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Outcome Analysis and Prognostic Factors in Patients of Glioblastoma Multiforme: An Indonesian Single Institution Experience

Sudibio Sudibio[1,2]*, Jellyca Anton[1,2], Handoko Handoko[1,2], Tiara Bunga Mayang Permata[1,2], Henry Kodrat[1,2], Endang Nuryadi[1,2], Henry Riyanto Sofyan[1,3], Rahmad Mulyadi[1,4], Renindra Ananda Aman[1,5], Soehartati Gondhowiardjo[1,2]

[1]Faculty of Medicine, Universitas Indonesia, Jakarta, Indonesia; [2]Department of Radiation Oncology, Dr. Cipto Mangunkusumo National General Hospital, Jakarta, Indonesia; [3]Department of Neurology, Dr. Cipto Mangunkusumo National General Hospital, Jakarta, Indonesia; [4]Department of Radiology, Dr. Cipto Mangunkusumo National General Hospital, Jakarta, Indonesia; [5]Department of Neurosurgery, Dr. Cipto Mangunkusumo National General Hospital, Jakarta, Indonesia

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***Correspondence:** Sudibio Sudibio, Department of Radiation Oncology, Faculty of Medicine, Universitas Indonesia, Dr.Cipto Mangunkusumo National General Hospital, Jakarta, Indonesia. E-mail: sudibio_su@yahoo.com
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Abstract

AIM: This study was done to assess the survival of patients with glioblastoma multiforme (GBM) and to identify factors that can affect patient survival.

MATERIALS AND METHODS: From January 2015 to December 2019, 55 patients with histopathologically confirmed GBM and received adjuvant radiation/chemoradiation in our department were retrospectively analyzed.

RESULTS: The median overall survival (OS) for entire cohort was 13 months and 1-year OS and 2-year OS rate were 52.7% and 3.6% with the mean follow-up period was 12 months. In univariate analysis, age (≤50 years vs. >50 years, p = 0.02), performance status (≥90 vs. 70–80 vs. <70, p < 0.001), radiation therapy oncology group recursive partitioning analysis (RTOG-RPA) classification (Class III vs. Class IV vs. Class V-VI, p < 0.001), parietal lobes tumor site (vs. others, p = 0.02), residual tumor volume (≤20.4 cm^3 vs. >20.4 cm^3, p = 0.001), and time to initiate adjuvant therapy (<4 weeks vs. 4-6 weeks vs. >6 weeks, p = 0.01) were significantly affect OS. In multivariate analysis, RTOG-RPA classification and involvement of parietal lobes were independent prognostic factors for OS.

CONCLUSIONS: RTOG-RPA classification that consisted of age and performance status is an independent prognostic factor for the clinical outcome of GBM. Besides this well-known factor, we also identified the involvement of parietal lobe gives a strong negative influence on survival of GBM patients.

Introduction

Glioblastoma multiforme (GBM) is an aggressive primary brain tumor with devastatingly poor prognosis and account for approximately 12–15% of all primary intracranial neoplasm and 60–75% of glial tumors [1], [2]. GBM usually present in sixth or seventh decades of life and most commonly found in male than female [1]. Standard treatment for GBM is based on multidisciplinary approach employing resection followed by radiotherapy with or without concurrent and adjuvant chemotherapy with Temozolomide (TMZ) [3]. Phase III randomized trial by Stupp *et al*. showed that concomitant and adjuvant TMZ in addition to standard post-operative radiotherapy relatively improved the survival, increasing the median survival to 12–15 months, even though this results is still considered to be dismal [4], [5]. In a developing country like Indonesia, not all of the patients with GBM received concomitant chemoradiotherapy and adjuvant TMZ. Sometimes radiotherapy alone is still the only adjuvant treatment option in these patients. The aim of this retrospective study was to present and discuss clinical features, various treatment schedules and identify independent prognostic factors that significantly predict survival in GBM from our institute and to compare the results with literature.

Materials and Methods

Medical records from 2015 to 2019 were retrospectively reviewed and patients with newly diagnosed and pathologically confirmed GBM were identified. The following data were collected from the medical records of patients: (1) Demographic profile (age and gender); (2) Karnofsky performance Status (KPS); (3) radiation therapy oncology group recursive

partitioning analysis (RTOG-RPA) Classification; (3) site of tumor; (4) treatment regimen; and (5) overall survival (OS), which was mainly collected when patients visited the outpatient clinic or during phone interview with patients and/or relatives. OS was calculated from date of diagnosis to date of death or date of last contact. Patients who were alive at the end of study were censored from analysis. Statistical analysis was done using SPSS 23.0. OS was calculated using Kaplan-Meier method, and prognostic factors were determined by log rank test. Cox proportional hazards model was used for multivariate analysis. $p < 0.05$ indicates statistical significance. This study was approved by the ethics committee of the Faculty of Medicine, University of Indonesia, Jakarta, Indonesia. This study was exempted form acquisition of written consent for publication from participants by the institutional ethics committee because of its retrospective and observational nature.

Results

The retrospective review identified 55 patients with newly diagnosed GBM who met the inclusion criteria. The characteristics of the patients are summarized in Table 1. Standard treatment included surgery and post-operative radiotherapy 59.4 Gy in 33 fractions or 60 Gy in 30 fractions with or without concurrent and/or adjuvant TMZ. The median OS for entire cohort was 13 months and 1-year OS and 2-year OS rate were 52.7% and 3.6% as shown in the figure 1 with the mean follow-up period was 12 months.

Table 1: Patients and treatment characteristics

Characteristics	Number	%
Age		
≤50	23	41.8
>50	32	58.2
Gender		
Male	24	43.6
Female	31	56.4
KPS		
≥90	18	32.7
70–80	19	34.5
<70	18	32.7
RTOG-RPA		
III	13	23.6
IV	31	56.4
V-VI	11	20
Site of tumor		
Frontal	30	31.5
Temporal	23	24.2
Parietal	25	26.3
Occipital	5	5
Basal Ganglia	6	6
Corpus callosum	4	4
Brainstem	2	3
Cerebellum	0	0
Extend of resection		
Gross tumor removal (GTR)	15	27.3
Subtotal tumor removal (STR)	16	29.1
Biopsy	2	3.6
Unknown	22	40
Residual tumor volume (RTV)	Median 50 cm^3 (3,2–364,4)	
Adjuvant Therapy		
Concurrent chemoradiation and adjuvant chemotherapy	27	49.1
Concurrent chemoradiation	9	16.4
Radiotherapy and adjuvant chemotherapy	3	5.5
Radiotherapy only	16	29.1
Time to initiate adjuvant therapy (TTI)	Median 42 days (16–181)	
MGMT		
Methylated	8	14.5
Unmethylated	14	25.5
Unknown	33	60

KPS: Karnofsky performance Status, RTOG-RPA: Radiation therapy oncology group recursive partitioning analysis, MGMT: O6-methylguanine-DNA methyl-transferase.

Table 2: Prognostic factors of OS in the univariate analysis

Characteristics	Median OS (months)	p-value
Age		
≤50	14	0.02
>50	12	
Gender		
Male	13.3	0.73
Female	12	
KPS		
≥90	16	<0.001
70–80	13	
<70	8.1	
RTOG-RPA		
III	18	<0.001
IV	13	
V-VI	6.7	
Site of tumor		
Frontal (vs. Others)	13	0.78
Temporal (vs. Others)	14	0.6
Parietal (vs. Others)	11	0.02
Occipital (vs. Others)	14	0.84
Basal Ganglia (vs. Others)	6.7	0.22
Corpus Callosum (vs. Others)	11	0.29
Brainstem (vs. Others)	4	0.34
Extend of resection		
Gross tumor removal (GTR)	15	0.14
Subtotal tumor removal (STR)	12	
Biopsy	1.9	
Unknown	13	
RTV		
MGMT	18	0.001
MGMT	12	
Adjuvant Therapy		
Concurrent chemoradiation and adjuvant chemotherapy	15	0.08
Concurrent chemoradiation without adjuvant chemotherapy	8.1	
Radiotherapy and adjuvant chemotherapy	13	
Radiotherapy only	11	
TTI		
<4 weeks	10.4	0.01
4–6 weeks	16	
>6 weeks	14	
MGMT		
Methylated	15	0.57
Unmethylated	12	
Unknown	13	

KPS: Karnofsky performance Status, RTOG-RPA: Radiation therapy oncology group recursive partitioning analysis, MGMT: O6-methylguanine-DNA methyl-transferase.

Prognostic factors

The impact of various patient and treatment related factors on OS is described in Table 2. In univariate analysis using log rank test, patients with age >50, KPS <90, RTOG-RPA V-VI, biopsy, residual tumor volume (RTV) >20.4 cm^3, time to initiate adjuvant therapy (TTI) <4 weeks and parietal lobe tumors had worse survival as compared to others. In multivariate analysis using cox proportional hazards RTOG-RPA and parietal lobe tumors was found to be independent prognostic factors for OS as shown in Table 3. A sequential Kaplan-Meier survival curve analyses revealed that the cutoff values for RTV were ≤20.4 cm^3 (HR: 0.30, 95% CI 0.14–0.65, p: 0.001). Receiver operating characteristic analysis was performed to internally validate the RTV cutoff values as well as to know its predictive accuracies, the maximum Youden index was 0.51 and referred to a cutoff volume of ≤20.4 cm^3. The area under the curve for RTV was 0.67 (95% CI 0.42–0.90).

Table 3: Prognostic of OS in multivariate analysis

Characteristics	Hazard Ratio	95% CI	p-value
RTOG-RPA	3.06	1.75–5.33	<0.001
Pariteal lobe tumors (vs. Others)	2.63	1.16–5.94	0.02
Basal Ganglia (vs. Others)	1.57	0.57–4.26	0.37
Extend of resection	0.84	0.57–1.23	0.57
RTV	2.21	0.89–5.49	0.08
Adjuvant therapy	1.11	0.85–1.52	0.36
TTI	0.71	0.46–1.09	0.11

RTOG-RPA: Radiation therapy oncology group recursive partitioning analysis, MGMT: O6-methylguanine-DNA methyl-transferase, TTI: Time to initiate adjuvant therapy, OS: Overall survival, RTV: Residual tumor volume.

Discussion

The prognosis of patients with GBM has not showed much improvement over the last few decades. The established standard treatment for GBM consists of maximal safe resection followed by radiotherapy with or without concurrent and adjuvant chemotherapy with TMZ [3].

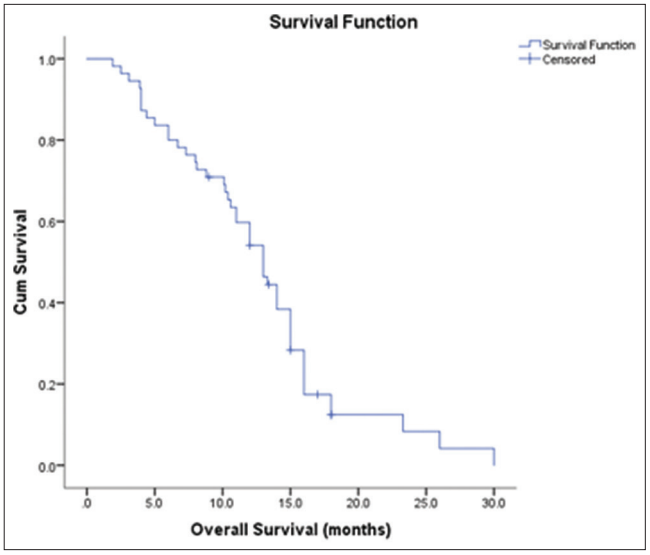

Figure 1: Overall survival

A complete resection is not always possible due to the tumor infiltration into the surrounding brain parenchyma. Adjuvant radiotherapy has to be delivered to take care of the residual/microscopic disease. Because the survival of GBM patients remains poor, determining prognostic factors affecting survival from GBM native patients are essential. We undertook this retrospective analysis to determine various factors influencing the survival of our patients. All patients in this study underwent craniotomy and adjuvant treatment. Patients who could not afford costly drugs and treated with adjuvant radiotherapy alone were also included in the study.

The baseline characteristics of our patients were similar to other reported series with male-female ratio of 1.3:1 and the median age of patients in this study is 45 years old. This difference result might be due to the lower life expectancy of the Indonesian population compared to the population of the United States [6].

There is no difference in survival between men and women. The findings in this study were in line with several studies [7], [8], [9]. However, several other studies showed better survival in women compared to men [10], [11], [12]. An *in vivo* study on rats with GBM expressing estrogen receptor-β (ERβ) demonstrated an increase of cytotoxic effect compared to GBM without ERβ expression. Overexpression of ERβ will reduce the proliferation of cancer cells and suppress the growth of GBM and also improve the response of therapy. ERβ can also modulate DNA repair genes and ATM signaling [13]. However, there is a lack of strong scientific evidence that theoretically could explain the effect of the reproductive hormone on GBM.

Age and performance status is the most important variables affecting patient's survival in GBM. Historically, a set of prognosis classes were developed by Curran *et al*. using RPA model and a better prognosis was seen in patients who were <50 years old and had KPS of 90–100. Li *et al*. validated and simplified the RPA classification and a better prognosis was shown in Class III with median survival of 16.3 months and 6.7 months in Class V + VI [14], [15]. Interestingly, similar results were also seen in our study, even though not all patients underwent chemoradiation in our study.

The current GBM studies consistently stated that the older the age of the patient when diagnosed with GBM, the poorer the survival [7], [9], [14], [16], [17]. Besides the different biological nature of GBM in older patients, poorer survival may be caused by a reduction to tolerate medication in older patients [18]. Poorer KPS often associated with the patient's inability in tolerating an overly aggressive therapy and increased morbidity [19]. There are limited prospective studies on GBM patients with poor KPS due to poor survival and the presumption that the benefit did not outweigh the cost, morbidity, and treatment received.

This study found that RTV >20.4 cm^3 showed poorer survival, although it did not reach significance in multivariate analysis. Some studies also showed that RTV independently affects survival [20], [21], [22], [23], [24], [25]. The cutoff value of RTV in each study tends to vary. However, the lower the volume, the better the survival of GBM patients. Yong *et al*. showed that RTV >30 cm^3 tended to have faster tumor regrowth (odds ratio 4.22 with p = 0.02) [26]. Grabowski *et al*. and Woo *et al*. stated that RTV was more predictor than EOR. Although total tumor resection is an independent prognostic factor of survival in several studies, it is not possible done in most cases. Therefore, reducing RTV to the smallest extent is very recommended.

TTI within 4–6 weeks provides better survival than TTI <4 weeks. However, the difference in survival between TTI 4 and 6 weeks and TTI >6 weeks was not statistically significant. Several studies showed that TTI 4–6 weeks affect survival

[27], [28], [29]. However, several studies also did not find a difference survival regard to TTI [30], [31], [32], [33]. There are some possible explanations for the worse outcomes seen in patients with shorter TTI. The possible detrimental effect of initiating radiation immediately within 2 weeks after surgery would be caused greater cerebral tissue damage in animal study [34]. Moreover, the brain is more edematous after surgery which contributes to hypoxia and reducing the radiosensitivity of tumor. Furthermore, the surgical cavity also has not really shrunk within the first 4 weeks after surgery, leading to larger radiation field, and increased normal tissue damage. There is also a possibility that early initiation radiation before the patient fully recovery from surgery could result in impaired healing and increased radiation toxicity [28], [35], [36], [37].

This study showed no statistically difference in survival from the administration of adjuvant therapy. However, there is a trend toward better survival in the group that received concurrent chemoradiation and adjuvant TMZ. Several randomized showed the benefit of survival in patient who received adjuvant concurrent chemoradiation and adjuvant TMZ compared to patients who received adjuvant radiation only [5], [38], [39], [40]. A randomized study also showed no difference of survival in patients who received concurrent chemoradiation without adjuvant TMZ compared to patients who received adjuvant radiation only [41]. Recent research in GBM treatment focuses on novel targeted molecular therapies, and in particular, those targeting the epidermal growth factor receptor (EGFR) pathway. Substantial evidence supports a causal role for aberrant EGFR signaling in cancer pathogenesis and resistance in glioma. Nimotuzumab, a humanized anti-EGFR monoclonal antibody has proven efficacy for various tumor types. However, in several studies conducted in patients with GBM, no survival benefit was seen in the addition of nimotuzumab concurrently with standard therapy [42], [43], [44], [45].

O6-methylguanine-DNA methyl-transferase (MGMT) methylation status was not examined in all patients; only 22 patients had data on MGMT methylation status (because the MGMT test was not covered by national insurance). The survival was not statistically difference in this study. However, there was a trend of better survival in methylated MGMT. As much as 87.5% of patients with methylated MGMT in this study received adjuvant concurrent chemoradiation with TMZ, followed by adjuvant TMZ. Methylation of MGMT promoter caused epigenetic silencing and reduced the mechanism of DNA repair which will increase the effectivity of received TMZ and radiation. Systematic review and meta-analyses revealed better survival in GBM patients with MGMT promoter methylation compared to GBM patients without MGMT promoter methylation [46], [47].

In this study, tumors involving the parietal lobe showed statistically significant poorer survival, while tumors involving the basal ganglia, corpus callosum, and brainstem also showed poorer survivability, although statistically insignificant. A number of studies have included tumor location in their data analysis. In a study by Kumar *et al*., found poorer survivability in GBM involving the parietal lobe, corpus callosum, and brainstem. The study by Awad *et al*., Tian *et al*., and Wee *et al*. also reported poor survival in patients with GBM located in the periventricular, brainstem, corpus callosum, and basal ganglia [9], [11], [16], [48]. However, several other studies showed that tumor location does not affect survival [49], [50], [51].

Conclusions

This is a valuable retrospective study with a full scale analysis. RTOG-RPA classification that consisted of age and performance status is an independent prognostic factor for the clinical outcome of GBM. Besides this well-known factor, we also identified the involvement of parietal lobe gives a strong negative influence on survival of GBM patients.

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