RESEARCH ARTICLE

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Survival Analysis of Glioblastoma Multiforme

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Abstract

Introduction: To evaluate the survival of Glioblastoma Multiforme (GBM). **Material and Methods:** Patients with a pathological diagnosis of Glioblastoma Multiforme (GBM) between 1 January 1994 and 30 November 2013, were retrospectively reviewed. Inclusion criteria: 1) GBM patients with confirmed pathology, 2) GBM patients were treated by multimodality therapy. Exclusion criteria: 1) GBM patients with unconfirmed pathology, 2) GBM patients with spinal involvement, 3) GBM patients with incomplete data records. Seventy-seven patients were treated by multimodality therapy such as surgery plus post-operative radiotherapy (PORT), post-operative Temozolomide (TMZ) concurrent with radiotherapy (CCRT), post-operative CCRT with adjuvant TMZ. The overall survival was calculated by the Kaplan-Meier method and the log-rank test was used to compare the survival curves. A p-value of ≤ 0.05 was considered to be statistically significant. **Results:** Seventy-seven patients with a median age of 53 years (range 4-76 years) showed a median survival time (MST) of 12 months. In subgroup analyses, the PORT patients revealed a MST of 11 months and 2 year overall survival (OS) rates were 17.2%, the patients with post-operative CCRT with or without adjuvant TMZ revealed a MST of 23 months and 2 year OS rates were 38.2%. The MST of patients by Recursive Partitioning Analysis (RPA), classifications III, IV, V, VI were 26.8 months, 14.2 months, 9.9 months, and 4.0 months, ($p < 0.001$). **Conclusions:** The MST of the patients who had post-operative CCRT with or without adjuvant TMZ was better than the PORT group. The RPA classification can be used to predict survival. Multimodality therapy demonstrated the most effective treatment outcome. Temozolomide might be beneficial for GBM patients in order to increase survival time.

Keywords: Glioblastoma multiforme- post-operative radiotherapy- median survival time- survival rate

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Introduction

Glioblastoma Multiforme (GBM) or WHO grade IV, is a common malignant brain tumor in adults (Louis et al., 2007; Wen and Kesari, 2008). The GBM occurs in about 80 % of the malignant gliomas (DeAngelis,2001; Thakkar et al., 2014). The patients with GBM have poor prognosis and usually die rapidly if left untreated. Most of the patients die within 2 years and the overall survival time is less than a year from the diagnosed date (Laws et al., 2003; Mirimanoff et al., 2006; Reardon and Wen, 2006; Wen and Kesari, 2008; Rock et al., 2012; Hanif et al., 2017). The prognostic factors affecting survival included age, Karnofsky performance status (KPS), chemotherapy administration, total dose of radiation, tumor location in the brain and ability of complete tumor resection (Nelson et al., 1988; Bleehen and Stenning, 1991; Simpson et al.,1993; Laws et al., 2003; Korshunov et al., 2005; Stummer et al., 2006; Pichlmeier et al., 2008; Scott et al., 2011, Okumus et al., 2012; Wang et al., 2012; Ahmadloo et al., 2013; Qin et al ., 2015) The Radiation Therapy Oncology Group (RTOG) reported the "Recursive partitioning analysis" and categorized prognosis of the patients with GBM (Curran et al., 1993). Core treatment of the patients with GBM is to remove as much as possible or all of the tumor mass with fewest neurological complications. The only way to prevent major neurological deficits for deep location or infiltrative tumor is to perform either tumor debulking or biopsy (Li et al., 2009; Helseth et al.,2010). The patients who had complete tumor resection with post-operative brain radiation therapy had a 2-year survival of less than 15 % (Nelson et al., 1998; DeAngelis, 2001; Stupp et al., 2005; Stupp et al.,2006). The chemotherapy for adjuvant treatment after tumor resection plus PORT plays an important role on preventing local recurrence as well as distant metastases (Norden and Wen, 2006., Combs et al., 2008; Ohka et al., 2012). Stupp et al., (2005) and Stupp et al., (2009) studied a randomized control trial which demonstrated effectiveness of Temozolomide (TMZ) in post-operative GBM patients.

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Materials and Methods

Patients with Glioblastoma Multiforme (GBM) at Srinagarind Hospital, Faculty of Medicine, Khon Kaen University, Thailand, between 1 January 1994 and 30 November 2013, were retrospectively reviewed. The study was approved by the Ethics Committee for Human Research of Khon Kaen University, HE 561484. Inclusion criteria: 1) GBM patients with confirmed pathology, 2) GBM patients were treated by multimodality therapy. Exclusion criteria: 1) GBM patients with unconfirmed pathology, 2) GBM patients with spinal involvement, 3) GBM patients with incomplete data records. Operating definitions: a) Eloquent area refers to temporo-parietal, parieto-occipital, thalamus, parietal, temporal, hypothalamus, fronto-temporal, basal ganglion, fronto-parietal lobe. b) Non-eloquent area refers to frontal and occipital lobes. c) Survival was calculated from the date of surgical management to the date of death. d) The patients who were treated with post-operative CCRT had to take TMZ orally with the dose of 75 mg/m^2 one hour before each radiation fraction. e) Adjuvant chemotherapy with TMZ was prescribed in some cases starting at 4 weeks after complete radiation treatment with the dose of 150-200 mg/m^2/day for 5 days every 28 days for 6 cycles. f) The titrational dose technique was usually used with whole brain radiation therapy (WBRT) in some cases with extensive brain edema to avoid brain herniation. The dose per fraction was gradually escalated from a low dose such as 50 cGy to 1 Gy, 1.5 Gy, 1.8 Gy and 2 Gy on the consecutive days.

Patient data were collected from the hospital and radiotherapy unit records in combination with the cancer registry of Srinagarind Hospital. Biographical data and social status of some patients were obtained from the Department of Provincial Administration, Ministry of Interior, Thailand. Statistical analysis was performed by using the STATA software version 10.1. Overall survival was calculated by the Kaplan-Meier method and the log-rank test was used to compare the survival curves. A p-value of ≤ 0.05 was considered to be statistically significant.

Results

Patients and treatment characteristics

This study consisted of 112 cases diagnosed with GBM. Thirty-five patients were excluded from the study. There were 7 patients with unconfirmed pathological results, 3 patients with spinal involvement, 20 patients with incomplete data records and 5 patients were lost to follow-up. There were 77 out of 112 cases who met the inclusion criteria. The most frequent tumor region was in the eloquent area (79.2%). In types of surgery, 41 patients underwent partial tumor removal (53.2%), 23 cases had total tumor removal (29.9%) and the rest only had tissue biopsies (16.9%). There were 51 out of 77 cases (66.2%) who received a total radiation dose of 54-60 Gy. Dose fractionation was used as follows: 57 cases (74.0%) were treated with a dose per fraction of 1.8-2 Gy/day, while 20 cases (26.0%) were treated with the WBRT (titrational dose technique). In cases of combined treatment of surgery plus TMZ, 14 cases were treated with post-operative CCRT, another 6 patients received post-operative CCRT plus adjuvant TMZ. Although 4 cases had a complete adjuvant TMZ, the other 2 cases failed to have complete adjuvant TMZ because of tumor progression during treatment and also loss of follow-up.

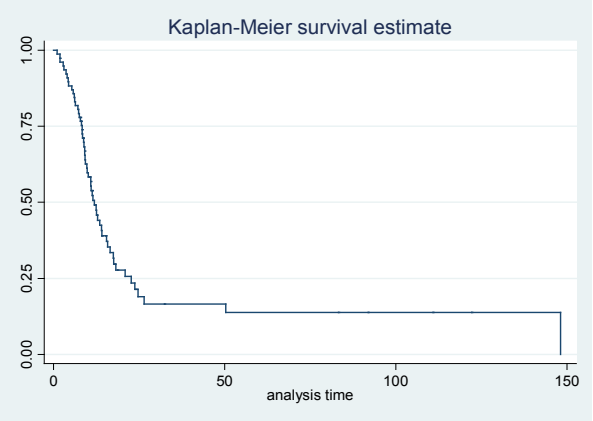

Figure 1. Survival Curve of GBM (Months)

Sixty-one out of 77 cases (79.2%) received two phases of radiation treatment. Either whole brain radiotherapy (WBRT) or 3D-CRT (3 dimension conformal radiotherapy) technique was used in the first phase of radiation while the second phase was tumor boosting with 2-dimensional radiotherapy (2D) or with 3D-CRT local field external beam radiotherapy(EBRT) technique.

Regarding RPA classification, 32 out of 77 cases (41.5%) were classified as class IV and 21/77 cases (27.3%) were class V. The patient and treatment characteristics are summarized in Table 1.

Survival

The median survival time (MST) of all GBM patients in this study was 12 months (n = 77; 95% confidence interval [CI], of 9.9-14 months). The 2 and 5 year overall survival rates were found to be 21.3% and 13.8% as shown in Figure 1.

The patients who underwent surgery plus PORT alone had a median survival time of 11 months (95% confidence interval [CI], 8.8-13.2 months) while in patients treated

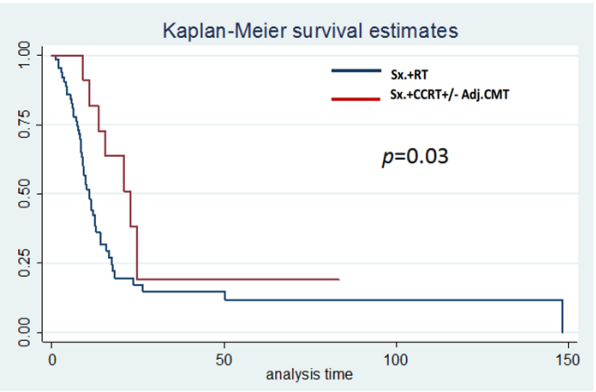

Figure 2. Survival Time in Months of Post-operative GBM Patients with "PORT Group" Versus " Post-operative CCRT± Adjuvant TMZ Group ".

Table 1. Patients and Treatment Characteristics

Characteristics	Cases	%
Age group		
< 20 years	9	11.7
20-50 years	25	32.5
> 50 years	43	55.8
Median age (range); years	53 (4-76)	
Gender		
Male	51	66.2
Female	26	33.8
KPS at start radiation (%)		
90-100	36	46.7
70-89	33	42.9
50-69	6	7.8
<50	2	2.6
Tumor size (cm.)		
< 5	29	37.7
≥ 5	48	62.3
Median (Range);cm.	5.1 (2.0-14.4)	
Mean (cm.) ± SD	5.5 ± 1.96	
Tumor location		
Confined to single lobe	48	62.3
Involved more than one lobe	29	37.7
Tumor location		
Eloquent area	61	79.2
Non-eloquent area	16	20.8
Modalities of treatment		
1) Post-operative CCRT+ complete adjuvant TMZ	4	5.2
2) Post-operative CCRT	8	10.4
3) Post-operative CCRT+ incomplete adjuvant TMZ	2	2.6
4) PORT alone	63	81.8
Type of surgery		
Biopsy	13	16.9
Partial tumor removal	41	53.2
Total tumor removal	23	29.9
Radiation technique		
2-D	70	90.9
3-D	7	9.1
Radiation field		
Local EBRT	12	15.6
2 D	5	
3D-CRT	7	
WBRT	65	84.4
Boost tumor& technique		
Yes	61	79.2
2D	20	
3D-CRT	34	
No	16	20.8
Total dose (Gy)		
< 40	7	9.1
40 - < 54	10	13
54 - 60	51	66.2
> 60	9	11.7

Table 1. Continued

Characteristics	Cases	%
No. fractions		
Mean ± SD	37.8 ±6.11	
Median (range)	30 (6-35)	
WBRT		
Titrational dose technique	20	26
Conventional fractionation	57	74
RPA classifications		
III	12	15.6
IV	32	41.5
V	21	27.3
VI	12	15.6
RPA classifications of patients used TMZ.	14	
III	1	7.2
IV	7	50
V	3	21.4
VI	3	21.4
Follow-up time (months)	54	70.1
Median (range)	3.9 (1-147.5)	

with CCRT with or without adjuvant TMZ was found to be 23 months (95% confidence interval [CI], 13.7-32 months, p = 0.03). The patients who underwent surgery plus PORT alone had 2 and 5 year- survival rates of 17.2% and 11.8% while in patients treated with CCRT with or without adjuvant TMZ of 38.2% and 19.1% were as shown in Figure 2.

In sub-group analysis, there were 4 sub-groups, 1) post-operative CCRT + complete adjuvant TMZ, 2) post-operative CCRT, 3) post-operative CCRT+ incomplete adjuvant TMZ, 4) PORT alone. Median survival times of each sub-group were 22.7, 20.9, 15.5 and 10.9 months (p = 0.181) as shown in Figure 3.

In the aspect of RPA classification, class III cases showed the longest median survival time (MST) of 26.8 months (95% CI, 10.9-NA months) while class IV cases showed MST of 14.2 months (95% CI, 9.2-18.1 months), class V cases showed MST of 9.9 months (95% CI, 8.4-14.0 months) and class VI cases showed the MST of 4.0 months (95 % CI, 1.8-10.8 months)

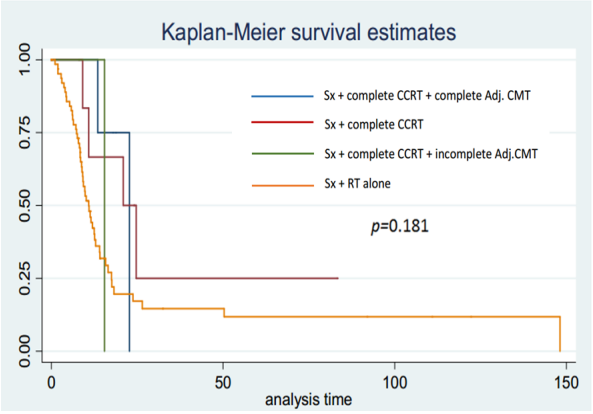

Figure 3. Mean Survival Time in Months of GBM in Each Treatment Modality

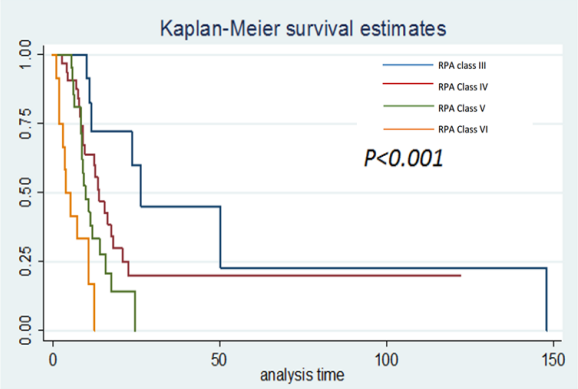

Figure 4. Survival Time of GBM Patients in Each RPA Classification (Months)

(p<0.001) as shown in Figure 4. The overall 2-year survival rates for RPA class III, IV, V and VI were 62.2%, 19.9%, 13.9% and 0%.

Discussion

The patients with post-operative TMZ concurrent with radiotherapy (CCRT) with adjuvant TMZ were interesting providing favorable survival outcomes in GBM (Zarnett et al., 2015; Illic et al., 2017; Binabaj et al., 2018). TMZ as alkylating agent reduces cellular activity of GBM both with a single agent and the combination of agents (Stupp et al., 2005; Hegi et al., 2005; Kesari et al., 2008; Hegi et al., 2008; Stupp et al., 2009; Prados et al., 2009). Currently, post-operative CCRT with adjuvant TMZ is the gold standard treatment for GBM (Stupp et al., 2005; Stupp et al., 2006; Hegi et al., 2008., Stupp et al., 2009).

The median survival time (MST) of all GBM cases in this present study was found to be 12 months (n=77; 95% confidence interval [CI], of 9.9-14 months). The 2 and 5 year-overall survival rates were 21.3% and 13.8%. The median survival times of the patient groups with PORT and post-operative CCRT with or without adjuvant TMZ were 11 and 23 months. (p = 0.03). The 2 and 5-years OS rates for these two groups were 17.2%, 11.8% and 38.2%, 19.1%. Stupp et al (Stupp et al., 2005; Stupp et al., 2009) studied in 573 GBM patients with an age range between 18 - 70 years and compared MST of each patient group. The first group had PORT and the second group underwent post-operative CCRT followed by 6 cycles of adjuvant TMZ. The MST showed 12.1 and 14.6 months and 2-year OS rates were 10.4% and 26.5% in the first and second groups. The MST tended to be significantly longer in the patient group with TMZ. The patients who had radiotherapy and TMZ from the other studies showed MST ranged from 9 to 21.7 months (Hegi et al., 2005; Hegi et al., 2008; Rock et al., 2012; Okumus et al., 2012; Ciammella et al., 2013; Teo et al., 2014; Yang et al., 2014) and 2-year OS rates ranged from 8 to 21.2 %.(Rock et al., 2012; Okumus et al., 2012; Ciammella et al., 2013; Teo et al., 2014; Yang et al., 2014).

The PORT patients of this study showed both the survival times and rates comparable to the studies of Stupp et al., (2005) and Stupp et al., (2009). The MST of the patients who had post-operative CCRT with or without adjuvant TMZ was better than the PORT group (p = 0.030) in this present study. In sub-group analysis, there were 4 groups of patients; 1) Surgery plus complete CCRT and adjuvant TMZ (4 cases, 5.2%), 2) Surgery plus complete CCRT (TMZ) (8 cases, 10.4%), 3) Surgery followed by complete CCRT with incomplete adjuvant TMZ (2 cases, 12.9%) and 4) Surgery plus PORT (63 cases, 81.8%). The first group showed the longest MST of 22.7 months. The second, third and fourth groups revealed MSTs of 20.9, 15.5 and 10.9 months (p = 0.181). This present study showed better results in post-operative CCRT cases with or without adjuvant TMZ. The data from RTOG classifications reported that MST of patients with RPA class III, IV, V and VI were 17.9, 11.1, 8.9 and 4.6 months and 2-year OS rates were 35%, 15%, 6% and 4% (Curran et al., 1993). This study revealed similar results as the RTOG trial. The patients with RPA class III, IV, V and VI showed the MSTs of 26.8, 14.2, 9.9 and 4.0 months (p < 0.001) and 2-year OS rates were 62.2%, 19.9%, 13.9% and 0%. The RPA class III had a longest MST and the best 2-year OS rate.

In conclusion, the MST of the patients who had post-operative CCRT with or without adjuvant TMZ was better than the PORT group. The RPA classification can be used to predict survival. While multimodality therapy demonstrated the most effective treatment outcome. Temozolomide might be beneficial for GBM patients in order to increase survival time.

Conflicts of interest

None.

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