Clinical Features, Management and Outcomes of high-grade glioma patients in Ramathibodi Hospital

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Objective*: To identify prognostic factors for survival and evaluate the effect of treatment on survival of patients with high-grade glioma treated at Ramathibodi Hospital.*
Material and Method*: Medical records of patients with diagnosis of high-grade glioma registered in Ramathibodi cancer registry were reviewed. A total of 36 patients were reviewed, only 27 patients were included on survival analysis.*
Results*: Of the 36 patients, the male: female ratio was 1:1. Mean age of diagnosis was 41.86 years (range 18-71 years). Histological findings were anaplastic glioma (22.20%), glioblastoma multiforme (63.90%) and mixed glioma (13.90%). Of fifteen patients underwent total tumor removal, 17 patients had partial resection and in 4 cases biopsy alone was done. Two third of the patients had received radiotherapy with mean total dose 5,372 cGy. Nine patients also received chemotherapy (6 temozolomide and 3 BCNU). Median follow-up time was 413.2 days. An overall survival time was 604.04 days and median disease free survival time was 402.45 days. In univariated analysis, the following favorable prognostic factors were identified: histological findings of glioblastoma multiforme (GBM) and mixed glioma, received radiotherapy. In multivariate analysis, radiotherapy improves overall survival significantly. Re-resection at recurrence did not appear to improve overall survival.*
Conclusion*: Adult high-grade glioma had poor prognosis despite aggressive treatment. Radiotherapy significantly improved survival while surgical tumor removal and chemotherapy did not. However due to the small number of patients the further studies should be performed.*

Keywords: *Malignant Glioma, Temozolomide*

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The incidence of primary brain tumors are about 10-19 cases per 100,000 of all malignant disease. The most common histology of primary malignant brain tumor is Glioma[1] that composed of low grade and high grade types. The high grade gliomas are grade III anaplastic astrocytoma (AA), grade IV glioblastoma multiforme (GBM) and mixed glioma. GBM is diagnosed 15-20% of all adult brain tumors and has high incidence in children and at age 50-60 years. The tumor registry of Ramathibodi Hospital in 2003 shows an incidence of adult with brain tumor is 70 cases and 17 cases were high-grade glioma[2] .

The high grade glioma patient has a standard therapy by received surgical resection and adjuvant radiotherapy. The treatment by adjuvant chemotherapy shows significant prolongation of survival and 15% relative decrease in the risk of death[3]. The new chemotherapy drug is temozolomide, an oral drug of alkylating agent chemotherapy, has recently been introduced for treat the high grade glioma patients. In recurrent glioma, temozolomide improve survival, safety and well tolerated[4]. In addition, a concurrent treatment of temozolomide and radiotherapy improve median survival from 12.4 months to 14.6 months[5]in new diagnosed high

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grade glioma patients.

In Ramathibodi, this retrospective study of adult high-grade glioma was undertaken to improve our understanding of the natural history of high-grade glioma, identified prognostic factors for survival and evaluate the effect of treatment on survival.

Material and Method

A retrospective review of the clinical records of patients diagnosed with high grade glioma (anaplastic glioma, glioblastoma multiforme, mixed glioma) from January 1994 to June 2005 was performed. 36 patients registered in Ramathibodi cancer registry were reviewed for age of incidence, sex, primary site, and symptoms at presentation, pathological finding, investigation and treatment. All patients were investigated by CT or MRI brain. Histological diagnosis was established on hematoxylin-eosin stained slides, classified by WHO classification of brain tumor[6].

Inclusion criteria

1. Histological proven malignant (high grade) glioma

2. Age > 15 years

3. Complete data for clinical, investigation treatment, and result of treatment

Data collection

The following clinical data were collected

1. At the time of diagnosis: age, sex, duration of symptom, main symptoms and sign, description on CT/MRI brains, pathological reports

2. Treatment administered at diagnosis of tumors

3. During follow-up: clinical and radiological course, treatment at recurrent, date and cause of death or date of the last visit if the patients were alive.

The radiological response to radiotherapy and chemotherapy was reported as[7]

- Complete response: disappearances of all tumors in imaging that were made following the complete of treatment.

- Partial response: a decrease of > 50% in the axial cross section of the greatest surface area.

- Progressive disease: > 25% increase in the axial cross section of the greatest surface area or have news lesions.

- Stable disease: all other situations.

Statistical analysis

A survival time was measured from the date of initial tissue diagnosis to the date of last follow-up or death. A disease free survival time was measure from the time of diagnosis to first failure or death as a result of any cause. A survival time was estimated by the Kaplan-Meier method and its 95% confidence interval. A survival curves were compared with a log rank test. The following parameters were evaluated for their association with survival: age of onset, sex and duration of symptoms, pathological report, radiotherapy and chemotherapy. The Cox proportional hazards model was used to test prognostic factors in multivariate analysis.

Results

Patient population

Between January 1994 and June 2005, 36 patients were diagnosed with high-grade glioma. The patients' characteristics are outlined in Table 1. The symptoms and sign of patients were presented in Table 2.

There were 27 patients received radiotherapy, 9 patients were not treated (6 patients neglect treatment, 1 patient loss follow-up and 2 patients had clinical instability and not proper to receive treatment). All cases were received external beam whole brain radiation and a mean dose of radiation was 5372 cGy.

There were 9 patients received chemotherapy (3 cases for BCNU, 6 cases for temozolomide). The regimens of chemotherapy were showed in Table 3.

Overall survival time and disease free survival time

A median follow-up time was 413 days. Because of 7 patients could not complete data of survival time, only 29 patients were included in the survival analysis. There were 18 patients died at the time of analysis. In 29 patients overall survival was 604 days and disease free survival time was 402 days.

Patients who received total tumor removal operation had median survival time of 1,075 days. But the median survival time of patients who had residual tumor after receiving operation was 847 days. There is not significantly difference between two groups of patients ($p = 0.841$). There was no significant survival time in types of chemotherapy regimens ($p = 0.213$). A univariate analysis and multivariate analysis of overall survival and disease free survival are shown in Table 4 and 5.

Treatment after disease progression

The median disease free survival time of patients was 402 days. If disease progression occurred, further treatment was depended on the physician's

Table 1. Patient characteristic

Characteristics	Number of patients
Sex (male: female)	18:18
Mean age (years)(range)	41.8 (18-71)
Histology (case)	
Glioblastoma multiforme	23
Anaplastic glioma	8
Mixed glioma	5
Tumor location (case)	
Frontal	14
Temporal	9
Temporo-pareital	4
Parietal	5
Brainstem	3
Pineal	1
Previous histology of low grade glioma (case)	1/36
Treatment before recurrent	
Extent of surgery (case)	
Total resection	15
Partial resection	17
Biopsy	4
Radiotherapy (case)	
Radiotherapy at Ramathibodi	22
Radiotherapy at other hospitals	5
Not received radiotherapy	9
Mean dose of radiation (Gy)	53.72 cGy
Chemotherapy (case)	9/36

Table 2. symptom and sign at presentation

Symptom and sign at presentation	Number of patients
Symptom	
Headache	69.4%
Seizure	19.4%
Weakness	27.7%
Numbness	2.8%
Alteration of consciousness	8.3%
Cognitive impairment	5.6%
Visual impairment	8.3%
Sign	
Normal	25.0%
Cranial nerve lesion	19.4%
Hemi paresis	8.9%
Increase intracranial pressure	38.3%
Other signs	8.4%

decision. There were 15 patients with disease progression and only 5 patients underwent a second surgery (partial tumor removal) which did not significantly improved in survival time.

Discussion

The high grade glioma is the most common primary brain malignant tumor in adults[8]. On patients who received surgery treatment and radiotherapy, a malignant glioma remains a fatal disease characterized by rapidly and devastating clinical course. Only approximately 15% survived beyond 2 years and less than 5% survived more than 5 years[9]. The median survival time for patients with GBM is 9-12 months. The major prognostic factors in Brain Tumor Cooperative Group trials are young age and good performance status[10]. In the WHO classification, the mitotic activity, the presence of micro vascular proliferation and necrosis were use to differentiate between GBM and AA. The micro vascular proliferation was associated with a significant shorter survival[11]. In this study, histological subtypes (glioblastoma multiforme and mixed glioma) and radiotherapy are favorable factors.

The treatment of high grade glioma was multimodality that surgical treatment had a critical role in the management of patients with newly diagnosed high-grade glioma. There was no prospective randomized trial of surgery compared with extent of resection[12]. There was retrospective study that showed the relation between the extent of resection and survival for high-grade glioma. The median survival for complete resection was longer than partial resection and biopsy[13,14]. But all retrospective reviews were subjected to selection bias because the extent of attempted resection was greatly influenced by the condition of patient, size and location of the tumor. However, in our study there is not different in median survival time of total resection or no resection ($p = 0.613$). A randomized trial by the medical Research Council found an improvement in median survival of 9-12 months when 60 Gy of external beam radiotherapy compared with 45 Gy[15]. The mean of radiation dose response that made survival advantage for high-grade glioma was 60 Gy[15]. Our study shows that radiotherapy results in a favorable survival outcome. More than 30 years, chemotherapy was given as an adjuvant to radiotherapy but it had limited success. A meta-analysis based on 12 randomized trials suggested a small survival benefit of chemotherapy treatment when compared with radiotherapy treatment alone[3].

In additional, there is a new chemotherapy that was used in treatment for GBM, Temozolomide. It is an oral cytotoxic agent of imidazotetrazine class that

Table 3. Characteristics of patients that received chemotherapy

No./Year	Histology	Surgery	RT (cGy)	Chemotherapy drug	Regimen of treatment	Result (days)	
						OS	DFS
1/2545	AA	Biopsy	5900	BCNU	Adjuvant treatment	958	958
2/2542	GBM	Partial	5400	BCNU	Adjuvant treatment	No	Data
3/2541	GBM	Partial	No data	BCNU	Adjuvant treatment	729	583
4/2546	GBM	Total	No data	Temozolomide	Adjuvant treatment	79	79
5/3547	GBM	Partial	6000	Temozolomide	Concurrent but no adjuvant treatment	386	218
6/2547	GBM	Total	5940	Temozolomide	Concurrent but no adjuvant treatment	111	67
7/2545	GBM	Partial	6300	Temozolomide	Concurrent but no adjuvant treatment	287	287
8/2546	GBM	Total	5400	Temozolomide	Treatment for recurrent	572	512
9/2545	GBM	Partial	5400	Temozolomide	Treatment for recurrent	426	330

*AA = anaplastic glioma **GBM= glioblastoma multiforme, OS = overall survival, DFS = disease free survival

Table 4. Univariate analysis in Overall survival and Disease free survival

Factors	Overall survival p	Disease free survival p
Age < 40	0.937	0.491
Pathology	0.019	0.015
Surgery total remove	0.841	0.613
Radiation	0.01	0.002
Chemotherapy	0.213	0.449

Table 5. Multivariate prognostic factors for Overall survival and Disease free survival

Factors	Overall survival p	Disease free survival p
Pathology	0.133	0.063
Radiotherapy	0.003	0.003

is chemically related to dacarbazine. It is rapidly and completely absorbed after oral administration; peak plasma concentrations occur in 1 hour and have good blood-brain barrier permeability achieving cerebrospinal fluid concentrations that are 20%-40% of plasma level[16,17]. In The US Food and Drug Administration approved temozolomide for the treatment of adult patients with refractory patient group of AA in 1999[4] and approved for newly diagnosed GBM patients on March 15, 2005[18]. Other chemotherapy drugs, BCNU, CCNU; Vincristine were not shown benefit[19].

Although our study shows the survival time of patients who received chemotherapy was shorter when compared with whole patients but this study had only 9 patients who received chemotherapy by the less number of patients, further study should be investigated. The results of treatment of patients are poor. A long-term control of high-grade glioma is rarely achieved, despite the patients received a surgical resection and external beam radiotherapy but GBM still recurred within 6-10 months[20]. Our study 15 patients had recurrent disease within 346 days; survival was not different between those who received treatment by re-surgery (5 cases of partial resection) and those who received supportive treatment.

There are many limitations in this study. Firstly, it is the incompleteness of retrospective data (data of performance status, dose of steroids treatment, performance status after treatment, quality of life). Secondly, the number of patients enrolled was too small. Thirdly, it had a selection bias because the treatment was selected by the condition of patients and economical status. Due to Temozolomide is not included in universal payment drug list; it could not be prescribed for all patients that fulfill indication. There

is a study that showed cost effectiveness of treatment by temozolomide in recurrent malignant glioma was accepted[21]. However, in Thailand there are no studies to prove cost effectiveness of this drug.

Conclusion

Adult high-grade glioma had poor prognosis despite aggressive treatment. Radiotherapy significantly improved survival while surgical tumor removal procedure and chemotherapy did not. However due to the small number of patients the further studies should be performed.

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การศึกษาย้อนหลังของอาการทางคลินิกของผู้ป่วยโรคมะเร็งสมองกลัยโอมาที่โรงพยาบาลรามาธิบดี

พิชัย จันทร์ศรีวงศ์, ธิติยา สิริสิงห

วัตถุประสงค์*: เพื่อศึกษาลักษณะของผู้ป่วย อาการแสดงทางคลินิก วิธีการรักษาและผลการรักษาโรคมะเร็งสมองชนิดกลัยโอมาที่รับการรักษาที่โรงพยาบาลรามาธิบดี*

วัสดุและวิธีการ*: เป็นการศึกษาย้อนหลัง โดยรวบรวมบันทึกข้อมูลทางคลินิกจากฐานข้อมูลที่โรงพยาบาลรามาธิบดี ตั้งแต่ปี พ.ศ. 2537-2548 โดยรวบรวมข้อมูลพื้นฐานอาการแสดงทางคลินิก วิธีการรักษาและผลการรักษา*

ผลการศึกษา*: พบผู้ป่วย 36 ราย (หญิง:ชาย 18:18) อายุระหว่าง 18 ถึง 71 ปี (อายุเฉลี่ย 41.86 ปี) อาการของโรคที่พบบ่อย คือปวดศีรษะ, อาการแขนขาอ่อนแรงและอาการชักเกร็ง ผลการตรวจทางพยาธิวิทยาแบ่งเป็นมะเร็งชนิด อะนาพลาสติกกลัยโอมา 8 ราย, มะเร็งชนิดกลัยโอบลาสโตมามัลติฟอร์เม 22 ราย และมะเร็งที่มีทั้งสองกลุ่มรวมกัน 5 ราย ผู้ป่วย 15 ราย ได้รับการผ่าตัดก้อนมะเร็งออกได้ทั้งหมด ผู้ป่วย 17 ราย ได้รับการผ่าตัดมะเร็งได้เพียงบางส่วน และมี 4 ราย ที่ได้รับเพียงการผ่าตัดชิ้นเนื้อ ผู้ป่วย 27 ราย ได้รับการรักษาด้วยรังสีรักษา ปริมาณรังสีที่ได้รับมีค่าเฉลี่ย 5,372 เซนติเกรย์ ผู้ป่วย 9 ราย ได้รับยาเคมีบำบัด คือ 3/9 รายได้รับยาบีซีเอนยู 6/9 ราย ได้รับยาทีโมโซลามายด์ระยะเวลารอดชีวิตเฉลี่ยคือ 604.04 วัน ปัจจัยที่มีผลต่อการรักษาคือการรักษาด้วยรังสีรักษา แต่ผลความสมบูรณ์ของการผ่าตัด และการรักษาด้วยยาเคมีบำบัดไม่มีผลกระทบในการรักษา*

สรุป*: มะเร็งสมองชนิดกลัยโอมาเป็นมะเร็งที่มีความรุนแรงของโรค การรักษาด้วยรังสีรักษามีผลช่วยเพิ่มระยะเวลาการกลับเป็นซ้ำของโรคและเพิ่มระยะเวลารอดชีวิตของผู้ป่วย โดยผลของการผ่าตัดในการตัดก้อนเนื้องอกออกได้หมดและการรักษาด้วยยาเคมีบำบัดไม่มีผลในการรักษา แต่เนื่องจากข้อจำกัดของปริมาณผู้ป่วยจึงควรมีการศึกษาเพิ่มเติม*