

A Multivariate Analysis of Patients with Glioma: A Treatment Outcome and Prognostic Factor for Survival

Chaiyot Siangprasertkij MD*,
Yot Navalitloha MD PhD*

* Division of Neurological Surgery, Department of Surgery, Faculty of Medicine, Chulalongkorn University, Bangkok

Objective: To evaluate the treatment outcome and to examine the influence of factors on survival of patients with glioma.

Material and Method: One hundred and eighty-nine patients were included. Data on the patient's age, sex, KPS score, tumor location and survival time were collected and analyzed.

Results: Tumor grade and age had effect on survival of the patients. The median survival time (MST) of patients with grade II-IV glioma was 80.0, 20.0 and 9 months, respectively. Only the tumor site had influence on survival of patients with grade II glioma. In patients with grade III glioma, only KPS score had an impact on survival. In patients with grade IV glioma, none of the factors had an effect on survival.

Conclusion: The treatment outcome of the patients in Chulalongkorn University is comparable to other series. Multivariate analysis identified factors that had influence on survival of the patients.

Keywords: Treatment outcome, Glioma, Survival

J Med Assoc Thai 2008; 91 (4): 491-6

Full text. e-Journal: <http://www.medassocthai.org/journal>

Glioma, an inclusive term for neoplasms of glial heritage, includes astrocytoma, oligodendroglioma and mixed oligoastrocytoma. They account for 42% of all primary CNS tumors and 77% of all malignant primary CNS tumors⁽¹⁾. The modern system of classification recommended by the WHO⁽²⁾, which classifies gliomas according to principle cell type, degree of differentiation, and defined several microscopic features that were associated with aggressive behavior⁽³⁾, considering them grade I-IV on the basis of increasing degree of malignancy. Classified as grade I, are three relatively different tumors: pilocytic astrocytoma, pleomorphic xanthoastrocytoma, and subependymal giant cell astrocytoma. This group of tumors has a low malignant potential with infrequent anaplastic progression and a more circumscribed growth pattern with limited microscopic infiltration of adjacent brain. These two properties, in combination, result in a more favorable prognosis for this group than for others.

Grade II gliomas are characterized by the presence of diffuse growth of well differentiated neoplastic glial cells. This group of tumors has significant potential to undergo anaplastic progression (grade III) and a high capacity for brain invasion with diffuse tumor cell infiltration beyond the macroscopic tumor into normal brain tissue. Finally, glioblastoma multiforme is classified as grade IV. The tumor is characterized by a heterogeneous histomorphological appearance within a single tumor, which often makes it difficult to determine its histological origin. The characteristic histology is defined by the presence of anaplastic features plus microvascular proliferation, necrosis, and pseudopalisading.

These types of primary CNS tumors are difficult to treat and generally considered incurable with the exception of the completely resected pilocytic astrocytoma⁽⁴⁾. The prognosis of these patients is affected by several factors, including the histological grading, the age of the patient, anatomical location and the functional status of the patient^(5,6). The authors' strategies for the treatment of these tumors are to perform surgery (either biopsy or safe, maximized tumor resection),

Correspondence to: Navalitloha Y, Division of Neurological Surgery, Department of Surgery, Faculty of Medicine, Chulalongkorn University, Bangkok 10330, Thailand. Phone & Fax: 0-2256-4105, E-mail: dr.yotm@gmail.com

followed by radiation therapy in grade II-IV tumors (with exception in children) and chemotherapy, using Temozolomide in grade III-IV tumors (since July 2005). The purpose of the present study was: 1) to evaluate the treatment outcome of patients with glioma at a single institution; 2) to examine the influence of factors on the length of survival by using multivariate analysis; and 3) to estimate survival of patients with grade III and IV gliomas prior to using Temozolomide as a concomitant therapy with radiation.

Material and Method

A total of 189 patients who underwent surgery for newly diagnosed supratentorial glioma between January 2001 and June 2005 in the authors' division were included. Patients with gliomatosis cerebri, oligodendroglioma or mixed oligoastrocytoma (because it has been well documented that these tumors have different natural history and prognosis from astrocytoma⁽¹⁾), those who did not comply with the authors' treatment plan and those who died within 30 days after initial surgery (perioperative mortality = 4.7% in total) were excluded from the present study. The authors reviewed the medical records to obtain information on the patients and treatment characteristics. Data on the patient's age, sex, KPS score, and tumor location at the time of presentation were collected. Patients were categorized using the WHO grading system. Age and KPS score were dichotomized. Age was dichotomized at 50 years as that in the Radiation Therapy Oncology Group (RTOG) Recursive Partitioning Analysis (RPA), which identified that age > 50 years was an important prognostic factor negatively correlating with survival⁽⁷⁾. KPS score was dichotomized at less than 80 because previous studies have shown that patients with KPS score \geq 80 had a greater survival probability than those with a KPS score of < 80^(8,9). Tumor location was defined using grading system described by Sawaya et al⁽¹⁰⁾ (Table 1).

Survival time was calculated from the date of first treatment until the date of death from any cause.

All enrolled patients were observed for survival. Patients still alive were censored at the end of June 2007. Survival curves were analyzed using the Kaplan-Meier method and the log-rank test. The interaction of each variable and its effect on survival were analyzed using the Cox proportional hazards model. All statistical analyses were done using the Statistical Package for the Social Sciences 13.0 (SPSS, Inc., Chicago, IL). A p value below 0.05 was regarded as significant.

Results

Clinical pretreatment factors included in the present study were: 1) age; 2) gender; 3) KPS score; 4) tumor site; and 5) extent of surgery. Table 2 summarizes the patients and treatment characteristics categorized by WHO grading system. Minimum follow-up time in the present study was 24 months with the median follow-up time 26 months. Mean age of the patients with grade I glioma was 18.6 ± 15.4 years (range, 7 months to 71 years). All patients with grade I glioma are alive, regardless of characteristics (with follow-up time of 24 months to 75 months). Therefore, the survival time and influence of factors on the survival of these patients cannot be calculated and analyzed. Thus this group of patients was not included in the subsequent analyses.

Patients with grade II-IV gliomas had a mean age of 36.4 ± 15.4 years (range, 3 to 80 years), 42.3 ± 17.5 years (range, 4 to 64 years), and 49.4 ± 18.6 years (range, 5 to 83 years), respectively. Fig.1 shows the survival curve of patients with grade II-IV gliomas. The MST of patients with grade II-IV glioma from the date of first treatment was 80.0 ± 0.0 (95% CI = 0), 20.0 ± 5.3 (95% CI 9.6-30.4) and 9 ± 1.0 (95% CI 15.9-28.1) months, respectively. The log rank test confirmed that tumor grade did impact on survival of these patients ($p = 0.00$). Then the Cox proportional hazards model was used to identify other factors that could have independently influenced survival. On univariate Cox analysis, tumor grade, age and KPS score did impact on survival of these patients (all $p = 0.00$). When a multivariate

Table 1. Grading of intraparenchymal tumors according to functional location⁽¹⁰⁾

Grade	Location
I: noneloquent brain	frontal or temporal pole of cerebrum, right parietooccipital lobe, cerebellar hemisphere
II: near eloquent brain	near motor or sensory cortex, near visual cortex, near language center, corpus callosum, near brainstem, near deep cerebellar nucleus
III: eloquent brain	motor or sensory cortex, visual center, language center, internal capsule, basal ganglia, hypothalamus or thalamus, brainstem, deep cerebellar nucleus

Table 2. Patient characteristics categorized by WHO grading system

		WHO Grade			
		I (n = 47)	II (n = 55)	III (n = 22)	IV (n = 65)
Age (years)	<50	45	46	13	2
	≥50	2	9	9	36
Sex	M	27	33	13	36
	F	20	22	9	29
KPS score	50-70	31	9	9	37
	80-100	16	46	13	28
Location	I	23	40	14	37
	II	20	13	3	20
	III	4	2	5	8
Surgery	B	2	5	2	5
	STR/GTR	12/33	31/19	13/7	42/18

M, male; F, female; KPS, Karnofsky performance status; B, biopsy; STR, subtotal tumor resection; GTR, gross total tumor resection

analysis was done, it was found that gender, KPS score, tumor site, and extent of surgery except tumor grade and age had no effect on survival ($p = 0.99, 0.13, 0.89, 0.91, 0.00,$ and $0.01,$ respectively).

Once univariate and multivariate analysis were done on patients with grade II glioma, only tumor site was found to have influence on survival (both $p = 0.02$). In patients with grade III glioma, only KPS score had an impact on survival in both univariate and multivariate analysis ($p = 0.00$ and 0.03). In patients with

grade IV glioma, none of the factors had an effect on survival.

Discussion

The treatment of patients with glioma has widely variable outcomes based on many clinical characteristics such as age, performance status, histology, progress-free survival time, tumor site and degree of its resectability, type of adjuvant therapies and use of concomitant medication. Besides histological grading, only age, KPS score, and extent of resection have been proven to be prognostic factors for survival^(11,12). As shown in Table 2, some subgroups in the present study comprised a relatively small number of patients, so the discriminative power of the analyses is limited. Thus, the present results might be different from other larger studies and need to be interpreted with some reservation.

The present study focused on the factors related to survival rather than on progression-free survival (PFS) because the survival end point is indisputable in contrast to the frequently used 6-month PFS, which is difficult to determine due to inconsistent interval time of follow-up and imaging study.

It has been universally accepted that tumor grading inversely affects survival of the patients. Outcomes of patients with grade I glioma are generally excellent, particularly for those who undergo a gross-total resection. Most patients can have a normal or near-normal neurological condition after treatment with reported 10-year survival approaching 100%⁽¹³⁻¹⁵⁾. Outcomes of patients with grade II-IV gliomas are not

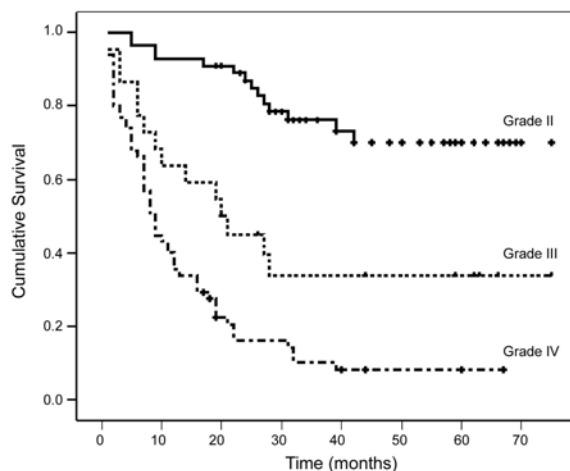


Fig. 1 A graph showing Kaplan-Meier survival curve of 142 patients with newly diagnosed intracerebral glioma plotted according to the WHO grade II-IV. The log rank test demonstrated that tumor grade did impact on survival of glioma patients ($p = 0.00$)

as good as it is in those with grade I glioma. It has been reported that the MST of patients with grade II-IV glioma, on average, were 3-5 years⁽¹⁶⁾, 20-30 months⁽¹⁷⁾ and about 9-12 months⁽¹⁸⁾, respectively. The presented treatment outcomes of the patients are comparable to other studies.

Age has been investigated for decades as a prognostic factor in glioma, especially in grade IV. Authors used a different age range to include patients into their studies, while some did not analyze the influence of age on the treatment outcome. Nevertheless, many studies found that younger age correlated with longer survival/PFS⁽¹⁹⁾. Some suggested that gliomas in older patients had greater proliferate potential than those in younger ones. Age may also influence the selection of patients for surgery with younger patients likely to have more extensive tumor resection⁽²⁰⁾.

Performance status of patients reflects physical and neurological conditions of patients. Even though various studies have different scoring systems and timing of evaluation, there is substantial evidence to show that performance status of patients is one of the stronger prognostic factors of treatment outcome. Better performance status has consistently been found to have a favorable effect on survival in numerous studies made in the last decade⁽¹⁹⁾.

Tumor location as a prognostic factor is arguable due to the different designations of tumor location used. Some studies compared frontal tumor to other tumor location or superficial to deep-seated location, while others used the separation between frontal, parietal, temporal, and occipital^(8,19). Tumor location might affect the treatment outcome of these patients due to the fact that superficial or frontal location is more accessible and could be removed more extensively than others. The authors decided to use the system described by Sawaya et al⁽¹⁰⁾ (Table 1) in the present study, because it has both anatomical and functional attributes. Some superficial locations are vital areas that cannot be removed in order to preserve neurological function. Thus, this system could have more profound impact on survival of the patients than others.

Extent of surgery for these patients is also partially affected by tumor location. Tumor in eloquent areas may only undergo biopsy or partial resection, whereas lesions in noneloquent brain regions may be more aggressively removed. The influence of the extent of surgery on survival of these patients, however, is still debatable. The definition of the extent of surgery depends on the neurosurgeon's impression of

resectability and estimation of both pre- and post-surgical tumor burden is subjective and inaccurate. More radical tumor resection should theoretically lead to better results from a cytokinetic point of view⁽²¹⁾. When the surgeon's subjective impression on resectability combined with inaccuracy to delineate the remaining tumor, it could explain why conflicting results concerning a benefit for more radically resected patients exist^(22,23).

Recent advances in molecular biology have revealed that tumors within the same WHO grade could have different genetic alternations and abnormalities in cellular pathways and functions causing them to dissimilarly behave. To make matters more complicated, the cellular heterogeneity of tumor cells within the same grade is not the only issue to consider. Heterogeneity in the intratumoral microenvironment and physiological properties between and within a tumor itself such as the blood-tumor barrier, interstitial fluid pressure, blood supply, could affect the treatment response of the tumor in varying degrees contributing in turn to initial treatment failure or early disease progression^(24,25). Thus, treatment of these tumors with the same radiation or chemotherapeutic dose might not be appropriate. Knowledge of these tumor biology and physiology should be used to stratify tumors and design the best treatment protocol for each individual tumor.

Conclusion

The treatment outcome of patients with gliomas in the authors' institute is comparable to other larger series. This multivariate analysis identified factors that had influence on survival of patients with gliomas in our institute. Future treatment plans of these tumors should incorporate all possible information regarding tumor biology and physiology and use this information to design the treatment protocol that is most beneficial to individual patients. It is hoped that this would ultimately lead to a cure.

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ผลการวิเคราะห์ทางสถิติแบบหลายตัวแปรในผู้ป่วยเนื้องอกสมองกลัยโอมา: ผลการรักษาและปัจจัยที่มีผลต่อระยะเวลาในการดำรงชีวิตของผู้ป่วย

ชัยยศ เสียงประเสริฐกิจ, ยศ นวฤทธิไธยะ

วัตถุประสงค์: เพื่อศึกษาถึงผลการรักษาและปัจจัยที่มีผลต่อระยะเวลาในการดำรงชีวิตของผู้ป่วยโรคเนื้องอกสมองกลัยโอมา

วัสดุและวิธีการ: ผู้ป่วยที่นำมาศึกษามีจำนวน 189 คน ข้อมูลที่ได้ทำการเก็บรวบรวมและนำมาวิเคราะห์ ได้แก่ อายุ, เพศ, คะแนน Karnofsky performance status (KPS), ตำแหน่งของเนื้องอก และระยะเวลา ในการดำรงชีวิตของผู้ป่วย

ผลการศึกษา: ลำดับชั้นของเนื้องอกและอายุมีผลต่อระยะเวลาในการดำรงชีวิตของผู้ป่วยค่าเฉลี่ยกลางของระยะเวลาในการดำรงชีวิตของผู้ป่วยกลัยโอมาลำดับชั้นที่ 2-4 คือ 80.0 เดือน, 20.0 เดือน, และ 9 เดือนตามลำดับ ในการวิเคราะห์ทางสถิติพบว่า ปัจจัยที่มีผลต่อระยะเวลาในการดำรงชีวิตของผู้ป่วยกลัยโอมาลำดับชั้นที่ 2 คือ ตำแหน่งของเนื้องอก ปัจจัยที่มีผลต่อระยะเวลาในการดำรงชีวิตของผู้ป่วยกลัยโอมาลำดับชั้นที่ 3 คือ คะแนน KPS ในผู้ป่วยกลัยโอมาลำดับชั้นที่ 4 ไม่พบว่าปัจจัยใดที่มีผลต่อระยะเวลาในการดำรงชีวิต

สรุป: ผลการรักษาผู้ป่วยโรคเนื้องอกสมองกลัยโอมาในโรงพยาบาลจุฬาลงกรณ์นั้น ใกล้เคียงกับผลการรักษาในหลาย ๆ การศึกษาที่ผ่านมา จากผลการศึกษารั้งนี้ทำให้ทราบถึงปัจจัยที่มีผลต่อระยะเวลาในการดำรงชีวิตของผู้ป่วยโรคเนื้องอกสมองกลัยโอมา
