

## Pre-operative clinical factors predict progression-free survival and tumor recurrence after initial surgery in patients with astrocytomas: A single-center analysis

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### ABSTRACT

**Objective:** Pre-operative predictive factors of progression-free survival (PFS) and tumor recurrence after initial surgery are important in counseling patients and decision making. Though PFS after initial surgery in patients with low grade astrocytomas has been described, little is described about PFS in patients with different tumor grades. Our objective was to investigate potential predictive factors of PFS, and devise a scale to predict PFS and tumor recurrence after initial surgery in patients with primary and recurrent astrocytomas of low and high tumor grades.

**Methods:** Clinical, radiographic, pathological and treatment data of 62 patients whose initial treatments of primary and recurrent astrocytomas were both surgeries were analyzed, and factors that had significant correlation with PFS was used to devise a scale.

**Results:** Factors significantly related with PFS were: the time from onset of symptoms to clinical and radiological diagnosis of astrocytomas (Spearman correlation coefficient  $r=0.298$ , significance level  $P=0.019$ ) and with the symptoms of seizures ( $r=0.292$ ,  $P=0.021$ ). Patients with age between 30 and 40 years had significant longer PFS than the rest age group ( $P=0.018$ , oneway ANOVA). A simple scale (from 0 to 3 points) comprised of the three factors distinguished four groups of patients with significant different post-operative PFS (0 point, 8.0 months; 1 point, 13.7 months; 2 points, 18.0 months; 3 points, 34.5 months) ( $P=0.004$ , oneway ANOVA).

**Conclusion:** The simple scale we devised comprised of the three pre-operative prognostic factors can significantly distinguish patients with different post-operative survival after initial treatment of astrocytomas with surgery.

**KEY WORDS:** Clinical factors, Progression-free survival, Tumor recurrence, Astrocytomas, Surgery.

doi: <http://dx.doi.org/10.12669/pjms.301.4110>

### How to cite this:

Zheng S, Hou X, Xu S, Pang Q. Pre-operative clinical factors predict progression-free survival and tumor recurrence after initial surgery in patients with astrocytomas: A single-center analysis. *Pak J Med Sci* 2014;30(1):136-139.

doi: <http://dx.doi.org/10.12669/pjms.301.4110>

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- \* Received for Publication: July 19, 2013
- \* Revision Received: November 11, 2013
- \* Revision Accepted: November 13, 2013

### INTRODUCTION

Astrocytomas always recur after initial surgery and following radiotherapy and chemotherapy, irrespective of tumor grades and locations. The reasons might be that local invasion of astrocytomas renders complete total resection impossible and subsequent radiotherapy and chemotherapy can't eradicate astrocytoma cells. Progression-free survival (PFS) after initial surgery in patients with astrocytomas is important in counseling patients and decision making, and predictive factors of PFS after initial surgery may offer great help.

One study has described pre-operative tumor size and tumor histology types prognostic of PFS after surgery in patients with low grade gliomas under 40 years' old.<sup>1</sup> Another study shows that patients with age over 50 years, low Karnofsky performance status (KPS) and larger tumor size had unfavorable prognosis of overall survival after surgery in low grade gliomas.<sup>2</sup> But no literature has described factors predictive of PFS after initial surgery in patients with astrocytomas of low and high tumor grades.

Our objective was to investigate potential predictive factors of PFS and devise a simple scale to predict PFS after initial surgery in astrocytomas using clinical, radiographic, pathological, and treatment factors. The scale may be useful in counseling the patients and their family members before surgery.

## METHODS

**Patients:** Patients whose initial treatments of primary and recurrent astrocytomas were gross total resection were included. All patients underwent surgery at Department of Neurosurgery, Provincial Hospital Affiliated to Shandong University from September, 1993 to April, 2010. Patients' characteristics can be seen in Table-I. The pathological diagnosis was made at Department of Pathology, Provincial Hospital Affiliated to Shandong University. Astrocytomas refer to astrocytic tumors in 2007 WHO classification of tumors of the central nervous system.<sup>3</sup> 61% of patients received radiotherapy and 21% received chemotherapy after primary surgery.

**Prognostic factors:** Clinical factors including patients' age, sex, symptoms of headache or seizure, the time from onset of symptoms to diagnosis, Karnofsky performance status (KPS) and progression-free survival after initial surgery were collected, as well as radiographic factors including tumor location and size, pathological factor including tumor grade and treatment of radiotherapy or chemotherapy after initial surgery. Tumor size was acquired from patients' radiography and tumor volume was calculated using the formula as  $4/3 \times \pi \times \text{radius}_x \times \text{radius}_y \times \text{radius}_z$ .<sup>4</sup> Progression-free survival (PFS) was defined as survival after primary surgery without onset of symptoms or worsening of present symptoms.

**Statistical analysis:** SPSS statistics 17.0 was used in all analyses. Kolmogorov-Smirnov test was done to test the normal distribution of PFS data ( $P=0.009$ ). Spearman rank correlation analysis and

oneway ANOVA analysis were used to investigate the relation between PFS and prognostic factors. P value  $<0.05$  on two sides was considered significant. Prognostic factors that had significant relation with PFS were used to devise the scale to predict PFS after initial surgery in patients with astrocytomas.

## RESULTS

**Factors significantly related with PFS were:** The time from onset of symptoms to clinical and radiological diagnosis of astrocytomas (Spearman

Table-I: Characteristics and progression-free survival of patients with different clinical, radiological and pathological factors.

Factors	Patients No. (%)	PFS (months) Average	Oneway ANOVA P value
<b>Age between 30 and 40 years</b>			
Yes	24 (39%)	24.7	0.018*
No	38 (61%)	13.1	
<b>Sex</b>			
Male	40 (65%)	14.9	0.136
Female	22 (35%)	22.4	
<b>KPS score</b>			
$\geq 70$	38 (61%)	20.0	0.205
$\leq 60$	24 (39%)	13.7	
<b>Headaches</b>			
Yes	38 (61%)	14.8	0.111
No	24 (39%)	22.0	
<b>Seizures</b>			
Yes	20 (32%)	26.1	0.014*
No	42 (68%)	13.5	
<b>Time from onset of symptoms to diagnosis</b>			
$\leq 1$ month	17 (27%)	9.1	0.032*
$> 1$ month	45 (73%)	20.8	
<b>Tumor malignancy</b>			
Low (Grade 1 & 2)	26 (42%)	21.0	0.233
High (Grade 3 & 4)	36 (58%)	15.1	
<b>Main lobe of tumor location</b>			
Frontal	35 (56%)	20.6	0.576
Parietal	12 (19%)	18.2	
Temporal	9 (15%)	12.0	
Others	6 (10%)	7.0	
<b>Tumor size (<math>4/3 \times \pi \times \text{radius}_x \times \text{radius}_y \times \text{radius}_z</math>)</b>			
$\leq 200\text{cm}^3$	15 (24%)	12.7	0.259
$> 200\text{cm}^3$	47 (76%)	19.1	
<b>Post-operative radiotherapy</b>			
Yes	38 (61%)	15.5	0.277
No	24 (39%)	20.9	
<b>Post-operative chemotherapy</b>			
Yes	13 (21%)	19.0	0.761
No	49 (79%)	17.2	

Table-II: Scale to predict progression-free survival after initial surgery in patients with gliomas.

Pre-operative clinical factors	Score
<b>Age between 30 and 40 years</b>	
Yes	1
No	0
<b>Time from onset of symptoms to diagnosis</b>	
≤1 month	0
>1 month	1
<b>Seizures</b>	
Yes	1
No	0

correlation coefficient  $r=0.298$ ,  $P=0.019$ ) and with the symptoms of seizures ( $r=0.292$ ,  $P=0.021$ ). Longer PFS was observed in patients with longer time from onset of symptoms to diagnosis (Table-I) and seizures (Table-I). Besides, patients with age between 30 and 40 years had significant longer PFS than the rest age group ( $P=0.018$ , see Table-I). No significant correlation with each other was observed among the above three clinical factors associated with PFS. Oneway ANOVA analysis of other prognostic factors can also be seen in Table-I.

A simple scale comprised of the three factors including time from onset of symptoms to diagnosis, seizures and patients' age (from 0 to 3 points, see Table-II) distinguished four groups of patients with significant different post-operative PFS (Table-III and Fig.1) ( $P=0.004$ , oneway ANOVA).

Table-III: Progression-free survival (months) in patients with different scores.

Number of patients	11	23	17	11
Patients' scores	0	1	2	3
Progression-free survival	8.0	13.7	18.0	34.5

### DISCUSSION

In this study, we showed three pre-operative clinical factors significantly prognostic of PFS after initial surgery including time from onset of symptoms to diagnosis, seizures and patients' age. With the three factors, we devised a simple scale to predict the PFS after initial gross total resection of astrocytomas with different malignancy. And the scale may be useful in discussion with patients and their family members before surgery.

Previous literature has described patients with age  $\leq 40$  years and seizures have longer PFS in low grade gliomas.<sup>5</sup> Our study showed similar results. Patients with age between 30 and 40 years have significant longer PFS than other age groups (Table-I). Seizures have significant association with low tumor grade ( $r=0.392$ ,  $P=0.002$ ). Patients with seizures have more low grade astrocytomas 70% (14/20) than patients without seizures 28.6% (12/42). 80% (16/20) of seizures occur in frontal lobe astrocytomas. In frontal lobe astrocytomas, patients with seizures have longer PFS (26.1 months) than patients without seizures (16.2) ( $P=0.052$ ).

One study has described the predictive role of  $KPS \leq 80$  and tumor volume  $\geq 50\text{cm}^3$  in predicting survival after surgery of glioblastoma recurrences.<sup>4</sup> Another study has showed tumor diameter  $\geq 4\text{cm}$  is prognostic of unfavorable PFS in low grade gliomas after gross total resection.<sup>1</sup> We didn't observe significant role of lower KPS score or larger tumor size in predicting survival after initial resection of astrocytomas perhaps because of different tumor grades and less number of patients.

Considering the inevitable recurrences of astrocytomas after initial surgical resection, early detection and treatment of recurrences is important for improving patients' prognosis. Our scale to predict post-operative PFS comprises of pre-operative clinical factors including time from onset of symptoms to diagnosis, seizures and patients' age within 30 and 40 years (for details see Table-II). The scale significantly differentiates post-operative patients with astrocytomas with different PFS (see Table-III and Fig.1) and, the end of PFS is also the time of tumor recurrences that may complicates patients' survival. So, with our simple scale we can

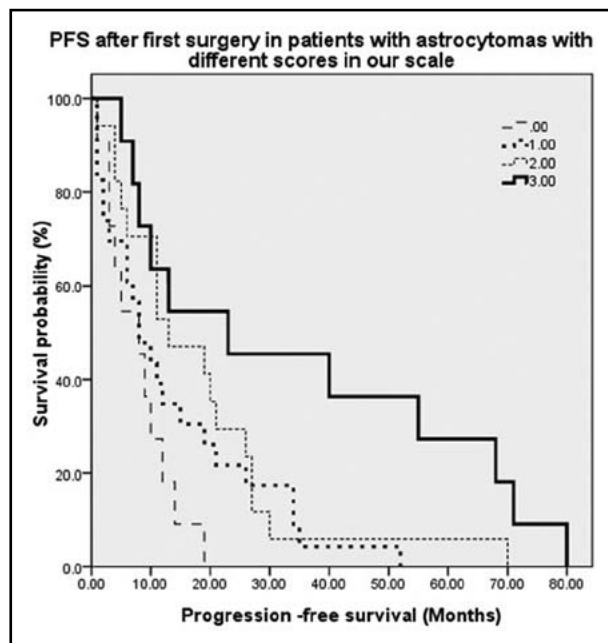


Fig.1: Progression-free survival increased in patients with higher scores.

predict not only patients' PFS but also recurrences in astrocytomas.

There is limitation of our study due to the small number of patients included. Without prospective multi-center investigations to confirm our results, the reliability of our scale to predict PFS after initial surgery is reduced. As tumor grades are considered as an important indicator of patients' prognosis, we also included tumor grades in this study. The results show that PFS in patients with low tumor grades (21.0 months) is longer than in patients with high tumor grades (15.1 months), but with no significant differences and the reason may be the small number of patients included. Though there are molecular prognostic indicators of gliomas such as cell proliferation index, micro vessel density, loss of heterozygosity in 10q or 19q, MGMT promoter and IDH1 mutations<sup>6</sup>, the scale in this study is very simple and easy to use and can still offer great help for the moment

In conclusion, the scale comprised of time from onset of symptoms to diagnosis, seizures and patients' age significantly distinguishes patients with PFS after initial resection of astrocytomas. The simple scale may be of great help in predicting patients' PFS after initial surgery and in predicting astrocytoma recurrences. However, the scale needs further prospective investigations.

#### ACKNOWLEDGEMENT

This study was supported by grant ZR2010HM013 from Natural Science Foundation of Shandong Province, China. This investigation was approved by the Medical Ethical Committee of our hospital in charge of human investigations

**Conflict of interests statement:** The authors have declared that they have no financial and personal relationships with other people or organizations that could inappropriately influence (bias) their work.

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#### Author Contributions:

SZ and XH contributed equally to this work. SZ and XH collected and analyzed the data, SZ, XH and SX wrote the paper; QP, XH and SX conceived and designed the study.