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Survival Outcome and Its Predictors for Treated Patients with Glioblastoma Multiforme-A Single Centre Retrospective Study

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Background:
Glioblastoma multiforme is the most aggressive form of primary brain tumour with a median survival 1 year.
Aim: To assess the survival outcome and predictive factors for theglioblastoma multiforme patients who were treated with combined modality approach.
Methods and materials:
We have analyzed retrospectively 30 patients of Glioblastoma multiforme (GBM) diagnosed and treated in our oncology department during the period of March 2014 to March 2017. Inclusion criteria for this study was biopsy proven GBM patients who underwent maximal safe resection and postoperative chemoradiotherapy. Data regarding age, gender, histopathology, extent of surgery, performance status, radiotherapy and chemotherapy details were collected. Kaplan meier analysis was used to find out the median survival of the patients. Both univariate and multivariate analysis were done to assess the predictive factors for survival by using Cox regression model.
Results:
The median survival time for patients with GBM is 4.1months. Both univariate and multivariate analysis showedperformance status had significant impact over the survival.(p=0.01,0.002 respectively).Patients who had completed full dose of radiotherapy showed a trend towards better survival in multivariate analysis(p=0.09).
Conclusion:
Despite multimodality aggressive management, survival of patients with newly diagnosed GBM is poor. Predictive factors will help to identify the subgroup of patients with better survival.
Key words*: GBM, predictive factors, High grade gliomas, Temozolamide,Radiotherapy*

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I. Introduction

High grade gliomas are the most common primary brain tumour of which Glioblastoma multiforme (GBM) being the most common.GBM is one of the most aggressive tumours with median survival of one year.[1,2]The standard of care for newly diagnosed GBM includes a combination of maximal safe resection of the tumour followed by 6 weeks course of radiotherapy with concurrent systemic chemotherapy with dailytemozolamide(TMZ) followed by adjuvant chemotherapy. Despite the multimodality treatment the prognosis for GBM is still poor. Multiple pretreatment variables were identified as predictive and prognostic variables for the survival of GBM.[3]In this retrospective study we have analyzed the survival outcome and its predictors for patients with GBM in a Government multispecialty hospital.

II. Methods and materials

We have analyzed 30 patients of Glioblastomamultiforme (GBM) diagnosed and treated in our oncology department during the period of March 2014 to March 2017. Inclusion criteria for this study includes biopsy proven GBM patients who underwent maximal safe surgery, postoperative radiotherapy and concurrent chemotherapy followed by adjuvant chemotherapy. Data regarding age, gender,histopathology,extent of surgery, performance status, radiotherapy and chemotherapy details were collected. Tumour characteristics like size of the tumour,location, extent of the lesion and associated edema were identified with the help of MRI brain. Treatment details and followup data regarding progression and status of the patients were collectedfrom the medical records of the patients and through telephonic conversation whenever necessary.

Radiotherapy and chemotherapy Treatment

After maximal safe surgery (biopsy/subtotal/near total resection), postoperative radiotherapy was started within 2-3 weeks. A total dose of 6000cGy in 200cGy per fraction over a period of 6-7 weeks was delivered in 2 phases. 5000 cGy was given to the tumour bed/residual tumour along with the surrounding edema with 3cm clearance in the initial phase. The next phase includes onlytumour with 3cm margin. The radiotherapy is delivered by two opposing lateral fields with telecobalt machine. Patients received concurrent TMZ ($75mg/m^2$/day) 7 days per week one hour before radiation and.6 cycles of adjuvant TMZ(150-$200mg/m^2$/day)day1 to day 5(every 28 days). Patients were monitored by completehaemogram, liver function test, and renal function test periodically. Only minor (grade 1&2) haematological toxicities were seen in patients who received TMZ. No treatment breaks required due to treatment toxicity.Patientsresponse were assessed at 6 weeks after completion of treatment by MRI brain and monthly followup was done.

Statistical methods

All the analysis were performed using IBM SPSS 21.0 version. Survival curves were analyzed in Kaplan meier method and confirmed by log rank test.Cox regression was used to test for the effect of the various risk factors on survival. Univariate and multivariate analyses of the factors were done. A p-value < 0.05isconsidered to be statistically significant.

Patients and treatment characteristics:

The mean age of the study group is 50.4±11.7years. There were 63% male patients (n=19)and 36% female patients (n=11). Frontal lobe tumors being the most common site of tumour.The demographic data of the patients were given in Table 1. Most of our patients had poor performance status (KPS<70,n=19) & Near total excision was done in 40% patients (n=9) . Only 56% of the patients were able to complete the full 6000cGy of radiation (n=17). Remaining patients defaulted and couldn't complete the full dose of radiation due to various reasons.47% patients received concurrent temozolamide (n=17) and 17% patients received the 6cycles of adjuvant temozolamide (N=5).The median duration of follow up was 4months and 3 patients were alive at the time of analysis.

Survival time

The median survival time for GBM was 4.1months. Figure 1 & 2 shows theKaplan meier estimate of survival based on KPS, gender respectively.Univariate analysis showed that KPS is the only significant prognostic indicator in our study (p=0.01) and it is confirmed in multivariate analysis (p=0.002) also. Gender also had a significant impact on survival in multivariate analysis (p=0.04). In univariate analysis dose of radiotherapy received also showed a trend towards survival benefit (p=0.09). Results of univariate and multivariate analysis are showed in Table 2.

III. Discussion

Malignant gliomas are heterogeneous, highly invasive primary brain tumors. GBM classified as a grade IV glioma by World Health Organization (WHO) is particularly aggressive. Most patients diagnosed with this tumor die within two years from the diagnosis.Over the last decade, a variety of different treatments were explored with very limited success. Many studies showed that incidence of GBM peaks at sixth decade of age and it is most common in males [3,4,5] A phase III trial by Stupp et al proved that multimodality treatment with surgery, postoperative radiotherapy (PORT) withconcurrent and adjuvant TMZincreased the median survival of newly diagnosed GBM.The median survival was 14.6m for the PORT with TMZ group and 12.1 m for the PORT group [6,7]

Several large retrospective studies identified age, performance status, histology, extent of surgical resection, and the addition of postoperative radiotherapy and chemotherapy as the predictive factors which may significantly affect the outcome of GBM.[8,9]Curran et al analyzed the RTOG recursive partition analysis (RPA)

as prognostic factor for GBM in which age, histology, mental status, KPS,symptom duration, extent of resection were used as variables.[10] Previous study proved that completion of 6 cycles of adjuvant TMZ was the significant prognostic factor which affects the survival in patients of GBM.[11] Radiotherapy significantly affect the survival patients with GBM & a dose response curve exist with the dose of 60 Gy, below which the results are inferiorand above 60 Gy the toxicities were increased without added benefit.[12-16]

We undertook this retrospective analysis to assess the prognostic factors that influence the survival in our group of patients. The baseline characteristics of our patients were similar to other studies with a median age of 50 years and male:female ratio of 2:1.[17,18] Considerable number of patients (63.3%)in our study were with unfavorable clinical characteristics especially with poor performance status (KPS<70) which is one of the determining factors for overall survival as seen in other studies.[19-21]An Indian study by Kumar et al.showed that median survival was 6.3 months for patients with KPS <70.[20]Another study reported that Median survival was 8.8months for patients with KPS ≥70 versus 6.7months for patients with KPS<70.[21]Similar findings was seen in our study where performance status had significantly affected the median survival.Median survival was more in patients with KPS >70 compared to those with KPS ≤70and it was statistically significant. The median survival in our study is 4.1 months which is comparable to the RTOG RPA prognostic classes 5 and6 (poor prognostic groups) in which the median survival is only 5 months.[10]In our study, patients who received full course of Radiotherapy showed a trend towards survival benefit (p=0.09) similar to previous studies.[12,13] Majority of the female patients were with good performance status and they were able to complete the full dose of radiotherapy and chemotherapy which could be the reason for better survival in this subgroup which reflected in multivariate analysis.

In our set up majority of patients are from low socioeconomic background. It is a major financial burden for the family members to come and stay along with the patient for a full course of radiotherapy (6-8 weeks). They find it difficult to bring the patients of poor performance status especially with neurological deficit for each cycle of adjuvant chemotherapy. This is the main factor for the patient to default for adjuvant chemotherapy after completion of radiotherapy. Majority of our patients in this study couldn't complete concurrent and adjuvant cycle of TMZdue to various reasons which affected the median survival.

Our study is the retrospectivestudy with less number of patients is the limitation. But we were able to correlate our demographic data& few prognostic variables with previous studies. We have found that the compliance of the patients to radiotherapy and chemotherapy is poor. Eventhough poor performance status had significantly affected the survival of patients with GBM, we have to exploremeans to improve patient's compliance to achieve maximum benefit out of combined modality treatment.

IV. Conclusion

Despite the multimodality aggressive management the survival outcome in Glioblastoma multiforme is poor and predictive factors are useful to identify the subgroups of patients with better survival.

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Table1: demographic data of the 30 patients with GBM

	Variable	No(%)
Age	<40yrs	6(20)
	40-59yrs	19(63.3)
	60&above	5(16.6)
Sex	Male	19(63.3)
	Female	11(36.7)
Kps	<70	19(63.3)
	>70	11(36.7)
Surgery	Biopsy	8(26.7)
	Subtotal resection	10(33.3)
	Near total resection	12(40)
RT	60Gy	17(56.7)
	<60gy	13(43.3)
Concurrent chemo	Yes	14(46.7)
	No	16(53.3)
Adjuvant chemo	Yes	5(16.7)
	No	25(83.3)

Table 2: Univarite and multivariate analysis for predictive factors influencing the survival

	Variable	Median survival in months	Univariate analysis p value	Multivariate Analysis P value
Age	<40yrs	4.16	0.24	1.9
	40-59yrs	14.0		
	60&above	5.0		
Sex	Male	7.5	0.23	0.04*
	Female	10.5		
KPS	<70	4.0	0.01	0.002*
	>70	13.6		
Surgery	Biopsy	8.75	0.62	0.93
	Subtotal resection	5.2		
	Near total resection	12		
RT	60Gy	13.6	0.09	0.95
	<60gy	4.7		
Concurrent chemo	Yes	13.5	0.12	0.96
	No	4.93		
Adjuvant chemo	Yes	17.6	0.19	0.95
	No	7.2		

*p-0.05, statistically significant

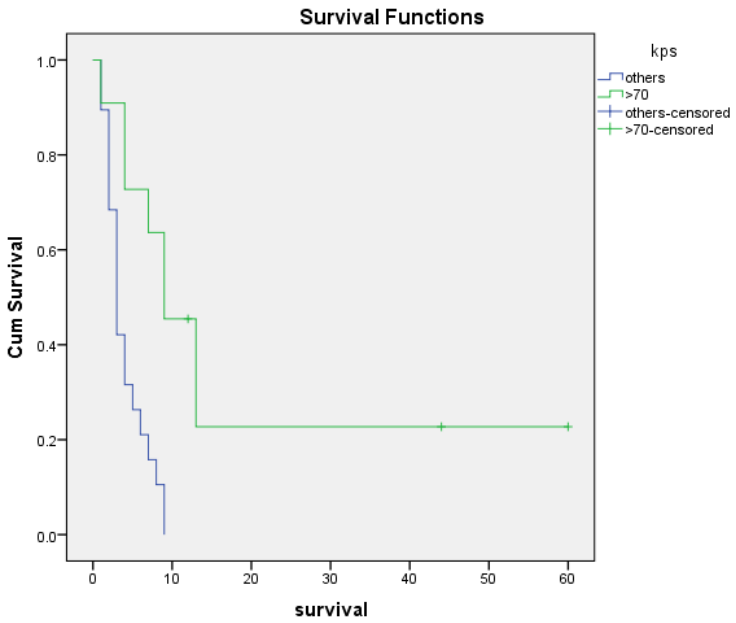

Fig 1: Kaplanmeier estimate of overall survival (kps<70 vs kps>70)

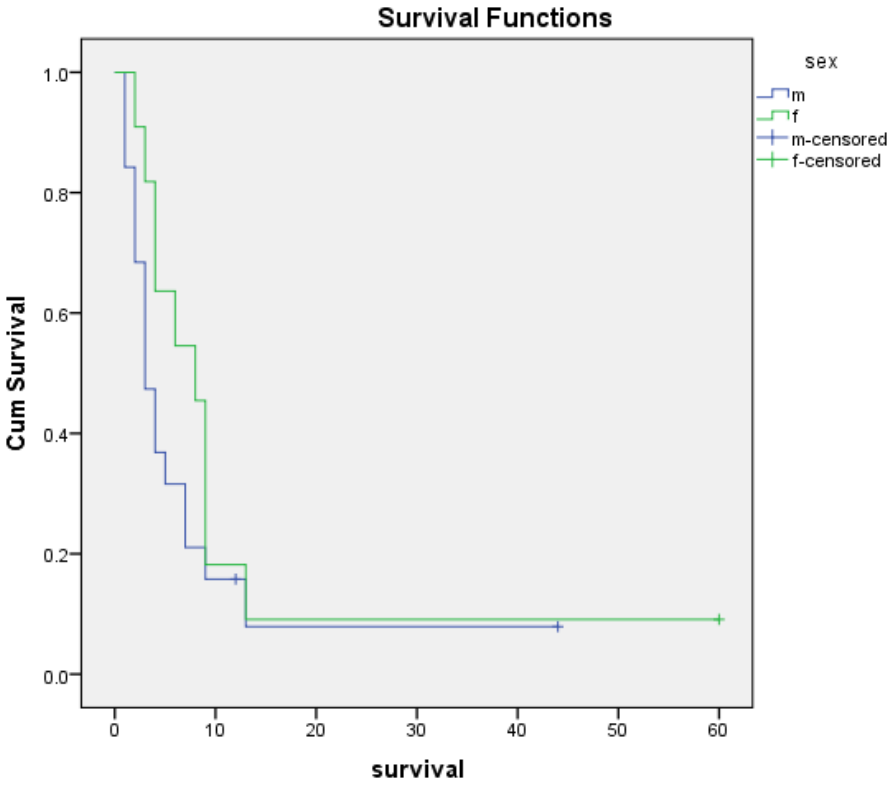

Figure2: Kaplan meier estimate of overall survival (Male vs Female)