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A Survival Score Based on Symptoms and Performance Status for Patients with High-grade Gliomas Receiving Radiochemotherapy

PHAM CAM PHUONG[1], LE VIET NAM[1], STEVEN E. SCHILD[2], DIRK RADES[3,4] and MAI TRONG KHOA[1,4]

[1]*The Nuclear Medicine and Oncology Center, Bach Mai Hospital, Hanoi, Vietnam;*
[2]*Department of Radiation Oncology, Mayo Clinic, Scottsdale, AZ, U.S.A.;*
[3]*Department of Radiation Oncology, University of Lübeck, Lübeck, Germany;*
[4]*Department of Nuclear Medicine, Ha Noi Medical University, Hanoi, Vietnam*

Abstract. *Aim: To create a simple survival score for patients with high-grade gliomas based on clinical symptoms and performance status. Patients and Methods: Thirty-six patients received neurosurgical intervention followed by radiochemotherapy for high-grade gliomas. Six pre-treatment symptoms were included in the score depending on their impairment of quality of life, scoring each between 1 and 3. For each patient, the points from the symptoms were added and another 4 points were added for Karnofsky performance status (KPS) <80%. Based on the survival rates of these scores, two groups were formed: 1-4 (group A) and 5-12 points (group B). Results: The 1-, 2- and 3-year survival rates in group A were 100%, 33% and 24% in group A and 47%, 7% and 0% in group B (p<0.001). In addition, complete tumor resection (p<0.001) and tumor grade III (p<0.001) were associated with improved survival. Conclusion: A simple survival score was developed helping physicians in decision-making for patients with high-grade gliomas.*

Despite modern treatment approaches, patients with high-grade gliomas, *i.e.* anaplastic astrocytomas (grade III) or glioblastomas (grade IV), generally have poor survival prognoses (1). In glioblastoma patients, the introduction of tri-modality approaches, including neurosurgical resection, modern radiotherapy and chemotherapy with temozolomide, increased the median survival time from 12 to 14 months (1-3). However, patients surviving three years or longer are still rare. In a historic cohort of glioma patients with grade II to IV tumors, the median survival time was 15 months (4). The two- and three-year survival rates were only 9% and 3%, respectively. Thus, the prognosis of patients with high-grade gliomas still needs improvement. In order to achieve this goal, considerable research has been performed (5-13). An improvement in prognosis may also be achieved with further improvement of neurosurgical and radiotherapeutic techniques, as well as with the introduction of personalized treatment programs. A personalized treatment approach should be optimally tailored to a patient's health condition and co-morbidities, age, social situation and personal preferences regarding treatment intensity and risk of adverse events. Another important aspect to consider when choosing a personalized treatment for an individual patient is their remaining lifespan. This may be difficult to judge by the physician, particularly when being pressed for time to make a treatment decision. Therefore, a simple tool that enables the physician to estimate the survival time of a patient and can be used easily and quickly would be helpful. Survival scores have already been developed for other oncologic situations involving cancer patients with a limited life expectancy, most commonly patients with metastatic disease (14-19). Also for patients with high-grade gliomas, predictive tools are available. One tool was based on clinical factors plus biomarkers, including messenger RNA expression, microRNA expression and single-nucleotide polymorphism (SNP) array data, and appears, therefore, difficult to use when a rapid treatment decision is required (20). Recently, a tool was presented that was based on clinical factors and developed to evaluate the benefit of gross tumor resection (21). This tool allows using a more personalized approach regarding surgical strategies, but not regarding multi-modality concepts. In the present study, we created a survival

Correspondence to: Pham Cam Phuong, MD, Ph.D., The Nuclear Medicine and Oncology Center, Bach Mai Hospital, 78 Giai Phong Street, Dong Da, Ha Noi, 100 000, Vietnam. Tel: +84 983920778, e-mail: phamcamphuong@gmail.com

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score based on clinical symptoms and the Karnofsky performance score (KPS) prior to treatment, which can be assessed easily and quickly, for patients receiving tri-modality treatment for high-grade glioma, including neurosurgical intervention, radiotherapy and chemotherapy with temozolomide.

Patients and Methods

Thirty-six patients treated at the Nuclear Medicine and Oncology Center of the Bach Mai Hospital in Hanoi, Vietnam, from January 2011 to October 2015 for a high-grade glioma (16 grade III and 20 grade IV tumors), were included in this retrospective study. The patients had received a neurosurgical intervention followed by radiochemotherapy with a median total radiation dose of 59.5 Gy (range=54-64) given in 1.8 to 2 Gy fractions on 5 consecutive days per week. Radiotherapy was supplemented by concurrent oral temozolomide (75 mg/m^2/day for 5 days per week). After 4 weeks rest, the patients received maintenance chemotherapy with temozolomide (150-200 mg/m^2/day on days 1-5 every 4 weeks) for 6 cycles. The distributions of the patients' characteristics and their symptoms prior to the start of treatment are summarized in Tables I and II, respectively.

Of the seven clinical symptoms assessed prior to treatment, the six that were present in at least five patients were included in the survival score. These six symptoms were hemiplegia, headache, nausea, seizures, dysphasia and impairment in neurocognitive functions, such as problems regarding memory or concentration. Depending on the severity regarding the impairment of quality of life, scoring points from 1 to 3 were assigned (Table III). To receive the survival score for an individual patient, the points -based on the six clinical symptoms- were summed up and another 4 points were added if the KPS was <80%. Thus, the patients' scores ranged from 1 to 12. Based on the survival rates of these scores (Table IV), two prognostic groups were formed: 1 to 4 points (group A, n=21) and 5 to 12 points (group B, n=15).

The survival rates of the two prognostic groups and the other evaluated patients' characteristics (Table I) were calculated using the Kaplan-Meier method. The corresponding Kaplan-Meier curves were compared with the log-rank test. All p-values <0.05, as obtained from the log-rank test, were regarded as significant.

Results

The 1-, 2- and 3-year survival rates of the patients in group A were 100%, 33% and 24%, respectively, and the corresponding survival rates of the patients in group B were 47%, 7% and 0%, respectively (p<0.001; Figure 1). Median survival times were 19 months and 11 months, respectively.

Additional analysis of the other investigated characteristics revealed that extent of surgery (p<0.001) and tumor grade (p<0.001) were also significantly associated with survival (Table V). A complete tumor resection resulted in a 2-year survival of 47% compared to 6% after partial resection and 0% after extended biopsy. The 2-year survival rate of patients with a grade III tumor was 50% compared to 0% in those patients with a grade IV tumor.

Table I. *Investigated patient's characteristics.*

Characteristic	Number of patients	Proportion (%)
Age		
<51 Years	17	47
≥51 Years	19	53
Gender		
Female	20	56
Male	16	44
Karnofsky performance score		
<80%	12	33
≥80%	24	67
Location of the glioma		
Frontal lobe	12	33
Parietal lobe	4	11
Temporal Lobe	18	50
Occipital lobe	2	6
Glioma size		
≤3 cm	5	14
3.1-5.0 cm	17	47
>5 cm	14	39
Midline compression		
No	12	33
Yes	24	67
Extent of upfront surgery		
Complete resection	15	42
Partial resection	17	47
Extended biopsy	4	11
Glioma grade		
Grade III	16	44
Grade IV	20	56

Table II. *Patient's symptoms prior to treatment initiation.*

Symptom	Number of patients	Proportion (%)
Headache	34	11
Nausea	16	44
Seizures	9	25
Vision disturbance	3	8
Dysphasia	5	14
Neurocognitive impairment	9	25
Hemiplegia	12	33

Discussion

The survival outcomes of patients with a high-grade glioma are often poor and require significant improvement (1). A certain prolongation of the median survival time has already been achieved with the introduction of multi-modality treatment programs involving neurosurgery, radiation oncology and administration of systemic agents (1-3). However, the number

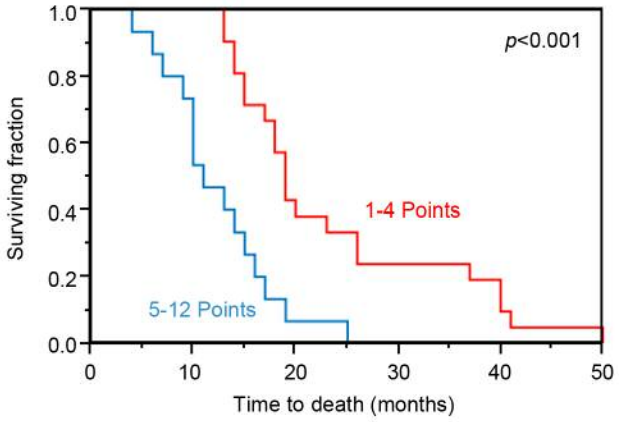

Figure 1. *Comparison of the two prognostic groups A (1-4 points) and B (5-12 points) with respect to survival (Kaplan-Meier curves). The p–value was calculated using the log-rank test.*

Table III. *Clinical symptoms and Karnofsky performance score prior to the start of treatment and the corresponding scoring points.*

Symptom	Number of patients	Scoring points
Vision problems	3	Not included
Headache	34	1
Nausea	16	1
Seizures	9	2
Dysphasia	5	2
Neurocognitive impairment	9	2
Hemiplegia	12	3
Karnofsky performance score <80%	12	4

of long-term survivors is still very low and further improvement is needed (4). Another approach to achieve more favorable survival rates is the personalization of anticancer therapies. Such an approach is generally based on several individual patient factors also including the patient's remaining lifespan. Patients with a very short lifespan should ideally receive a treatment program that is not too aggressive with the major indication of symptom relief and improvement of the patient's quality of life. In patients with a more favorable survival prognosis, local control of the glioma and treatment-related late morbidity are more important, since these patients may live long enough to experience a local recurrence of their disease and/or significant late toxicities impairing their quality of life. These patients should receive a more intensive treatment providing best possible local control without being too toxic. However, estimating an individual patient's survival prognosis can be quite challenging for the treating physicians. This problem may be overcome with the availability of a

Table IV. *Survival rates of the patients' scores up to 3 years following radiotherapy.*

Patients' scores	At 1 year (%)	At 2 years (%)	At 3 years (%)
1 point	100	50	25
2 points	100	33	33
3 points	100	33	33
4 points	100	20	0
5 points	50	0	0
6 points	50	50	0
7 points	0	0	0
8 points	50	0	0
9 points	67	0	0
10 points	0	0	0
11 points	100	0	0
12 points	0	0	0

Table V. *Survival rates of the investigated patients' characteristics up to 3 years following radiotherapy. The p-values were calculated with the log-rank-test.*

Characteristic	At 1 year (%)	At 2 years (%)	At 3 years (%)	*p*-Value
Age				
<51 Years	88	29	18	
≥51 Years	68	16	11	0.22
Gender				
Female	75	20	15	
Male	81	25	13	0.71
Karnofsky performance score				
<80%	42	0	0	
≥80%	96	33	21	**<0.001**
Glioma location				
Frontal	83	17	0	
Parietal	100	25	25	
Temporal	67	17	17	
Occipital	100	100	50	0.63
Glioma size				
1-3 cm	100	20	20	
3-5 cm	88	29	12	
>5 cm	57	14	14	0.37
Midline compression				
No	92	25	17	
Yes	71	21	13	0.63
Extent of surgery				
Complete resection	100	47	27	
Partial resection	71	6	6	
Extended biopsy	25	0	0	**<0.001**
Tumor grade				
Grade III	88	50	31	
Grade IV	70	0	0	**<0.001**

Significant *p*-values are given in bold.

simple scoring system designed to predict the survival of individual patients with the diagnosis of a high-grade glioma. Very few scoring systems are available. However, one system was mainly based on biomarkers in addition to clinical factors (20). The assessment of such biomarkers, including messenger RNA expression, microRNA expression and SNP array data, is time-consuming and not available in many centers worldwide. Therefore, such a model may not be suitable for use in many centers. More recently, a propensity score analysis from China was presented (21). In this retrospective study of patients with a grade IV glioma, the median survival time of the patients receiving a complete tumor resection was significantly longer than of those patients who did not undergo a complete resection (20.5 *vs*. 16 months, $p<0.001$). On multivariate analysis, the superiority of a complete resection maintained significance (hazard ratio=0.48, $p<0.001$). A risk score was developed based on age, seizures, location of the glioma, glioma size and performance status, with the patients being grouped as low-risk, moderate-risk or high-risk. Improved survival after complete tumor resection *vs*. incomplete resection was limited to low-risk and moderate-risk patients.

In addition to the available scoring system, we created a new score in patients receiving tri-modality treatment for a high-grade glioma that was based on six pre-treatment clinical symptoms plus pre-treatment KPS. These factors can be assessed easily and quickly without sophisticated imaging or biomarker profiles. Taking into account these seven factors, two prognostic groups were identified. In group A (1-4 points), all patients survived for at least one year and almost one-fourth of patients lived for at least three years following radiotherapy. Thus, these patients should receive an intensive treatment program providing long-term local control with least possible late morbidity. In group B (5-12 points), less than half of the patients survived for one year and no patient for three years following radiotherapy. Hence, the situation of many patients of this group has to be described as palliative. Therefore, these patients appear better treated with a less burdensome treatment program focusing on symptom control and quality of life.

In addition to the new scoring system, the KPS *per se*, extent of neurosurgical resection and glioma grade were significantly associated with survival. These findings agree well with those of previous studies (20, 22-25), thus demonstrating consistency with the results of the present study.

In conclusion, a new and easy-to-use scoring system was developed that can help physicians when compelled to make a rapid treatment decision for patients with a high-grade glioma.

Conflicts of Interest

On behalf of all Authors, the corresponding Author states that there is no conflict of interest related to this study.

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