Clinical Outcome of Postoperative Radiotherapy with or without Chemotherapy in Adult Glioblastoma Multiforme in Ramathibodi Hospital: A Retrospective Study

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Objective: *To identify the treatment outcome of glioblastoma multiforme (GBM) in Ramathibodi Hospital from overall survival rate and related prognostic factors.*

Material and Method: *Medical records of patients with histological diagnosis of GBM treated at Radiation Oncology Division, Radiology Department, Ramathibodi Hospital between 2000 and 2010 were reviewed and available data extracted for evaluation of treatment outcome.*

Results: *There were 47 patients with mean age at diagnosis of 51.9 years (range from 18 to 82 years). Surgery (partial 76.6%, total 12.8%, and biopsy 10.6%) followed by postoperative radiotherapy (mean dose 52 gray) was the treatment of choice with or without concurrent and adjuvant Temozolomide (TMZ). With median follow-up time of 0.9 years, the median survival of the patients was 2.1 years (95% CI 1.08-7.36), whereas one and two-year overall survival rates were 78.0% and 57.8%, respectively. In univariate analysis, persistent neurological deficit after surgery and presenting symptom of visual disturbance were identified to lower overall survival while multivariate analysis, younger age, and higher radiation dose were identified as favorable prognostic factors to improve overall survival. Re-surgery or re-irradiation in some selected cases of recurrent or progressive disease was considered as a choice for palliative treatment.*

Conclusion: *Proper management of GBM patient was surgical removal and postoperative radiotherapy with or without chemotherapy. Proper palliative treatment modality was considered in selected cases of recurrent or progressive disease.*

Keywords: *Glioblastoma multiforme (GBM), Radiotherapy, Postoperative*

J Med Assoc Thai 2014; 97 (6): 655-61
Full text. e-Journal: *http://www.jmatonline.com*

Glioblastoma multiforme (GBM) is classified as World Health Organization (WHO) grade IV gliomas with very poor prognosis from its aggressive behavior. The incidence mean age of diagnosis is 50 to 60 years old[1,2]. Most patients diagnosed with this tumor die within one year from the diagnosis and only 1 to 5% survives more than three years despite aggressive therapies[3-5]. Maximal surgical resection or biopsy with postoperative radiotherapy with or without chemotherapy has been established as the standard treatment[6]. In Ramathibodi Hospital, new cases of adult GBM is found around 10 cases per year while the real survival rate after treatment is still inconclusive[7]. The present retrospective study was designed to evaluate patients' medical record files diagnosed as GBM at age more than 18 years old and received radiotherapy at Radiation Oncology Division, Radiology department, Ramathibodi Hospital for the past 11 years. The objective of the present study was to demonstrate the overall survival rate after treatment and identify prognostic factors related to treatment outcome. It also aimed to improve understanding of natural history of GBM so as to make a proper management for each patient in the future.

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Material and Method

Ethic Clearance Committee on Human Rights Related to Researches Involving Human Subjects, Mahidol University, approved the protocol of the present study; protocol number ID 03-55-39. The available patients' medical record files were collected between 2000 and 2010 for evaluation of the results.

Within this time period, 47 patients were included into the study. Patient characteristics included

age >18 years, histological proven GBM, intention of curative radiotherapy with complete data for clinical, investigation, treatment and result of treatment.

Data collection

The clinical and treatment data were collected as follow:

1. Patient characteristics at the time of diagnosis including age, sex, performance status, recursive partitioning analysis (RPA)[8] and presenting symptom.

2. Detail of each treatment modality

a. Surgery: types of surgery, biopsy, partial or total tumor removal according to operative note.

b. Radiotherapy: dose per fraction (TD), total tumor dose (TTD), radiation technique, machine and completeness of treatment, chemotherapy (type of chemotherapy and concurrent and/or adjuvant)

c. Chemotherapy: Temozolomide (TMZ) or other chemotherapy given (concurrent, adjuvant, or both).

During or after completing the first treatment course, available clinical data, radiographic images, other treatments for progressive or recurrent disease (if presented) and date of last follow-up were evaluated for calculation of overall survival rate and related prognostic factors.

Statistical methods

Mean and standard deviation (SD) or median and range were used to describe continuous data, while frequency and percentage were used to describe categorical data. The Kaplan-Meier test was used to estimate the probability of survival and median time to survive after diagnosis. The log-rank test was used to compare survival distribution between different groups of each factor. The Cox proportional hazard model was used to determine the factors that might be associated with death after diagnosis by adjustment for confounding factors. The hazard ratio and its 95% confidence interval were estimated. All analyses were performed using STATA version 12. A *p*-value less than 0.05 was considered statistically significant.

Results

Forty-seven patients (male 44.7% and female 55.3%) with the mean age of 51.9 years (range 18-82 years) were included in the analysis. Patients' characteristics and treatment modalities are presented in detail in Table 1. Most of them presented with

Table 1. Patient characteristics and treatment

Characteristics	Total (n = 47) number of patients (%)
Sex	
Male	21 (44.7)
Female	26 (55.3)
Age (years), mean (SD)	51.9 (17.5)
<50	21 (44.7)
≥50	26 (55.3)
Karnofsky performance status (KPS)	
90-100	15 (31.9)
70-<90	28 (59.6)
<70	4 (8.5)
Presenting symptom	
Weakness	24 (51.1)
Visual change	3 (6.4)
Seizure	8 (17.0)
Headache	8 (17.0)
Personality change	4 (8.5)
Extent of surgery	
Biopsy	5 (10.6)
Partial tumor removal (PTR)	36 (76.6)
Total tumor removal (TTR)	6 (12.8)
Recursive partitioning analysis (RPA)	
3	10 (21.3)
4	18 (38.3)
5	19 (40.4)
Persistent neurological deficit after surgery (PNDS)	
Yes	31 (66.0)
No	16 (34.0)
Time to start radiation after surgery (TTRT)	
<3 weeks	12 (25.5)
≥3 weeks	35 (74.5)
Radiotherapy	
Tumor dose per fraction (TD) (Gy)	
≤2.0	45 (95.7)
>2.0	2 (4.3)
Total tumor dose (TTD) (Gy)	
<45	7 (14.9)
45-54.4	11 (23.4)
>54.4	29 (61.7)
Mean dose of radiation (Gy); median (range)	52.4 (19.8-60.9)
Radiation technique	
2 dimensional radiotherapy technique (2D)	7 (14.9)
3 dimensional radiotherapy technique (3D)	40 (85.1)
Chemotherapy	
Yes	29 (61.7)
No	18 (38.3)
Concurrent (alone)	7 (14.9)
Temozolomide (TMZ)	7 (14.9)
Adjuvant (alone)	7 (14.9)
TMZ	6 (12.8)
Carmustine (BCNU)	1 (2.1)
CCRT with adjuvant	15 (31.9)
TMZ	11 (23.4)
BCNU or vincristine (VCR)	4 (8.5)

RPA class V which only partial tumor removal was performed and persistent neurological deficit still detected after surgery. Postoperative radiotherapy was mostly performed by three-dimensional conformal radiotherapy (3DCRT) computerized planning after 3 weeks with mean total radiation dose of 52.4 gray (Gy) in five to six weeks (61.7% of cases received more than 54.4Gy in 6 weeks). Chemotherapy with TMZ was also added in most of the patients. No severe toxicity from the treatment was detected.

Table 2. Factor associate with overall survival (univariate analysis)

Factor	Total subjects	No. of death	Death rate/100/year	HR (95% CI)	*p*-value
Age (years)					0.009
<50	21	6	11	1	
≥50	26	11	40	3.8 (1.3-11.1)	
Presenting symptom					0.028
Seizure	8	3	11	1	
Weakness	24	8	40	4.7 (1.0-21.7)	
Visual change	3	2	87	15.4 (1.8-128.9)	
Headache	8	2	8	0.9 (0.1-5.5)	
Personality change	4	2	32	3.3 (0.5-23.2)	
RPA					0.007
3	10	3	7	1	
4	18	7	30	5.8 (1.1-29.2)	
5	19	7	49	10.2 (1.9-53.7)	
Type of surgery					0.622
PTR	36	11	18	1	
Biopsy	5	3	43	1.8 (0.5-6.6)	
TTR	6	3	23	0.9 (0.2-3.3)	
TTRT					0.402
≥3 weeks	35	11	20	1	
<3 weeks	12	6	24	1.5 (0.6-4.2)	
TTD (Gy)					0.002
<45	7	4	90	8.2 (1.7-39.3)	
45-54.4	11	3	15	1	
>54.4	29	10	18	1.4 (0.4-5.1)	
Type of technique					0.202
3D	40	13	20	1	
2D	7	4	25	2.1 (0.7-6.9)	
Chemotherapy					0.704
No	18	6	31	1	
Yes	29	11	18	0.8 (0.3-2.3)	
PNDS					0.009
No	16	6	11	1	
Yes	31	11	42	4.3 (1.3-13.9)	
Retreatment					
Re-irradiation					0.694
No	40	13	20	1	
Yes	7	4	28	1.3 (0.4-3.9)	
Re-surgery					0.151
No	39	15	26	1	
Yes	8	2	8	0.3 (0.1-1.6)	

HR = hazard ratio; RPA = recursive partitioning analysis; PTR = partial tumor removal; TTR = total tumor removal; TTRT = time to start radiation after surgery; TTD = total tumor dose; 2D = 2 dimensional radiotherapy; 3D = 3 dimensional radiotherapy; PNDS = persistent neurological deficit after surgery

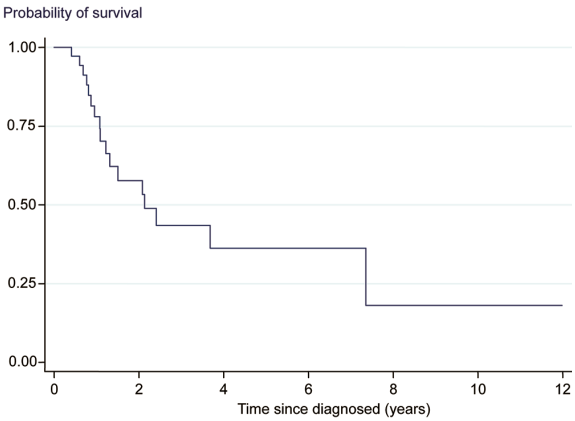

Fig. 1 Overall survival curve of patients by years since diagnosed.

The progressive cases during or after radiotherapy were managed by re-surgery or more complicated re-irradiation technique. At the time of this report (median follow-up time of 0.9 years, 17 patients (36.2%) were officially recorded as dead while seven patients (14.9%) were alive. The remaining patients (49.0%) were analyzed as dead at the time of last follow-up with the median survival time of 2.1 years (95% CI 1.08-7.36). The Kaplan-Meier estimated 1 and 2-year overall survivals for all patients were approximated around 78.0% and 58.0%, respectively (Fig. 1). In univariate analysis, the unfavorable prognostic factors including age ≥50 years, higher RPA, presenting symptom with headache, persistent neurological deficit after surgery and lower total tumor dose were identified related to lower overall survival (OS), whereas sex, Karnofsky performance status (KPS) and extent of surgery were not affected (Table 2). In multivariate analysis, total radiotherapy dose more than 45 Gy in five weeks and young age (<50 years) were proved related significantly to improved overall survival (Table 3).

Table 3. Multivariate survival analysis

Factor	Adjusted HR (95% CI)	*p*-value
TTD (Gy)		
<45	10.2 (2.52-41.43)	0.675
45-54.4	0.8 (0.20-2.80)	0.001
>54.4	1	
Age (years)		
≥50	5.3 (1.63-17.17)	0.005
<50	1	

TTD = total tumor dose

Re-treatment

Fifteen patients with clinical and image detected as progressive or recurrent disease received re-treatment by re-surgery (6 cases), re-irradiation (7 cases) or both modalities (2 cases) with poor survival outcome (only 3 cases lived more than 5 years post treatment).

Discussion

The proper management of GBM to improve survival outcome remains a challenging problem. Patient performance status and age at diagnosis are the major host factors to be considered for proper management. For tumor factors, many previous studies revealed the importance of relationship between gross total tumor resection and better survival outcome[2,9-12], but the rate of complete tumor resection was limited by the problems of diffusely infiltrative tumor behavior and complication risk of neurological dysfunction from surgery.

Postoperative radiotherapy for GBM with or without complicated technique is recommended in every case within two to four weeks after surgery or biopsy with the accepted dose of 50-60Gy in five to seven weeks[6,13-16] to improve local tumor control and survival compared to surgery alone[17]. However, prolonged starting postoperative radiotherapy is still inconclusive, whether it may affect survival or not[18,19]. Adjuvant chemotherapy also plays an important role in the management of GBM, especially TMZ which has been proved to significantly prolong survival in many reports[8,20-22].

From these reasons, the accepted proper management for GBM nowadays is maximal tumor removal with postoperative chemo-radiotherapy with the median overall survival around eight to ten months[2,23].

Re-treatment

The effective treatment for recurrent or progressive GBM is limited. Extent of second craniotomy is an important predictor of overall survival regardless of the initial resection[2,9]. Re-irradiation with fractionated stereotactic radiotherapy technique concomitant with TMZ is a feasible treatment option in selected patients[24].

The present retrospective study was limited by number of cases and some missing data in the patients' medical record files. The data cannot demonstrate the significant relationship between extent of surgery, prolonged starting postoperative

radiotherapy, and affected overall survival. However, some significant prognostic factors could be identified to improve treatment outcome and survival of patients (young age and high radiation dose).

The present report supports the basic concept of GBM, whose prognoses are dependent on both host (age) and treatment (radiation dose) factors with accepted overall survival compared to the others.

For the management of recurrent or progressive disease, although the data are not conclusive, second craniotomy seems to be a treatment of choice in some patients.

Conclusion

GBM, although presented with aggressive behavior and poor survival outcome, aggressive and proper management for patients still should be offered to improve quality of life as much as possible. In the case of progressive disease during or after complete treatment, re-surgery or re-irradiation with more complicated technique is considered as a palliative treatment in some selected cases.

The result of the present study is helpful to be used as a basic guidance for selection of a proper management for GBM patients.

What is already known on this topic?

Glioblastoma multiforme was already known for its aggressiveness brain malignancy. The standard management nowadays is surgery with postoperative radio-chemotherapy to improve survival. The known prognostic factors include tumor factor and treatment factors. For radiotherapy, the radiation dose and technique were varies.

What this study adds?

The present paper is the first study of glioblastoma multiforme in Thailand about natural history and response to treatment with radiotherapy that included patients after an introduction of temozolomide. It reflected the past management in these patients and hope to initiate the improvement of the treatment both dosage and radiotherapy technique.

Acknowledgement

The authors wish to thank Professor Amnuay Thithapandha for his help with the English editing.

Potential conflicts of interest

None.

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ผลลัพธ์ทางคลินิกการฉายรังสีหลังผ่าตัดและ/หรือร่วมกับเคมีบำบัดผู้ป่วยโรคมะเร็งสมองชนิดกลัยโอบลาสโตมา มัลติฟอร์เม ที่โรงพยาบาลรามาธิบดี: การศึกษาย้อนหลัง

ภรมน พุทธิการันต์, ธิติ สว่างศิลป์, มัณฑนา ธนะไชย, ลดาวัลย์ นาควงศ์, ชมพร สีตะธนี, พุฒิพรรณ พัวทวีพงศ์, ชุลีพร เจียรพินิจนันท์, ปฐมิณฑิตา วิทูรพณิชย์, รวี เรืองกาญจนเศรษฐ์

วัตถุประสงค์: *เพื่อศึกษาผลลัพธ์จากการรักษาโรคมะเร็งชนิดกลัยโอบลาสโตมา มัลติฟอร์เม โดยประเมินอัตราการรอดชีวิตโดยรวมและปัจจัยที่มีผลต่อการพยากรณ์โรค*

วัสดุและวิธีการ: *เป็นการศึกษาย้อนหลังโดยรวบรวมข้อมูลทางคลินิกจากเวชระเบียนของผู้ป่วยที่ได้รับการวินิจฉัยว่าเป็นโรคที่โรงพยาบาลรามาธิบดี ตั้งแต่ปี พ.ศ. 2543 ถึง พ.ศ. 2553เพื่อประเมินผลการรักษาและอาการทางคลินิก*

ผลการรักษา: *พบผู้ป่วย 47 ราย อายุอยู่ในช่วง 18-82 ปี เฉลี่ย 51.9 ปี ได้รับการผ่าตัดก้อนมะเร็งออกได้บางส่วน 70.6% ผ่าตัดออกได้ทั้งหมด 12.8% และมีอัตราส่วนผู้ป่วย 10.6% ที่ได้รับเพียงการผ่าตัดชิ้นเนื้อเพื่อพิสูจน์ ผู้ป่วยทั้งหมดได้รับการฉายรังสีหลังการผ่าตัด ปริมาณรังสีที่ได้รับมีค่าเฉลี่ย 52 เกรย์ และมีผู้ป่วยบางส่วนได้รับยาเคมีบำบัดเทโมโซโลไมด์ ที่ระยะเวลาติดตามเฉลี่ย 1 ปี พบว่ามีระยะเวลารอดชีวิตเฉลี่ย 2.1 ปี และอัตราการรอดชีวิตที่ 1 และ 2 ปี เท่ากับ 78% และ 57.8% ตามลำดับ ปัจจัยที่มีผลต่อการรอดชีวิตคือ อายุของผู้ป่วยและปริมาณรังสีที่ได้รับ ในกลุ่มผู้ป่วยที่มีโรคแผ่ขยายหรือกลับเป็นซ้ำ อาจพิจารณาการรักษาเพิ่มโดยการผ่าตัดหรือฉายรังสีซ้ำ*

สรุป: *การรักษาผู้ป่วยมะเร็งสมองชนิดกลัยโอบลาสโตมา มัลติฟอร์เม ประกอบไปด้วยการฉายรังสีหลังผ่าตัด และ/หรือ ร่วมกับการให้ยาเคมีบำบัดส่วนในกรณีมีโรคแผ่ขยายหรือกลับเป็นซ้ำอาจพิจารณาวิธีการรักษาที่เหมาะสมเพื่อบรรเทาอาการสำหรับผู้ป่วยเป็นราย ๆ ไป*