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ORIGINAL ARTICLE

Clinical predictors for survival and treatment outcome of high-grade glioma in Prasat Neurological Institute

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ABSTRACT

Objective: The aim was to identify clinical predictors for survival and examine treatment outcome in patients with high-grade glioma (HGG).

Materials and Methods: The authors retrospectively reviewed medical records of patients who was diagnosed HGG between January 2007 and December 2009. Demographic data, radiological data and treatment data of patients were reviewed and analyzed.

Results: A total of 100 patients were analyzed. There was no difference in demographic data between Grade III and IV glioma. Patients with HGG had median survival time (MST) 18 months, The MST of patients with Grade III and IV glioma were 26 and 13 months, respectively. In this study, only anaplastic oligoastrocytoma and radiotherapy did impact strongly on survival of patients with HGG. In patients with Grade III and IV glioma, radiotherapy found to have influence on survival.

Conclusion: Patients with HGG in Prasat Neurological Institute had short survival resemble to other previous study. The clinical predictors for survival of patients were identified on multivariate analysis.

Key words: High-grade glioma, prognostic factor, survival

Introduction

Glioma was classified into 4 grades according to WHO classification of tumor of the central nervous system (CNS) on the basis of their degree of malignancy.[1] Grade III and IV glioma, anaplastic astrocytoma (AA), anaplastic oligodendroglioma (AO), mixed anaplastic oligoastrocytoma (AOA) and glioblastoma (GBM), were known as high-grade glioma (HGG),[2] which carried poor prognosis despite intensive treatments with surgery, radiotherapy, and chemotherapy.

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Although the current standard treatment for HGG are maximal resection followed by radiotherapy with concomitant and adjuvant chemotherapy including temozolomide,[3-5] median survival time (MST) of GBM and AA were only <2 years and 2-5 years, respectively.[4-7]

There are several variables that could influence prognosis of patients with HGG such as age, performance status, tumor location, and extent of resection.[8-14] Therefore, assessment of patients by these variables may enable them receiving appropriate treatments and improve treatment outcome.

The purpose of this study was to identify clinical predictors of treatment outcome in HGG treated with combined modality approach in Prasat Neurological Institute and to examine the survival time of HGG patients at a single institute.

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Materials and Methods

All patients who underwent surgery for diagnosed HGG (AA, AO, AOA and GBM) between January 2007 and December 2009 were included in this study. The authors reviewed medical records on patient characteristics and all of treatment modalities in each patient. The incomplete data on medical records were excluded.

Patient characteristics

Age, sex, Karnofsky performance status (KPS),[15] payment and neurological status in each patients were reviewed. The KPS was dichotomized at <70 based on Radiation Therapy Oncology Group (RTOG) Recursive Partitioning Analysis (RPA).[16]

Radiological data

Tumor imaging characteristics were reviewed. Tumor size had a cut-off value at 4 cm because the previous studies have shown that it was significant for survival at this value.[10,17] Tumor location with regard to proximity to eloquent brain was characterized by functional grade as described by Sawaya, *et al*.[18] [Table 1]. Tumor necrosis [Figure 1], degree of mass effect, surrounding edema[11] and enhancement of tumor mass were also measured and recorded using the methods of Hammoud, *et al*.[19] [Table 2].

Treatment data

All treatment modalities included surgery, radiotherapy and chemotherapy were reviewed. Extent of tumor resection were classified into total resection, which defined as no residual gross tumor intraoperatively and on postoperative image, subtotal resection and biopsy. The radiotherapy and chemotherapy data derived from the medical records. Duration from surgery to radiotherapy was also calculated in all patients.

Statistical analysis

Parametric data were expressed as means ± standard deviations and compared via the Student's *t*-test. Nonparametric data were expressed as median values (interquartile range) and compared via the Mann-Whitney U-test. Percentages were compared via the Chi-square test or Fisher exact test based on sample size. Survival time was calculated from the date of first treatment until the date of death. The record was ended at January 2012. Survival curves were analyzed using Kaplan-Meier method[20] and the log-rank test.[21] The univariate and multivariate analysis of prognostic factors for survival were performed using Cox proportional hazards model.[22] Hazard ratios and their 95% confidence intervals (CIs) were calculated. Statistical analyses were performed using the Statistical Package for the Social Sciences 19.0 (SPSS, Inc., Chicago, IL, USA). The author defined *P* value below 0.05 as significant.

Results

There were 121 patients who were diagnosed HGG during that time. Twenty one patients were excluded from this study because of incomplete data. Table 3 shows a demographic data of all 100 patients. Median follow-up time was 14 months (1-44 months). The data of each subgroups those are WHO Grade III and Grade IV glioma are also shown. There were no significant difference in age, sex, KPS, weakness, aphasia and imaging characteristics between the 2 subgroups. Surgical treatment was mostly resection rather than biopsy, especially in patients with Grade IV glioma ($P = 0.06$). Hence, the duration of operation and estimated blood loss in patients

Table 1: Grading of intraparenchymal tumors according to functional location*

Grade	Functional location
Noneloquent brain	Frontal or temporal pole of cerebrum
	Right parietooccipital lobe
	Cerebellar hemisphere
Near eloquent brain	Near motor or sensory cortex#
	Near calcarine fissure
	Near speech center
	Corpus callosum
	Near dentate nucleus
	Near brainstem
Eloquent brain	Motor or sensory cortex
	Visual center
	Speech center
	Internal capsule
	Basal ganglia
	Hypothalamus or thalamus
	Brainstem
	Dentate nucleus

*Adapted from Sawaya, *et al.*; #Included tumors in the supplementary motor area

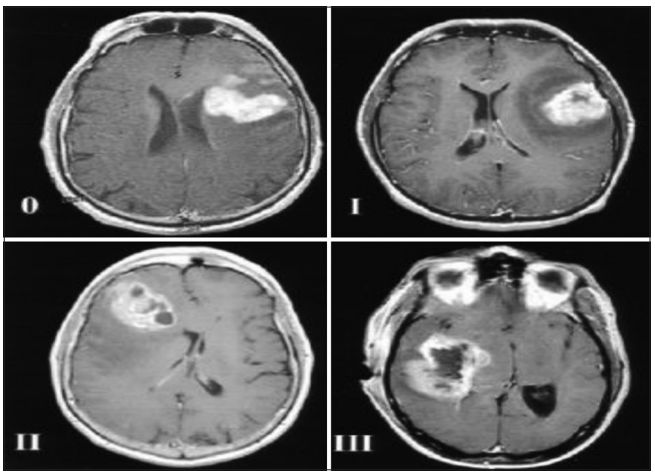

Figure 1: Grades of tumor necrosis adapted from Hammoud, *et al.* are demonstrated on magnetic resonance (MR) images. The amount of tumor necrosis, which appears as an area of decreased signal intensity on T1-weighted images, was divided into four grades as follow: Grade 0, no necrosis apparent on the MR images; Grade I, amount of necrosis <25% of the tumor volume; Grade II, amount of necrosis 25-50% of the tumor volume; and Grade III, amount of necrosis >50% of the tumor volume

Table 2: Grading of tumor characteristic on preoperative MRI

Characteristic	Grade
Mass effect	
None apparent	0
Minimal midline shift (<0.5 cm)	1
Moderate midline shift (0.5–1 cm)	2
Significant midline shift (>1 cm), subfalcian or uncal herniation	3
Edema*	
None apparent	0
Less than tumor volume	1
Approximately equal to tumor volume	2
Greater than tumor volume	3
Enhancement#	
None	0
Low-intermediate signal intensity	1
High-intermediate signal intensity	2
Signal intensity equal to that of fat	3

*Edema on T_2-weighted images is seen as an area of increased signal intensity surrounding the gadolinium-enhanced region of tumor (modified from Hammoud, *et al.*); #Enhancement of the tumor nodule as seen on gadolinium-enhanced T_1-weighted images (modified from Hammoud, *et al.*)

Table 3: Demographic data of 100 patients with high grade glioma

Characterisrics	All (*n*=100)	Grade III (*n*=56)	Grade IV (*n*=44)	*P*
Sex				
Male	58	38	20	0.06
Female	42	18	24	
Mean age (SD)	48 (15)	48 (17)	48 (14)	0.97
KPS				
<70	43	23	20	0.66
>70	57	33	24	
Payment				
Universal	59	32	27	0.711
Civil	29	18	11	
Social	12	6	6	
Weakness				
Yes	63	34	29	0.593
No	37	22	15	
Aphasia				
Yes	16	10	6	0.45
No	84	47	37	
Diameter				
<4 cm	45	26	19	0.746
>4 cm	55	30	25	
Func gr				
I	23	13	10	0.43
II	39	19	20	
III	38	24	14	
Necrosis				
0	22	16	6	0.074
I-III	78	40	38	
Mass effect				
0-1	41	24	17	0.67
2-3	59	32	27	
Edema				
0-1	50	36	14	0.001
2-3	50	20	30	
Enhancement				
0-1	28	19	9	0.136
2-3	72	37	35	
Resection				
Total	34	16	18	0.06
Subtotal	53	30	23	
Bx	13	11	2	
Operative time (min)	284	259	313	0.01
EBL (ml)	300	250	350	0.01
Histology				
AA	42	42		NA
AO	7	7		
AOA	7	7		
GBM	44		44	
Radiotherapy				
Yes	62	38	24	0.41
No	38	18	20	
Duration (days)	53.5	53	54	
Temozolomide				
Yes	7	3	4	0.47
No	93	53	40	
Gliadel				
Yes	2	0	2	0.46
No	98	56	42	
Chemotherapy				
Yes	4	1	3	0.33
No	96	55	41	
Death (%)	88 (88)	46 (82.1)	42 (95.5)	

Universal – Universal health care coverage; Civil – Civil servants medical scheme; Social – Social insurance; Func gr – Tumor functional grade [Table 1]; Bx – Biopsy; NA – Not applicable. Chemotherapy – Chemotherapeutic agents other than temozolomide and gliadel; SD – Standard deviation; KPS – Karnofsky performance status; EBL – Estimated blood loss; AA – Anaplastic astrocytoma; AO – Anaplastic oligodendroglioma; AOA – Anaplastic oligoastrocytoma; GBM – Glioblastoma

with Grade IV glioma were much more than in patients with Grade III glioma (P = 0.01, 0.01). No difference between patients in both Grade III and Grade IV glioma received the adjuvant therapy (temozolomide, gliadel and other chemotherapy) (P = 0.47, 0.46, 0.33, respectively).

Survival time

The MST for all patients from the time of surgery was 18 (95% CI 13.4-22.6) months. The MST of patients with Grade III and IV glioma was 26 (95% CI 19-33) and 13 (95% CI 10.2-15.8) months, respectively. Figure 2 shows the survival curve of patients with Grade III and IV glioma. The log-rank test showed that patient with Grade III glioma had significantly longer survival time than Grade IV glioma (P = 0.004). The authors also analyzed the survival curve of patients with each histological type [Figure 3]. The

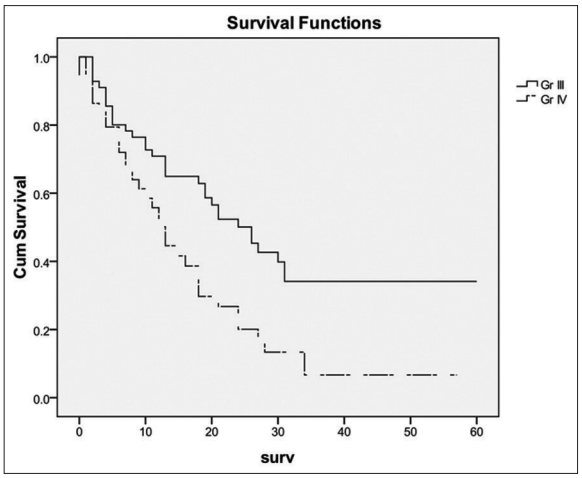

Figure 2: A comparison of survival times among patients with Grade III or IV glioma. Patients with Grade III glioma had significantly longer survival time than Grade IV glioma ($P = 0.004$)

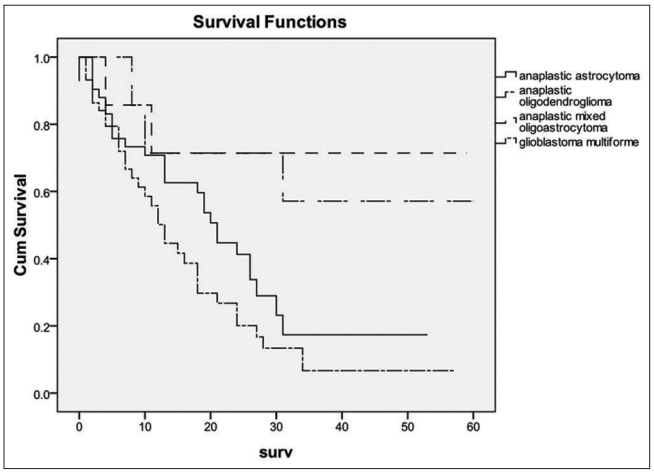

Figure 3: A comparison of survival times among tumor histology. Tumor histology did impact on survival of these patients ($P = 0.004$)

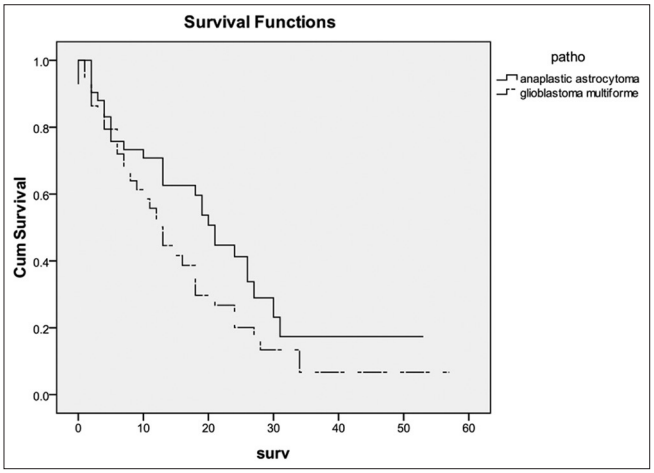

Figure 4: A comparison of survival times among patients with anaplastic astrocytoma or glioblastoma. The difference was not significant between these two groups ($P = 0.85$)

log-rank test also confirmed that histological type did impact on survival of these patients ($P = 0.004$). It is shown that there were little patients diagnosed AO and AOA and they had better survival time than AA ($P = 0.042$). When compared the survival time between patients with AA (MST = 21 months, 95% CI = 17.7-24.3) and GBM [Figure 4], the log-rank test showed that the difference was not significant between these two groups ($P = 0.85$).

Univariate and multivariate analysis

The clinical predictors for survival of all patients were analyzed by Cox proportional hazards model. On univariate analysis, KPS, histological type (those were AO and AOA) and radiotherapy had effect on survival ($P = 0.023$, 0.019 0.014, and 0.000, respectively). On multivariate analysis, only

Table 4: Prognostic factors for survival of all patients

Overall	MST (month)	Univariate analysis		Multivariate analysis	
		Hazard ratio (95% CI)	*P*	Hazard ratio (95% CI)	*P*
KPS					
<70	11	1.8 (1.1-3.0)	0.023	NA	0.175
>70	24	1 (NA)	NA	NA	NA
Histological type					
AA	21	NA	0.1	NA	NA
AO	41.3	0.2 (0.1-0.8)	0.019	NA	0.066
AOA	44.3	0.2 (0-0.7)	0.014	0.2 (0.0-0.9)	0.035
GBM	13	1 (NA)	NA	1 (NA)	NA
RT					
Yes	26	0.2 (0.1-0.3)	0.000	0.2 (0.1-0.4)	0.000
No	5	1 (NA)	NA	1 (NA)	NA

RT – Radiotherapy; CI – Confidence interval; MST – Median survival time; KPS – Karnofsky performance status; AA – Anaplastic astrocytoma; AO – Anaplastic oligodendroglioma; AOA – Anaplastic oligoastrocytoma; GBM – Glioblastoma, NA – Not available

Table 5: Prognostic factors for survival of patients with grade III and grade IV glioma

Prognostic factors	MST (month)	Univariate analysis		Multivariate analysis	
		Hazard ratio (95% CI)	*P*	Hazard ratio (95% CI)	*P*
Grade III					
Payment					
Universal	31	1 (NA)	NA	NA	NA
Civil	13	2.9 (1.4-5.9)	0.005	NA	0.093
Social	35.8	NA	0.356	NA	NA
RT					
Yes	31	0.2 (0.1-0.4)	0.000	0.1 (0.1-0.3)	<0.001
No	5	1 (NA)	NA	1 (NA)	NA
Grade IV					
RT					
Yes	18	0.2 (0.1-0.5)	0.000	0.2 (0.1-0.5)	<0.001
No	6	1 (NA)	NA	1 (NA)	NA

Universal – Universal health care coverage; Civil – Civil servants medical scheme; Social – Social insurance; RT – Radiotherapy; MST – Median survival time; NA – Not available

AOA and radiotherapy did impact on survival of these patients ($P = 0.035$ and 0.000, respectively) [Table 4].

In patients with Grade IV glioma, there was only radiotherapy found to have influence on survival in both univariate and multivariate analysis ($P = 0.000$, <0.001). Finally, the Cox analysis was performed on patients with Grade III glioma. Patients with civil servants medical scheme and radiotherapy had influence on survival in univariate analysis ($P = 0.005$ and 0.000, respectively). However in multivariate analysis, only radiotherapy was the significant factor on survival ($P < 0.001$) [Table 5].

Discussion

High-grade glioma composed of WHO Grade III and Grade IV glioma which is the most common primary brain tumors. They represent 80% of malignant CNS tumors.[23] Although there are combination treatment between surgery, radiotherapy and chemotherapy, they carry poor prognosis and have short MST.[24]

The previous studies have shown that MST of patients with Grade III and Grade IV glioma, on average, were 2-5 years and <2 years, respectively[4,7,25] In Thailand, Siangprasertkij and Navalitloha from Chulalongkorn University, reported the MST of Grade III and Grade IV glioma was 20 and 9 months, respectively.[26] Chansriwong and Sirisinha from Ramathibodi Hospital, Mahidol University, reported the overall survival time in patients with HGG was 604.04 days.[27] The treatment outcomes in this study are comparable to other previous studies [Table 6].

There are many studies about clinical predictors for survival in patients with HGG. Most studies have been reported that age, performance status and tumor grade were independent important prognostic factors.[11,28,29] The RTOG used RPA to analyze survival in 1,578 patients with HGG. There are six prognostic classes that primarily used the variable of age, histology, mental status, KPS, symptom duration and extent of resection.[16] Laws *et al*. published data from the Glioma Outcome Project that resection instead of biopsy, age <60 and KPS >70 were all significantly correlated with outcome.[17] McGirt *et al*. have recently reported extent of resection was associated with improved survival independent of age, KPS, tumor grade, or adjuvant treatment for HGG.[13] The independent prognostic factors in this study are oligodendroglial component and radiotherapy.

The natural history of HGG is different according to tumor grade and histopathology. It has been universally accepted that the prognosis of Grade IV glioma is worse than Grade III glioma.[30] Furthermore, this study shows mixed oligoastrocytoma subtype had a better prognosis which is compatible with the previous studies.[25,29-31]

Radiotherapy has been well-documented as one of the advance treatment modalities for HGG.[1,4,32-34] It is strongly correlated with survival in HGG.[30] The multivariate Cox analysis in this study also reported it was a significant predictor for survival in patients with HGG. Patients in this study were received radiotherapy 62% (67.9% in Grade III, 54.5% in Grade IV). Median time from surgery to radiation was about 2 months. This seems to be less effective treatment and may have effect on survival.[35] Because there is no radiotherapy in our institute. All patients need to be transferred for radiation in the other hospitals. Hence, there may be some patients loss between the transferring. Furthermore, some patients refused to be treated with radiation due to their personal opinions. This is an important problem for the current health care system and have to be improved immediately [Table 7].

It is important to note that there were some limitations to this study. This study is retrospective, thus potentially subject to sources of bias and variation. The number of patients is quite low. Data in this study were from medical records and population database of the ministry of public health. There was no detail in some aspects such as dose and technique of radiation, dose and duration of temozolomide and other chemotherapy. However, it is encouraging that the demographic characteristics of the patients and the overall survival data are very similar to those reported in other published studies.

Table 6: Survival time (months) of patients with high-grade glioma

Tumor grade	PNI	Chula	Rama	Stupp *et al.*	Wen and Kesari	McGirt *et al.*
High-grade glioma	18	NA	20.1	-	11.6-13.9	NA
Grade III	26	20	NA	-	24-60	34-58
Grade IV (GBM)	13	9	NA	12.1-14.6	12-15	8-13

Chula – Chulalongkorn University; Rama – Ramathibodi Hospital; PNI – Prasat Neurological Institute; GBM – Glioblastoma; NA – Not available

Table 7: Causes of patients with high-grade glioma not receive radiation

Causes	Number (%)
Patient refusal	12 (31.6)
Poor condition	7 (18.4)
Death before radiation	6 (15.8)
Loss follow-up	4 (10.5)
No data	9 (23.7)

Conclusions

This retrospective study at a single institute shows that patients with HGG had a short survival resemble to the other previous studies. The clinical predictors for survival of patients

were identified on multivariate analysis. Patients should be encouraged to received suitable treatment by the new health care system.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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