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

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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

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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),
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(11)), 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 ≥ 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 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 not impact on survival of these patients (all p = 0.00). When a multivariate

<table>
<thead>
<tr>
<th>Grade</th>
<th>Location</th>
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<tbody>
<tr>
<td>I: noneloquent brain</td>
<td>frontal or temporal pole of cerebrum, right parietooccipital lobe, cerebellar hemisphere near motor or sensory cortex, visual cortex, language center, corpus callosum, near brainstem, near deep cerebellar nucleus</td>
</tr>
<tr>
<td>II: near eloquent brain</td>
<td>motor or sensory cortex, visual center, language center, internal capsule, basal ganglia, hypothalamus or thalamus, brainstem, deep cerebellar nucleus</td>
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<tr>
<td>III: eloquent brain</td>
<td></td>
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Table 2. Patient characteristics categorized by WHO grading system

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

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. Neverthe-
less, many studies found that younger age correlated
with longer survival/PFS(19). Some suggested that glio-
mas in older patients had greater proliferate potential
than those in younger ones. Age may also influence
the selection of patients for surgery with younger pa-
tients 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 loca-
tion 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 nonequient brain regions may be
more aggressively removed. The influence of the
extent of surgery on survival of these patients, how-
ever, 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 resecability 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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ผลการวิเคราะห์ทางสถิติแบบหลายตัวแปรในผู้ป่วยเนื้องอกกลัยโอมา: ผลการรักษาและปัจจัยที่มีผลต่อระยะเวลาในการดำรงชีวิตของผู้ป่วย

ชัยยศ เสียงประเสริฐกิจ, ยศ นวฤทธิโลหะ

วัตถุประสงค์: เพื่อศึกษาเกี่ยวกับผลการรักษาและปัจจัยที่มีผลต่อระยะเวลาในการดำรงชีวิตของผู้ป่วยโรคเนื้องอกกลัยโอมา

วัสดุและวิธีการ: ผู้ป่วยที่นำมาศึกษามีจำนวน 189 คน ข้อมูลที่ได้จากการเก็บรวบรวมและนำมาวิเคราะห์ได้แก่ อายุ, เพศ, คะแนน Karnofsky performance status (KPS), ตำแหน่งของเนื้องอก, ระยะเวลาในการดำรงชีวิตของผู้ป่วย

ผลการศึกษา: ลำดับชั้นของเนื้องอกและอายุมีผลต่อระยะเวลาในการดำรงชีวิตของผู้ป่วย ลำดับชั้นที่ 2-4 มีค่าเฉลี่ยเป็น 80.0 เดือน, 20.0 เดือน, และ 9 เดือนตามลำดับ ในการศึกษาทางสถิติพบว่า ปัจจัยที่มีผลต่อระยะเวลาในการดำรงชีวิตของผู้ป่วยกลัยโอมาลำดับชั้นที่ 2 คือ ตำแหน่งของเนื้องอกเป็นปัจจัยที่มีผลต่อระยะเวลาในการดำรงชีวิตของผู้ป่วยกลัยโอมาลำดับชั้นที่ 3 คือ คะแนน KPS ในผู้ป่วยกลัยโอมาลำดับชั้นที่ 4 ไม่พบปัจจัยใดที่มีผลต่อระยะเวลาในการดำรงชีวิต

สรุป: ผลการรักษาผู้ป่วยโรคเนื้องอกกลัยโอมาในโรงพยาบาลจุฬาลงกรณ์มีผลดีอย่างมาก ใกล้เคียงกับผลการรักษาในหลายๆการศึกษาที่ผ่านมา จากผลการศึกษาครั้งนี้ทำให้ทราบถึงปัจจัยที่มีผลต่อระยะเวลาในการดำรงชีวิตของผู้ป่วยเนื้องอกกลัยโอมา