Original Research Article

Predictive factors for survival and outcome in patients with high grade gliomas: A single centre retrospective study

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Abstract

Background: Patients with high grade gliomas have poor survival even with aggressive multimodality approach. The aim of our study is to evaluate the predicting factors affecting the survival outcome in patients with high grade gliomas (HGG).

Materials and methods: 46 patients diagnosed to have high grade gliomas (HGG) treated in our Radiotherapy department during the period of March 2014 to March 2017 were analyzed in this single centre retrospective study. All patients underwent maximal safe surgery followed by postoperative radiotherapy with or without temozolamide chemotherapy. Data regarding the patient age, gender, performance status, histology, grade of the tumor, tumor location, extent of surgery, radiotherapy, and chemotherapy details were collected and analyzed. The differences in clinical characteristics and treatment variables were analyzed by chi square test and overall survival analysis using Kaplan Mayer method. The Cox proportional hazards regression model was used to determine statistically significant variables related to survival.

Results: The median survival of patients with HGG in this study was 9 months. The median survival of patients with grade III and IV glioma was 19 and 4 months respectively. In univariate analysis histology, grade, laterality were identified to have prognostic significance. The result of multivariate analysis showed that performance status, grade, histology, extent of surgery is significant for survival.

Conclusion: Our study showed that histology, grade, extent of surgery is the significant factors in assessing the prognosis of patients with HGG. The survival of HGG was poor in spite of combined modality treatment.

Key words

High Grade Glioma, GBM, Concurrent Temozolamide.

Introduction

High Grade Glioma (HGG) is the most common type of primary brain tumor accounts for 50% of primary malignant brain tumors, Glioblastoma multiforme (GBM) is the most common [1]. The term HGG is used to describe WHO grade III, IV Gliomas. Of these, GBM accounts for 60% to 70%, anaplastic astrocytoma (AA) 10% to 15%, Anaplastic Oligodendroglioma (AOD), Anaplastic Oligo astrocytoma (AOA) the remaining. Recently the incidence of Glioma is increasing due to availability of better diagnostic modalities [5]. The median age of onset is 45 for Grade III & 60 for Grade IV Gliomas. GBM is very aggressive and median survial is 1 year [1, 2, 3]. Maximal safe surgery followed by Postoperative Radiotherapy (PORT) which showed a survival benefit of 6% in one year [3]. A phase III trial by Stupp, et al. showed that an oral alkylating agent temozolamide (TMZ) along with post-operative radiotherapy (PORT) increased the median survival from 12m to 14.6 m [4]. Now the standard of care is maximal safe surgery, PORT with concurrent TMZ followed by adjuvant TMZ for HGG. In our study we have evaluated the predictive factors for the survival of grade III and IV HGG.

Materials and methods

We retrospectively reviewed 46 patients of Grade III and IV HGG treated in Department of Radiation Oncology at our hospital during the period of March 2014 to April 2017. Inclusion criteria for this analysis were biopsy proven Grade III, IV HGG. Data regarding the following prognostic variables were collected: patient age, performance status, histology, grade, tumor size, location, extent of surgery, radiotherapy and chemotherapy details. MRI brain was used to assess the size, location and extent of the tumor. After maximal safe surgical resection the patients underwent PORT within 2-3 weeks of surgery. Treatment was delivered by opposing lateral field with telecobalt machine. A total of 60 Gy, 30 fractions in 2 Gy per fraction was prescribed. Target volume includes tumor, edema with the margin of 3cm in the initial phase. After 50 Gy the target volume was reduced to only tumor with the margin 3cm up to 60 Gy. Out of 46 patients 29 patients were completed 60 Gy. 25 patients received concurrent TMZ during the course of radiation therapy at a dose of 75 mg/m^2/day, 7 days per week one hour before radiation. Only 14 patients received adjuvant 6 cycle of chemotherapy of dose 150 mg/m^2/day for 5 days every 28 days. During the course of treatment the patients were monitored with complete hemogram, liver function test and renal function tests. After completion of treatment, response was assessed at 6 weeks with MRI brain. Follow up data was collected from medical case records and telephonic contact whenever necessary.

Statistical analysis

All of the analyses were performed using the SPSS statistical software program package (SPSS version 11.5 for Windows, SPSS Inc., Chicago, IL, USA). Survival curves were analyzed in Kaplan-meyer method and confirmed by log rank test. The univariate and multivariate analysis of prognostic factors for survival were performed using cox proportional hazard model. Hazard ratios and 95% confidence intervals were calculated.

Results

Patient and treatment characteristics

The median age of the patient was 46 years (range 26-70 years). The demographic data of

each subgroup of WHO Grade III and Grade IV Glioma are also shown in **Table - 1** and there were no significant difference in patient and tumor character between the two subgroups. Majority of the tumors in our analysis is grade IV (n=28). Most of the grade IV tumors are (n=19) Left sided. Even though there is no difference in terms of Radiotherapy dose and adjuvant and concurrent chemotherapy cycles in both subgroups (p=0.313,0.220,0.186 respectively), only 50% of the patients received concurrent TMZ (n=29) and one fourth patients only received full 6 cycles of adjuvant TMZ due to various reasons (n=14). The median duration of follow up is 6m. 9 patients were alive at the time of our analysis (**Table – 2, 3**).

Table - 1: Demographic data of 46 patients with High grade gliomas.

Characteristics	All (n=46)	Grade III (n=17)	Grade IV(n=29)	P-Value
Sex				
Male	25	6	19	0.046
Female	21	11	10	
Mean Age(SD)	46(13.4)	29	17	0.302
KPS				
<70	25	7	18	0.043
>70	21	10	11	
Tumor Size				
<4	10	6	4	0.092
>4	36	11	25	
Laterality				
Left	22	3	19	0.007
Middle	5	3	2	0.005
Right	19	11	8	0.003
Biopsy				
GBM	29	1	28	
Anaplastic	13	13	0	0.000
Astrocytoma	2	2	0	
Anaplastic oligoden.	1	0	1	
Gliosarcoma	1	1	0	
Status				
Died	37	11	26	0.049
alive	9	6	3	
Surgery				
Biopsy	16	9	7	0.132
Subtotal	13	3	10	
Neartotal	17	5	12	
RT				
No	17	5	12	0.313
Yes	29	12	17	
Con Chemo				
No	21	6	15	0.220
Yes	25	11	14	
Adjuvant Chemo				
No	32	10	22	0.189
Yes	14	7	7	

Table - 2: Univariate analysis.

Variable	Median OS in months(95% CI)	p-Value
Age	NA	0.4
Sex		
Male	4.4(0.0-8.8)	0.35
Female	9(7.9-10.1)	
KPS		
(<70)	13(11.6-14.4)	0.2
(>70)	4(2.4-5.6)	
Tumor size		
(<4)	13(10.5-15.4)	0.1
(>4)	6(1.6-10.4)	
Laterality		
Left	4(2.9-5.1)	0.02
Middle	15.6(0.0-31.3)	
Right	13(9.8-16.1)	
Histopathology	NA	0.004
Grade		
III	19(1.5-36.6)	0.01
IV	4(2.7-5.3)	
Surgery		0.5
Biopsy	9.4(0.0-18.7)	
Sub total	8(2.9-13.1)	
Near total	7(2.0-12.0)	
PORT		
Yes	12(6.4-17.6)	0.3
No	6(6.6-11.4)	
Con.chemo		
Yes	12(5.8-18.2)	0.5
No	6(2.6-9.4)	
Adjuvant chemo		
Yes	15(8.2-21.9)	0.3
No	6(1.8-10.2)	

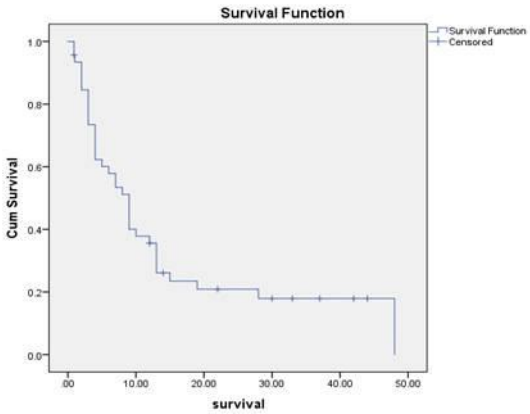
Survival time

The median survival time (MST) for all patients from the time of surgery was 9 (95% CI 6.5-11.4) months. The MST of patients with Grade III and IV glioma was 19 (95% CI 1.4-36.5) and 4 (95% CI 2.7-5.2) months, respectively. **Figure - 1** showed the Overall survival curve of patients and **Figure - 2** showed the survival curve of patients with Grade III and IV glioma. The log-rank test confirmed the significance of grade as the predictive factor in survival (P = 0.004). We analyzed the kaplan meyer survival curves of patients with performance status, radiotherapy dose, concurrent and adjuvant TMZ (**Figure - 3 to 6**). The log-rank test also confirmed the significance of the above (p= 0.001, 0.039, 0.011 0.014 respectively). On univariate analysis only the histological type, tumor grade and laterality had effect on survival (p= 0.004, 0.01, 0.02 respectively. On multivariate analysis the variables KPS, grade, histological type, extent of surgery are significant (p=0.01, 0.04, 0.05, 0.05 respectively).

Table - 3: Multivariate Analysis.

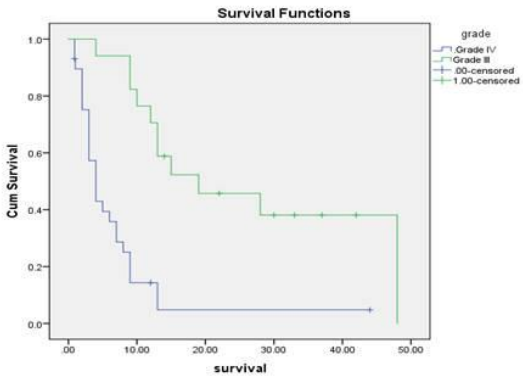
Variable	p-Value	Hazard Ratio	Confidence Interval
Age	.107	0.968	0.930-1.000
Sex	.876	1.225	0.097-15.528
KPS	.015	1.154	0.346-3.845
Tumor size	.647	0.672	0.122-3.688
Laterality	.308	1.377	0.744-2.549
Tumorlocation	.706	1.030	0.884-1.199
Histopathology	.05	0.678	0.242-1.894
Grade	.041	0.163	0.024-1.086
Surgery	.05	1.888	0.969-3.679
RT	.677	0.676	0.107-4.265
Concurrent chemo	.583	1.638	0.282-9.513
Adjuvant chemo	.241	0.426	0.102-1.773

Figure - 1: Overall Survival.



(Median overall survival - 9 m)

Figure - 2: Survival by Grade.

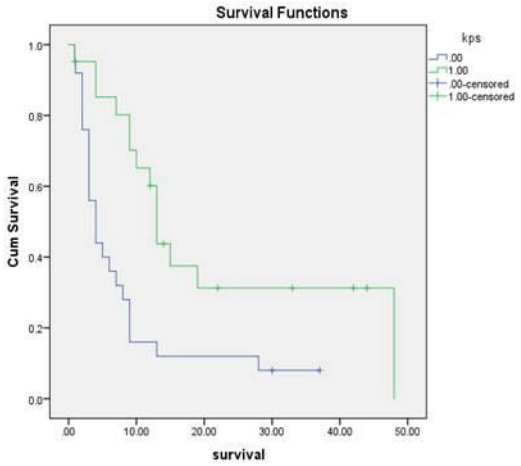


Median overall survival for grade III - 14 m

Discussion

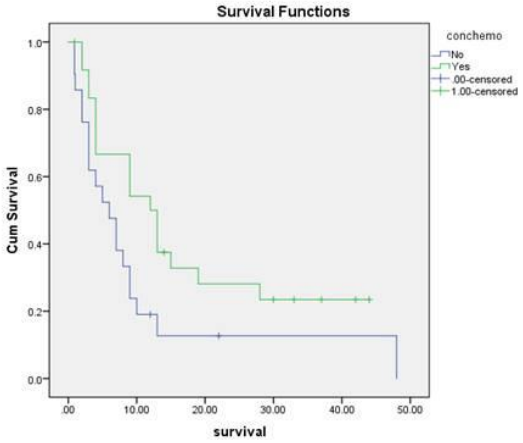
Despite aggressive multimodality treatment high grade gliomas carry poor prognosis and have short MST (24m). Previous studies shown that MST of patient with Grade III and IV Glioma on average where 2 to 5 years and less than 2 years respectively [4, 7, 8]. Many studies identified the prognostic factors of survival in HGG. They have reported that age, KPS, Tumor grade where independent prognostic factors [9, 10, 11]. The prognostic factors were used to identify the subgroups of patients with HGG who may need newer modalities of treatment options. Currain, et al. analyzed the RTOG Recursive partition analysis for HGG in which 6 prognostic classes were identified that primarily used variables of age, histology, mental status, KPS , symptom duration , extent of resection [12]. Laws et al analyzed the data from the Glioma outcome project and confirmed that resection instead of biopsy, age less than 60 and KPS more than 70 were all significantly correlated with outcome [13].

Figure - 3: Survival curve for KPS.



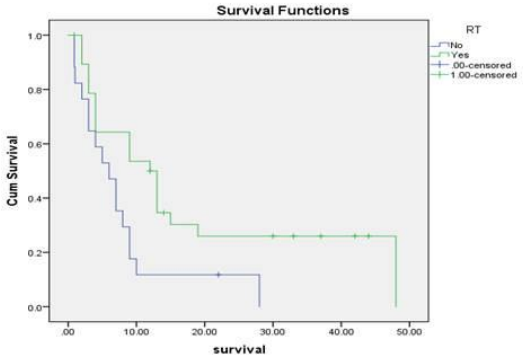
Median Survival if KPS<70 is 4
Median Survival if KPS>70 is 13

Figure - 4: Survival Plot Vs Con Chemo.



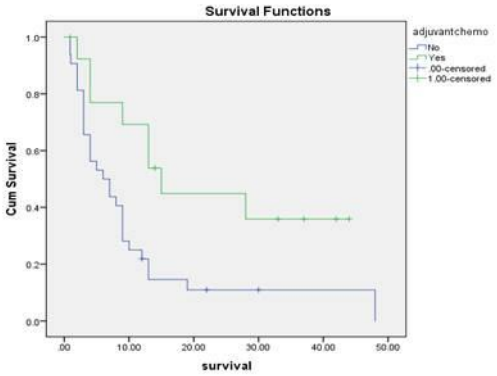
Median Survival if yes: 12 months
Median Survival if no: 6 months

Figure - 5: Survival Plot Vs Adjuvant Chemo.



Median Survival if adj chemo No is 6
Median Survival if adj chemo yes is 15

Figure - 6: Survival plot Vs RT.



Median Survival if yes: 12 months
Median Survival if no: 6 months

In a trial by Devaux, et al. [15] tumor grade, histopathology, radiotherapy have been accepted as significant prognostic factors. A trial by the European Organization for Research and Treatment of Cancer (EORTC) and the National Cancer Institute of Canada (NCIC) showed that PORT with concurrent and adjuvant TMZ significantly increased the survival in patients with GBM. The median survival was 14.6 months for the PORT plus TMZ group and 12.1 months for the PORT alone group ($p < 0.001$). The 2-year survival rate was 26.5% for the combined treatment group [4]. A trial by Erpolat, et al. [14] demonstrated that patients who completed 6 cycles of adjuvant TMZ had significantly better survival than patients who had not received 6 cycles (MST=22.7mVs12m, $p=0.011$).

In our retrospective study results are similar to the previous studies .The multivariate analysis showed that grade, performance status and extent of surgery were significant prognostic indicators. Only 63% of patients in our study had completed 60 Gy of PORT. Remaining patients defaulted in between due to various personal reasons. The MST of HGG in our study was less than other previous studies. Compared to those studies the percentage of patients received the full dose of PORT were less in our study may be due poor performance status. The patients who received concurrent and adjuvant TMZ were also significantly less. Majority of our patients defaulted after PORT and lost follow-up within few months and hence they didn't complete the full course of adjuvant TMZ. This is an important problem for our health care system and has to be improved immediately. 54 % of the patients had poor performance status with KPS < 70 which would also have affected the survival outcome.

It is important to note that there were some limitations to this study. This study is retrospective in nature and the number patients were less. However the demographic data is similar to the standard studies and we are able to correlate the survival outcome with prognostic factors like grade, histological type, extent of surgery and performance status.

Conclusion

This retrospective study showed that HGG had a short survival. The pre-treatment patient tumor and treatment characteristics which affected the prognosis in this analysis were histological type, grade of the tumor and the performance status. We have to identify the ways to encourage the patients to complete the PORT, concurrent and adjuvant TMZ cycles. Because these prognostic factors also significantly improves the survival outcome.

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