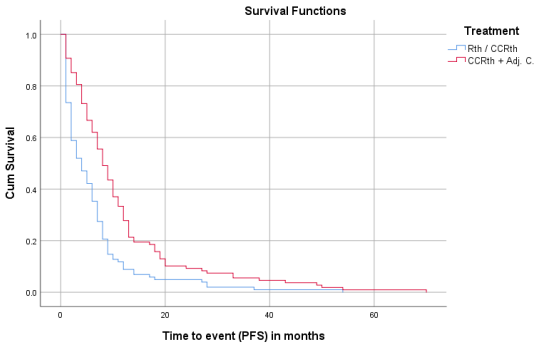

Figure 3: Effect of treatment on PFS

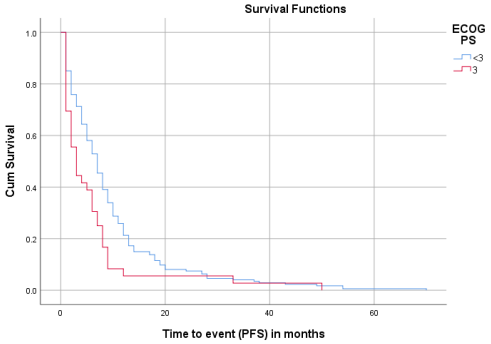

Figure 4: Effect of ECOG PS on PFS

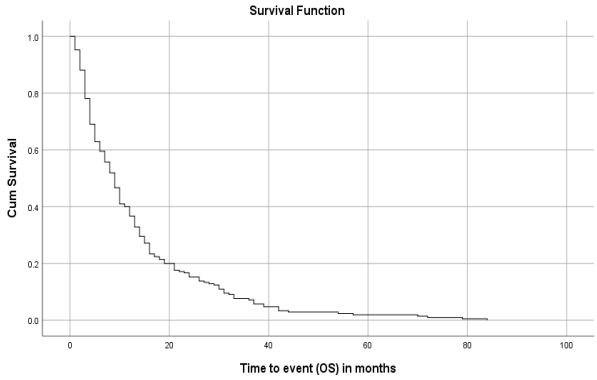

Figure 5: OS in GBM patients

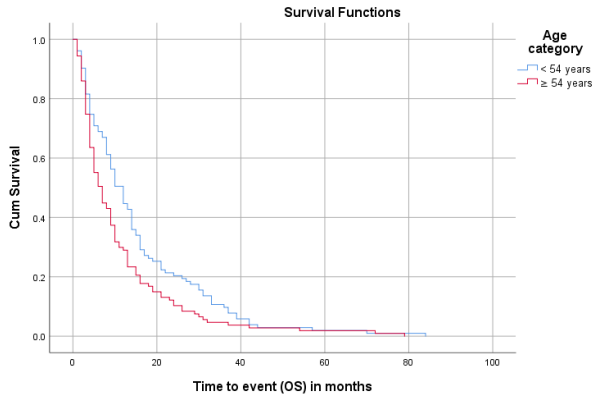

Figure 6: Effect of age on OS

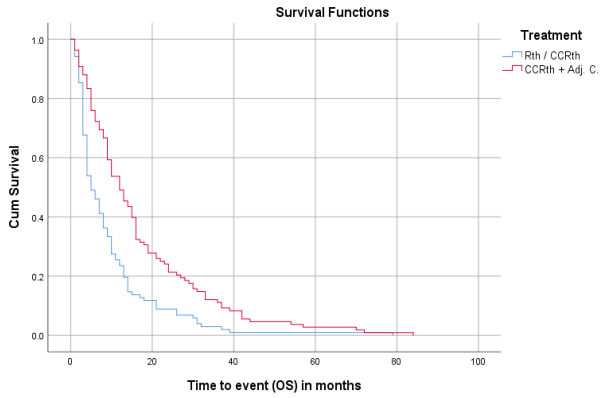

Figure 7: Effect of treatment on OS

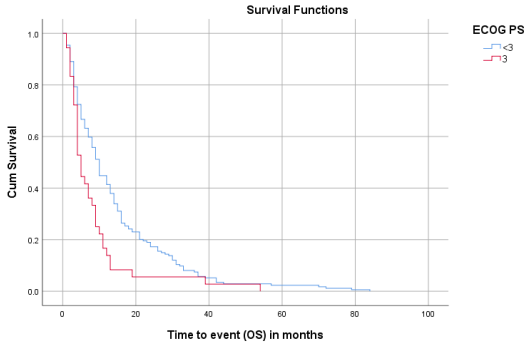

Figure 8: Effect of ECOG PS on OS

Discussion:

A systematic approach is required for the treatment of newly diagnosed GBM. The current standard of care involves a maximum safe surgical resection followed by concomitant temozolomide (TMZ), an oral alkylating chemotherapy drug, and adjuvant TMZ chemotherapy [5].

Our patients' median age was 54 years, with a range of (18-72 years), which is similar to the results reported by Vand Rajabpour et al., 2017 [9] , where the mean age in their study was 52.12 ± 1.64 and Abd El Moumen et al., 2019 [10], where the median age in their study was 52 years (range: 18-80) .

We also found a 63.8 percent male predominance, which is similar to Abd El Moumen et al., 2019 , who found that males make up 66.7 percent of the study sample[10].

Most of the patients in our study (82.9) presented with PS (ECOG 1-2), as those of Ahmadloo et al., 2013 [11] and Abd El Moumen et al., 2019 [10], where 83% of patients had and an ECOG PS of 1 & 2.

GBMs are more commonly located in the supratentorial region (frontal, temporal, parietal, and occipital lobes), are rarely seen in the cerebellum, and are very rare in the spinal cord [12].

Our study showed that most of the lesions were located in more than one site of cerebral hemispheres followed by parietal region then temporal region then frontal region then occipital region in percentages of 48.1%, 20.5%, 14.3%,13.8% and 3.3% respectively, it was near to the figures reported by 2 trials [14,3]. who documented that the locations of the tumors were frontal (25%), temporal (20%), parietal (13%), and occipital (3 %).

In our study, neurologic deficit was the predominant presentation in 100 patients (47.6%) followed by increased ICT (headache, vomiting, blurred vision) in 64 patients (30.5%) similar to that reported by Salah Uddin and Jarmi, 2015 [15], where focal neurological deficit and cognitive impairments recorded in 40-60% followed by increased ICT resulting in headaches (30-50% of GBM patients).

Also our study showed seizure in 17 (8.1%) patients which is lower than figures that reported by others [15,16], where 20-40% of cases present with seizures and Perry et al. 2006 [17], who reported that in as many as 25% of individuals, a seizure is the first symptom, and in as many as 50% of patients, a seizure might arise later in the disease.

The incidence of gross total tumor resection was only 4.8% which is similar to what reported by Abd El Moumen et al. 2019 [10], (4.3%). However, it is much less than the 53% reported by other studies [18,19]. (33%). This may be due to the large mean tumor size among our patients which was 5.1 cm.

The rate of biopsy alone was greater (42.4 % vs. 20 %) than that registered by Oszvald et al. 2012 [20], but nearly to that of Abd El Moumen et al. 2019 (57 %) [10].

Table 1: Patients and tumor characteristics (N=210):

Characteristic	NO %
Sex N (%)	
Male	134 (63.8%)
Female	76 (36.2%)
Median age (range)	54 (18 -72)
Presentation	
Convulsions	17 (8.1%)
Disturbed conscious level	29 (13.8%)
Neurologic deficit (hemiplegia-weakness- tremors –dysarthria-aphasia- amnesia & short memory-fascial palsy)	100 (47.6%)
Increased ICT (headache, vomiting, blurred vision)	64 (30.5%)
Duration of complaints (months)	
Median	2
Range (Minimum – Maximum)	0.5 – 12
ECOG performance status	
1	85 (40.5%)
2	89 (42.4%)
3	36 (17.2%)
Tumor location	
Frontal	29 (13.8%)
Parietal	43 (20.5%)
Temporal	30 (14.3%)
Occipital	7 (3.3%)
> one site	101 (48.1%)
Diameter of tumor size (cm)	
Mean ± SD	5.12 ± 1.54
Median (minimum – maximum)	5 (1.5 – 10)
Extent of Surgical Resection	
Biopsy	89 (42.4%)
Subtotal resection	111 (52.9%)
Total resection	10 (4.8%)
Radiotherapy dose	
60 Gy	187 (89%)
< 60 Gy	14 (6.7%)
Hypofractionation	9 (4.3%)
Concurrent Temozolomide chemotherapy	168 (80%)
Treatment modality	
Radiotherapy	42 (20%)
Chemoradiotherapy	60 (28.6%)
Chemoradiotherapy *plus* adjuvant chemotherapy	108 (51.4%)

Table 2: Factors affecting PFS

Factor	N	Median (95% CI)	Log Rank (Mantel-Cox) test	
			χ^2	P value
Age				
< 54 years	103	8 (6.6 – 9.4)	6.642	0.010
≥ 54 years	107	5 (3.8 – 6.2)		
Sex				
Male	134	6 (4.9 – 7.1)	1.210	0.271
Female	76	5 (2.6 – 7.4)		
ECOG PS				
<3 (1-2)	174	7 (5.8 – 8.2)	7.260	0.007
3	36	3 (1.5 – 4.5)		
Tumor size				
≤ 5 cm	113	7 (5.5 – 8.5)	1.096	0.295
> 5 cm	97	6 (4.5 – 7.5)		
Treatment				
Rth / CCRth	102	4 (2.3 – 5.7)	1.290	<0.001
CCRth + Adj. Ch.	108	8 (6.4 – 9.6)		
Extentof Surgical resection				
			2.996	0.083
Biopsy /Subtotal	200	6 (4.9 – 7.1)		
resectionTotal resection	10	11 (7.9 – 14.1)		
Tumor Location				
Frontal or parietal	72	8 (6.6 – 9.4)	4.380	0.036
Other sites	138	6 (4.9 – 7.1)		
Radiotherapy dose				
60 Gy	187	6 (4.9 – 7.1)	3.811	0.149
< 60 Gy	14	2 (0.00 – 4.6)		
Hypofractionation	9	7 (0.00 –14.3)		
Temozolomide chemotherapy				
No	42	7 (4.2 – 9.8)	0.422	0.516
Yes	168	6 (4.8 – 7.2)		
Duration of complaint				
<2 months	86	6 (3.7-8.3)	0.022	0.883
≥2 months	124	6 (4.8-7.2)		

Rth: radiotherapy alone
CCRth: concurrent chemoradiotherapy
CCRth + Adj. Ch.: concurrent chemoradiotherapy +adjuvant chemotherapy

Table 3: Cox proportional hazards model to predict disease progression

Predictor variable	Univariate		Multivariate	
	HR (95% CI)	P value	HR (95% CI)	P value
Age ≥ 54 years	1.4 (1.06-1.84)	0.017	1.18 (0.63-1.15)	0.287
Female sex	1.16 (0.87-1.55)	0.305	1.14 (0.85-1.53)	0.388
ECOG PS 3	1.6 (1.1-2.3)	0.012	1.44 (0.98-2.13)	0.054
Tumor size > 5 cm	0.87 (0.66-1.15)	0.328	0.81 (0.61-1.08)	0.154
No adjuvant temozolamide	1.8 (1.3-2.3)	<0.001	2.1 (1.5-2.9)	<0.001
Biopsy / Subtotal resection	1.7 (0.89-3.2)	0.110	1.48 (0.78-2.8)	0.234
Tumor site other than frontal or parietal	1.3 (0.998-1.78)	0.051	1.4 (1.05-1.9)	0.023
Radiotherapy dose < 60 Gy	1.3 (0.78-2.17)	0.313	1.4 (0.83-2.4)	0.202

Table 4: Factors affecting OS

Factor	N	Median (95% CI)	Log Rank (Mantel-Cox) test	
			χ^2	P value
Age				
< 54 years	103	12 (9.53 – 14.47)	6.339	0.012
≥ 54 years	107	7 (5.17 – 8.83)		
Sex				
Male	134	9 (7.6 – 10.4)	1.467	0.226
Female	76	7 (3.4 – 10.6)		
ECOG PS				
< 3 (1-2)	174	10 (8.65 – 11.35)	8.659	0.003
3	36	5 (3.83 – 6.17)		
Tumor size				
≤ 5 cm	113	10 (7.93 – 12.07)	0.418	0.518
> 5 cm	97	8 (5.93 – 10.07)		
Treatment				
Rth / CCRth	102	5 (3.53 – 6.47)	19.609	<0.001
CCRth + Adj. Ch.	108	12 (9.01 – 15)		
Extent of Surgical resection				
Biopsy / Subtotal resection	200	8 (6.5 – 9.5)	2.547	0.110
Total resection	10	15 (3.6 – 26.4)		
Tumor Location				
Frontal or parietal	72	12 (9.45 – 14.55)	2.893	0.089
Other sites	138	8 (6.36 – 9.64)		
Radiotherapy dose				
60 Gy	187	9 (7.6 – 10.4)	0.685	0.710
< 60 Gy	14	4 (1.4 – 6.6)		
Hypofractionation	9	13 (7.5 –18.5)		
Temozolomide chemotherapy				
No	42	9 (3.6 – 14.4)	0.383	0.536
Yes	168	9 (7.6 – 10.4)		
Duration of complaint				
<2 months	86	9 (6.7-11.3)	0.065	0.799
≥2 months	124	9 (7.2-10.8)		

Rth: radiotherapy alone
CCRth: concurrent chemoradiotherapy
CCRth + Adj. Ch.: concurrent chemoradiotherapy +adjuvant chemotherapy

Table 5: Cox proportional hazards model to predict overall survival

Predictor variable	Univariate		Multivariate	
	HR (95% CI)	P value	HR (95% CI)	P value
Age ≥ 54 years	1.4 (1.06-1.84)	0.016	1.2 (0.89-1.63)	0.236
Female sex	1.18 (0.89-1.58)	0.247	1.19 (0.89-1.61)	0.247
ECOG PS 3	1.68 (1.17-2.42)	0.005	1.72 (1.16-2.56)	0.007
Tumor size > 5 cm	1.1 (0.83-1.44)	0.536	1.29 (0.96-1.75)	0.095
No adjuvant temozolamide	1.81 (1.37-2.39)	<0.001	1.94 (1.41-2.67)	<0.001
Biopsy / Subtotal resection	1.4 (1.05-1.94)	0.025	1.36 (0.98-1.87)	0.063
Tumor site other than frontal or parietal	1.27 (0.95-1.69)	0.014	1.43 (1.05-1.94)	0.023
Radiotherapy dose < 60 Gy	1.07 (0.64-1.78)	0.805	1.02 (0.6-1.73)	0.945

Two trials found various clinicopathological variables to be predictors of GBM prognosis in large-scale retrospective studies. Age, performance status, histology, surgical resection extent, and adjuvants such as radiation and chemotherapy are all considerations to assess [21,22].

In our study, younger patients (<54 years) showed longer OS and PFS when compared to older patients. This is in line with Li et al. 2009 and Abd El Moumen et al. 2019 [23,10].

Good ECOG PS was associated with significantly better PFS and OS in our patients, which is in accordance with the results other trials produced by Darefsky et al., 2012; Thumma et al., 2012; Ahmadloo et al., 2013; Abd El Moumen et al., 2019 21,22,11 ,10.

In our study, treatment outcome of frontal or parietal lobe tumors are better compared to other sites in the brain. This is in agreement with the results of Paldor et al. 2016 [24]. They concluded that frontal lobe tumor are generally more amenable to complete surgical resection and may carry a better prognosis.

The biology of differently localized GBM has been reported scarcely in terms of prognostic markers including IDH1 mutation and MGMT methylation. They assessed the rate of IDH1 positivity, MGMT methylation and Ki 67 index for GBM located in the frontal lobes alone, lobar GBM, in other supra- tentorial lobes and multilobar GBM. They found that IDH1 mutated tumors were localized in the frontal lobes in 50% whereas only 20.3% of IDH1 wild type tumors were localized in the frontal lobe (P=0.006), MGMT methylated tumors were localized to the frontal lobe in 32% of the cases. Only 13.75% of the MGMT unmethylated tumors were localized to the frontal lobe (P=0.005). Therefore they concluded that frontal lobe GBMs may be intrinsically biologically distinct from GBM in other lobes and from multilobar tumors.

As regard parietal tumor location, similar to our study, a trial reported that parietal primary tumor site is associated with positive survival outcomes [25].

Surgical resection of malignant gliomas is one of the most significant prognostic factors in GBM. In our study, patients who underwent complete surgical excision showed a median PFS of 11 months vs 6 months for those who underwent biopsy or subtotal excision. Similar results was applied to the OS (15 Vs 8 months), however the difference was not statistically significant P =0.08 and this may be attributed to the small number of our patients who performed total resection. This data is similar to other data reported by Abd El Moumen et al. 2019 [10], who reported median OS of 22 months for patients who underwent surgical excision vs 14 months for those who underwent only only biopsy. Also, Stummer 2007 proved that, the absence of postoperative enhancing lesion by MRI significantly improved survival (median OS 17.9 vs. 12.9 months for residual disease, $p < 0.001$) [26]. Similar results was also reported by Witteler et al., 2020 [27].

For long, surgery followed by adjuvant radiotherapy was the standard treatment for GBM. In late 1970s, trials began to evaluate the role of chemotherapy [28] .In the pivotal phase III European Organization for Research and Treatment of Cancer / National Cancer Institute of Canada (EORTC-NCIC) study, the addition of temozolomide as concurrent and adjuvant treatment prolonged survival for GBM patients [29]. This is strongly evident in our study.

Many trials have documented the role of concomitant and adjuvant temozolomide as a good predictor of overall survival [29,30].

We reported in our study a median OS of 9 months and median PFS of 6 months .Our study's survival outcomes are more or less comparable to those reported by Abd El Moumen et al., 2019 [10], where the median PFS was 8 months and the median of OS was 10 months and also similar to Ahmadloo et al., 2013 [11] and Vand Rajabpour et al., 2017 [9], where the median of PFS was 6 months and the median of OS was 11 months and also similar to others [31,32].

The majority of patients in our study received multimodal treatment, which was the accepted standard, according to the current standard [5,29].

Our findings support previous research showing that adjuvant radiation combined with temozolomide-based treatment improves survival in individuals with GBM [10,31,33]. Patients who treated with adjuvant temozolamide had a significant longer median PFS of 8 months vs 4 months for those who did not receive adjuvant chemotherapy. Also the median OS was significantly higher (12 months Vs 5 months).

Conclusion:

Glioblastoma multiforme still an aggressive disease with short PFS and OS. Good performance status, TMZ chemotherapy and tumor location (frontal or parietal) improve treatment outcome. Total resection also affects survival outcome, however it did not reach a statistically significant value.

Recommendations: large prospective studies are needed to study prognostic factors and to consider novel treatment strategies for glioblastoma multiforme.

Study limitation: the retrospective nature of the study.

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