

Original Article

Analysis of survival-related factors in elderly patients following glioma operation

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Abstract: Objective: To investigate and analyze survival-related factors, cognitive function, and quality of life of elderly patients after operation for glioma. Methods: Clinical and follow-up data of 156 elderly patients with glioma surgically treated in China-Japan Union Hospital of Jilin University from January 2011 to December 2014 were retrospectively analyzed. The effects of the patient's gender, age, preoperative Karnofsky Performance Status (KPS) score, tumor diameter, pathological grading, postoperative radiotherapy, postoperative chemotherapy, degree of surgical resection, and expression of tumor molecular markers on survival time were analyzed by Kaplan-Meier method, and changes in cognitive function (Mini-mental State Examination (MMSE) score) and quality of life (KPS score) of patients before operation and 1 month after operation were compared. Results: Total MMSE score and scores of dimension of cognitive function of elderly patients with glioma 1 month after operation were significantly increased compared with those before operation (all $P < 0.05$), and the KPS score of elderly patients with glioma 1 month after operation was significantly higher than that before operation ($P < 0.05$). Univariate analyses revealed that age, tumor diameter, preoperative KPS score, preoperative pathological grading, postoperative radiotherapy/chemotherapy, degree of surgical resection, and matrix metalloprotein-9 expression had significant influences on the survival prognosis of patients (all $P < 0.05$). According to results of COX multivariate regression analyses, preoperative pathological grading, tumor diameter, preoperative KPS score, and postoperative radiotherapy/chemotherapy were independent risk factors affecting the postoperative prognosis of elderly patients with glioma (all $P < 0.05$). Conclusion: Cognitive function and quality of life of elderly patients can be effectively improved via glioma operation. Preoperative pathological grading, tumor diameter, preoperative KPS score, and postoperative radiotherapy/chemotherapy are independent risk factors affecting the postoperative prognosis of patients.

Keywords: Elderly, glioma, survival factors, neurological function, quality of life

Introduction

Glioma is a common intracranial malignant tumor, as well as the most common and most refractory tumor in the central nervous system, accounting for 40-50% of brain tumors [1]. Due to the diversity of tumor cells, glioma is still a type of central nervous system tumor with the worst prognosis after comprehensive tumor treatment [2]. At present, the most effective treatment method for glioma is still surgical treatment, in which total or partial resection of tumor tissues is performed, thus effectively improving or alleviating the preoperative clinical symptoms of patients [3]. With the development of modern microsurgical techniques, traditional open operation is being gradually replaced with fiberoptic surgery in clinical treat-

ment of glioma, but the clinical prognosis of patients is still not optimistic after treatment [4]. Elderly patients suffer from failure of physical function complicated with a variety of basic diseases, and their clinical prognosis is poor and survival time is short. Therefore, grasping the factors affecting postoperative survival prognosis of patients is of great value in improving the surgical effect and the clinical prognosis in these patients [5]. In this study, clinical data of 156 elderly patients with glioma surgically treated in China-Japan Union Hospital of Jilin University were retrospectively analyzed, and survival-related factors, cognitive function, and quality of life of elderly patients with glioma after operation were also analyzed. It is now reported as follows.

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Figure 1. Analysis of postoperative survival condition of elderly patients with glioma. Among 156 patients, 103 died, and the median survival time was 30.5 months.

Table 1. Changes in cognitive function and living quality of elderly patients with glioma before and after operation (n=156, $\bar{x} \pm sd$)

Cognitive function	Before operation	One month after operation	t	P
MMSE score	17.21±1.05	24.11±2.31	33.964	<0.001
Orientation score	5.28±0.52	7.94±0.83	33.921	<0.001
Immediate memory score	1.52±0.38	2.56±0.33	25.809	<0.001
Delayed recall score	1.10±0.32	1.55±0.41	10.807	<0.001
Attention and calculation score	2.19±0.45	3.58±0.55	24.430	<0.001
Language score	6.12±0.89	7.52±1.21	11.641	<0.001
KPS score	72.19±12.31	83.41±9.23	9.108	<0.001

Note: KPS, Karnofsky Performance Status.

Materials and methods

Clinical materials

Clinical and follow-up data of 156 elderly patients with glioma surgically treated in China-Japan Union Hospital of Jilin University from January 2011 to December 2014 were retrospectively analyzed. There were 93 male patients and 63 female patients aged 60-85 years old with an average age of (71.25±9.21) years old. The course of disease was 3-17 months with an average of (8.22±3.01) months. According to the World Health Organization criteria for classification and grading of brain glioma, there were 22 cases in grade I, 69 cases in grade II, 37 cases in grade III, and 28 cases in grade IV. Patients were diagnosed via imaging examination before operation. The tumor diameter was 0.5-10.0 cm with an average of (5.10±1.95) cm. All patients had multiple lesions, and the maximum diameter of each lesion was added up. A total of 127 patients

received total resection and 29 patients underwent partial resection.

Inclusion criteria: Patients aged 60 years old or above, with the course of disease of 3 months or above; patients underwent glioma operation.

Exclusion criteria: Patients complicated with nervous system disease, systemic infection, other malignant tumors or autoimmune disease.

Patients voluntarily signed the informed consent, and this study was approved by the Ethics Committee of China-Japan Union Hospital of Jilin University.

Operation and postoperative treatment methods

All patients underwent imaging examinations, such as computed tomography or magnetic resonance imaging, before operation

the size and location of the patient's tumor and its correlation with the surrounding tissues were determined. The surgical approach included functional area, non-functional area, and important vascular area, and surgical treatment included total or subtotal resection. After operation, radiotherapy was performed using the linear accelerator. Patients with low-grade glioma were treated with two- or multi-field local radiotherapy (radiotherapy dose: 40-50 Gy) 28-32 times for a total of 5-7 weeks, while those were high-grade glioma were treated with local extended radiotherapy (radiotherapy dose: 40-60 Gy) 28-32 times for a total of 5-7 weeks. One of the following three chemotherapy regimens was adopted in postoperative chemotherapy: 1) carmustine (125 mg/d for 3 d), 2) BCNU (125 mg/d for 3 d), 3) nimustine (150 mg/d for 1 d).

Postoperative follow-up

All patients were followed up after operation via outpatient clinic or telephone until September

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Table 2. Univariate analyses of factors affecting postoperative prognosis of elderly patients with glioma

Factor	Case	Survival rate			$\chi^2_{\text{Log-rank}}$	P
		1-year	2-year	3-year		
Gender					0.313	0.576
Male	93	80.65	61.29	35.48		
Female	63	82.54	66.67	31.75		
Age (years old)					8.653	0.003
60-70	71	84.51	73.24	38.03		
>70	85	78.82	55.29	30.59		
Preoperative KPS score (point)					9.477	0.002
≤70	87	80.46	60.92	21.84		
>70	69	82.61	66.67	49.28		
Tumor diameter (cm)					5.801	0.016
<5	73	87.67	69.86	38.36		
≥5	83	75.90	57.83	27.71		
Preoperative pathological grading					12.644	<0.001
I-II	91	86.81	72.53	40.66		
III-IV	65	73.85	50.77	24.61		
Postoperative radiotherapy/chemotherapy					9.085	0.003
Yes	71	80.28	78.87	47.89		
No	85	94.12	50.59	22.35		
Degree of surgical resection					4.707	0.030
Total resection	127	82.68	65.35	37.79		
Partial resection	29	75.86	55.17	17.24		
MMP-9					5.510	0.019
+	73	76.71	42.47	28.77		
-	83	85.54	81.93	38.55		
P53					0.509	0.476
+	64	84.38	62.50	25.00		
-	92	79.35	64.13	40.22		

Note: KPS, Karnofsky Performance Status; MMP-9, matrix metalloproteinase-9.

30, 2017. The patient's follow-up began from the second day after operation, and the patient's survival time was from the second day after operation until the death or final follow-up time.

Observation indexes

First, the patient's gender, age, preoperative Karnofsky Performance Status (KPS) score, tumor diameter, pathological grading, postoperative radiotherapy, postoperative chemotherapy and degree of surgical resection were collected and recorded. Second, the expression of tumor molecular markers was as follows: Matrix metalloproteinase-9 (MMP-9) and tumor suppressor gene p53 were detected via streptavidin-peroxidase immunohistochemistry, and ph-

osphate buffered saline, instead of primary antibody, was used as the negative control. The specific steps were as follows: section baking → dewaxing → inactivation → antigen retrieval → sealing in goat serum → incubation with primary antibody at room temperature for 2-3 h → incubation with secondary antibody at room temperature for 15-20 min → dropwise addition of horseradish peroxidase → color development via DAB-Kit → hematoxylin counterstaining → transparency → section sealing. Positive expression of MMP-9 protein displayed brown-yellow particles in the cytoplasm, and the positive expression of p53 showed yellow particles in the nucleus. Interpretation of immunohistochemical results: 1,000 tumor cells were randomly observed in 10 high-power fields in each section, and the percentage of

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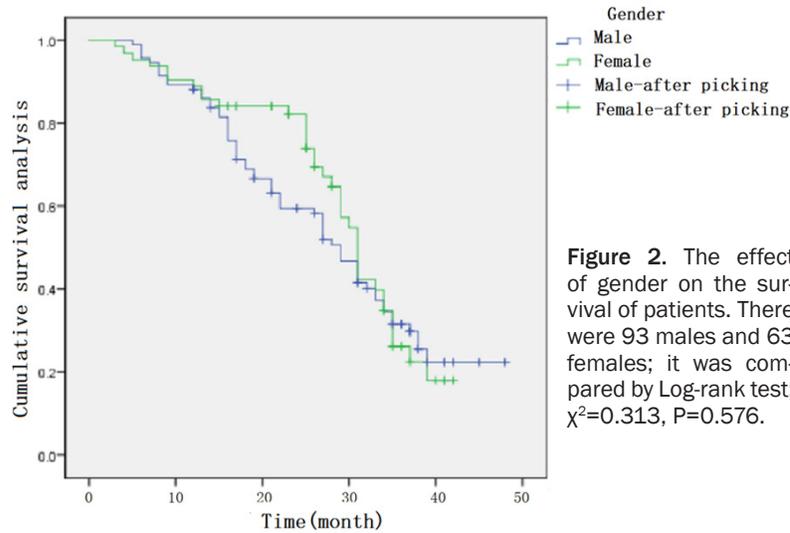


Figure 2. The effect of gender on the survival of patients. There were 93 males and 63 females; it was compared by Log-rank test; $\chi^2=0.313$, $P=0.576$.

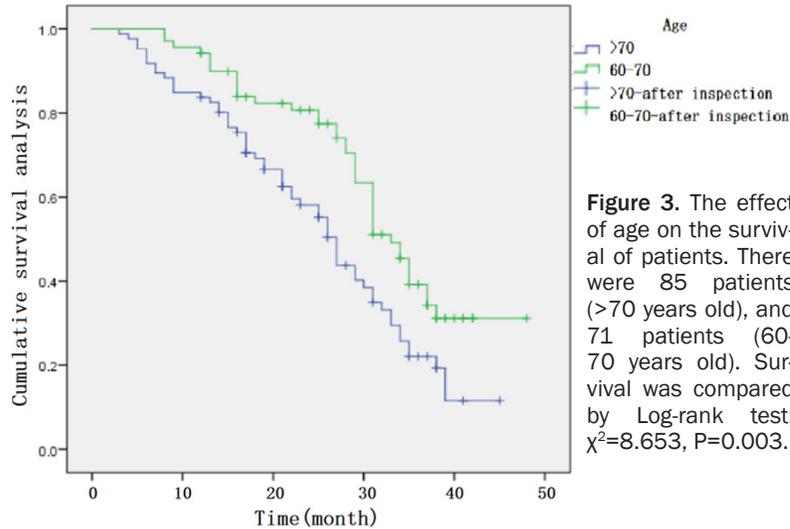


Figure 3. The effect of age on the survival of patients. There were 85 patients (>70 years old), and 71 patients (60-70 years old). Survival was compared by Log-rank test; $\chi^2=8.653$, $P=0.003$.

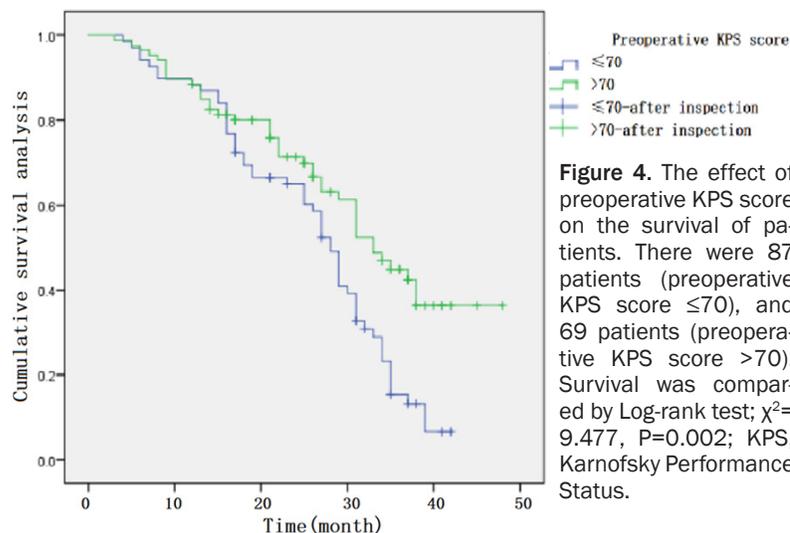


Figure 4. The effect of preoperative KPS score on the survival of patients. There were 87 patients (preoperative KPS score ≤ 70), and 69 patients (preoperative KPS score > 70). Survival was compared by Log-rank test; $\chi^2=9.477$, $P=0.002$; KPS, Karnofsky Performance Status.

positive tumor cells was counted. The percentage of positive cells was scored as follows: 0-10% (0 point), 11-24% (1 point), 25-49% (2 points), 50-74% (3 points), and $\geq 75\%$ (4 points). The staining intensity was also scored as follows: no staining (0 point), light yellow (1 point), brown yellow (2 points), and dark brown (3 points). The above two scores were multiplied with each other, and the final score is obtained: 0-1 point (negative), 2-3 points (weakly positive), 4-5 points (moderately positive) and > 5 points (strongly positive). Third, the cognitive function of patients was evaluated using the Chinese version of Mini-mental State Examination (MMSE) before operation and 1 month after operation. MMSE includes five dimensions: orientation, immediate memory, delayed recall, attention and calculation, and language. The higher the score of each dimension and the total score, the better the cognitive function of patients. Fourth, the quality of life of patients was evaluated using KPS score before operation and 1 month after operation. The total score is 100 points, and the higher the score is, the better the patient's quality of life.

Statistical analysis

SPSS 22.0 software was used for data processing and analysis. Survival of patients was analyzed using Kaplan-Meier method. Log-rank test was performed for the intergroup comparison of survival. Cox

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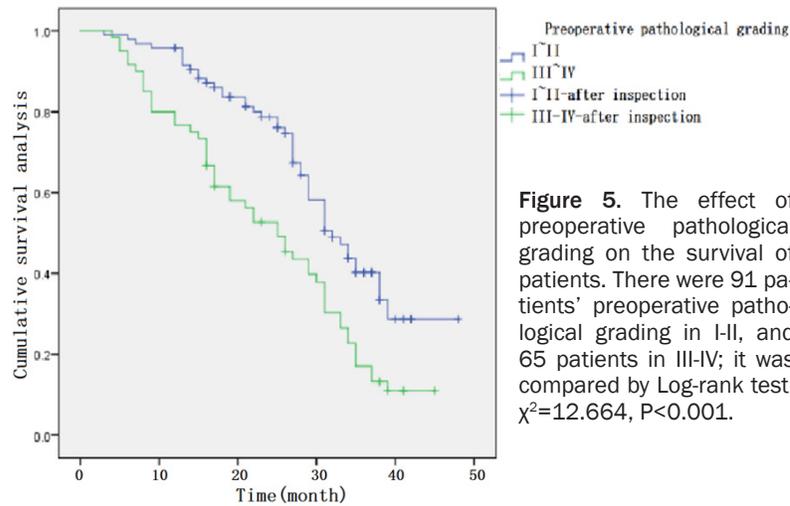


Figure 5. The effect of preoperative pathological grading on the survival of patients. There were 91 patients' preoperative pathological grading in I-II, and 65 patients in III-IV; it was compared by Log-rank test; $\chi^2=12.664$, $P<0.001$.

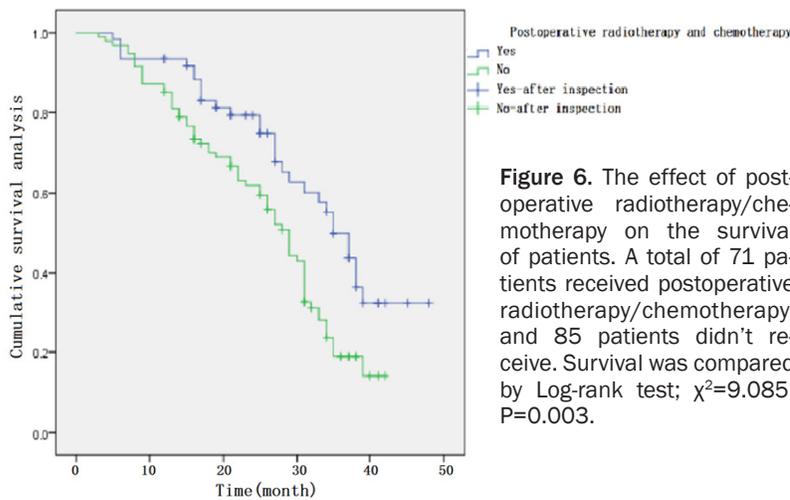


Figure 6. The effect of post-operative radiotherapy/chemotherapy on the survival of patients. A total of 71 patients received postoperative radiotherapy/chemotherapy, and 85 patients didn't receive. Survival was compared by Log-rank test; $\chi^2=9.085$, $P=0.003$.

regression model was used for multivariate analysis and t test or analysis of variance was used for the comparison of neurological function and quality of life. $P<0.05$ suggests that the difference is statistically significant.

Results

Overall survival condition

As of the final follow-up, 103 out of 156 elderly patients with glioma died after operation. The 1-, 2- and 3-year survival rates of patients were 81.41%, 63.46% and 33.97% (Figure 1).

Changes in cognitive function and quality of life of elderly patients with glioma before and after operation

The total MMSE score and the scores of dimension of cognitive function of elderly patients

with glioma 1 month after operation were significantly increased compared with those before operation (all $P<0.05$). The KPS score of patients was (72.19 ± 12.31) points before operation and (83.41 ± 9.23) points 1 month after operation. Therefore, the KPS score of patients 1 month after operation was significantly higher than that before operation ($P<0.05$). See Table 1.

Univariate analyses of factors affecting postoperative prognosis of elderly patients with glioma

Univariate analyses were performed for factors that might affect postoperative prognosis of elderly patients with glioma, and results revealed that age, tumor diameter, preoperative KPS score, preoperative pathological grading, postoperative radiotherapy/chemotherapy, degree of surgical resection and MMP-9 expression had significant influences on the prognosis

of patients (all $P<0.05$). See Table 2, Figures 2-9.

Multivariate analyses of factors affecting postoperative prognosis of elderly patients with glioma

COX multivariate regression analyses showed that preoperative pathological grading, tumor diameter, preoperative KPS score and postoperative radiotherapy/chemotherapy were independent risk factors affecting the postoperative prognosis of elderly patients with glioma (all $P<0.05$). See Table 3.

Discussion

At present, the standard treatment strategy for glioma is surgical treatment combined with radiotherapy and chemotherapy. The principle of surgical treatment is to completely remove

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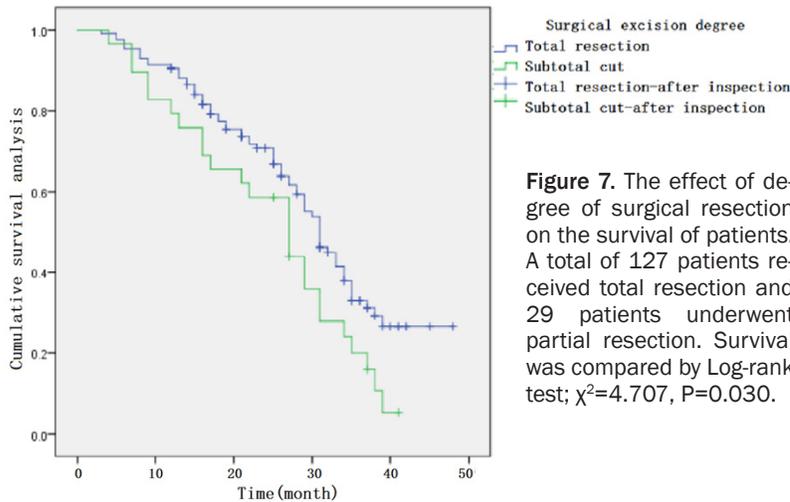


Figure 7. The effect of degree of surgical resection on the survival of patients. A total of 127 patients received total resection and 29 patients underwent partial resection. Survival was compared by Log-rank test; $\chi^2=4.707$, $P=0.030$.

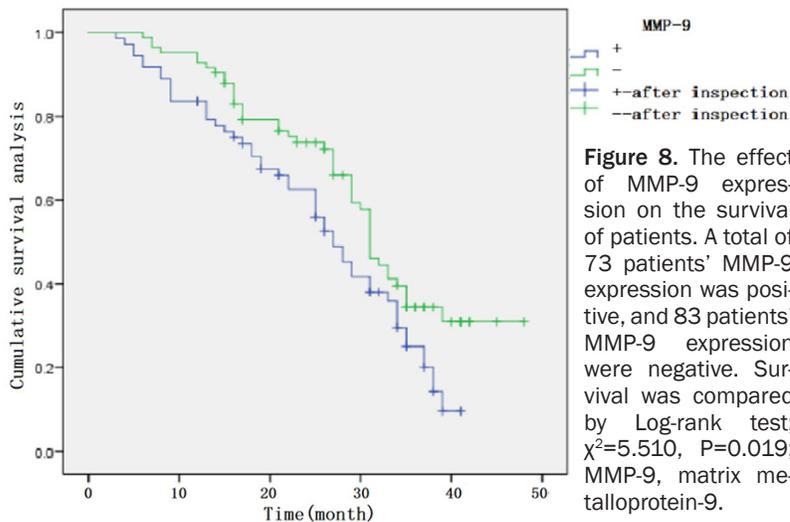


Figure 8. The effect of MMP-9 expression on the survival of patients. A total of 73 patients' MMP-9 expression was positive, and 83 patients' MMP-9 expression were negative. Survival was compared by Log-rank test; $\chi^2=5.510$, $P=0.019$; MMP-9, matrix metalloprotein-9.

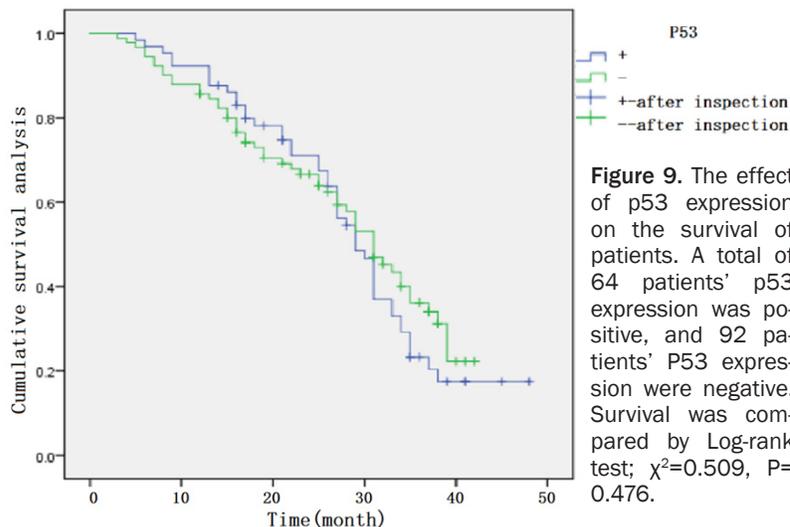


Figure 9. The effect of p53 expression on the survival of patients. A total of 64 patients' p53 expression was positive, and 92 patients' P53 expression were negative. Survival was compared by Log-rank test; $\chi^2=0.509$, $P=0.476$.

the lesions while minimizing the impact on brain function of patients [6]. In traditional craniotomy for brain glioma, positioning of the tumor and normal brain tissues mainly depends on the surgeon's direct vision. However, the unclear operated area and the complex structure of brain tissues will affect the accurate identification. As a result, surgeons fail to completely remove the diseased tissues during operation, or may even cause damage to normal tissues [7]. A study has confirmed that excessive brain tissue resection will lead to brain dysfunction and neurological impairment in patients, and serious sequelae may be left even if the patients undergo operation successfully [8]. Microsurgical treatment can accurately excise the tumor under the microscope while minimizing the exposure and damage to normal brain tissues, so it has a higher safety [9]. However, current studies and reports have shown that the postoperative survival rate of patients with glioma is low with unsatisfactory prognosis [10]. In this study, the 1-, 2- and 3-year survival rates of patients were 81.41%, 63.46% and 33.97%, respectively, indicating that the long-term survival rate of patients is low after operation. Therefore, understanding relevant factors affecting the postoperative prognosis of patients and making appropriate intervention measures have important clinical value in improving the postoperative survival rate of patients.

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Table 3. COX multivariate analyses of factors affecting postoperative prognosis of elderly patients with glioma

Factor	β	SE	χ^2	P	OR
Preoperative pathological grading	3.271	0.722	26.483	0.000	21.271
Tumor diameter	2.653	0.553	21.291	0.000	12.420
Preoperative KPS score	2.594	0.492	17.482	0.000	11.819
Postoperative radiotherapy/chemotherapy	-1.921	0.418	3.985	0.028	3.985

Note: KPS, Karnofsky Performance Status.

In recent years, increasingly more studies have revealed that cognitive dysfunction widely exists in patients with glioma, especially in elderly patients whose cognitive dysfunction is more serious. Cognitive impairment in patients is an important factor affecting the survival quality of patients [11]. Scholars have found that glioma will lead to decreased pituitary function, thus resulting in decline in cognitive function of patients, whereas surgical treatment has a positive effect on the patient's cognitive function [12]. Results of this study demonstrate that the total MMSE score and the scores of dimension of cognitive function in elderly patients with glioma 1 month after operation are significantly increased compared with those before operation (all $P < 0.05$), and the score of postoperative quality of life was obviously higher than that before operation ($P < 0.05$), suggesting that glioma operation could effectively improve cognitive function and quality of life of elderly patients with glioma.

In this study, survival-related factors of elderly patients with glioma after operation were explored. Results of univariate and multivariate analyses revealed that the preoperative pathological grading, tumor diameter, preoperative KPS score and postoperative radiotherapy/chemotherapy were independent risk factors affecting postoperative prognosis of elderly patients with glioma (all $P < 0.05$). The lower the preoperative pathological grading of the glioma, the lower the degree of tumor malignancy and slower tumor growth is observed. The extent of tumor infiltration is more limited, so difficulty in resection during operation is lower and the surgical resection is more complete [13]. Grade-IV glioma is also known as glioblastoma, and the clinical prognosis of patients is extremely poor [14]. In terms of tumor diameter and clinical prognosis, there is a close relationship between tumor size and number of tumor cells, which has a significant influence on the

patient's clinical prognosis, so it can be used as one of the criteria for the prognosis evaluation. Most studies have argued that the preoperative KPS score is one of the independent risk factors affecting postoperative prognosis of

patients with glioma, and the preoperative KPS score may be related to whether the patient is tolerant of surgery, radiotherapy and chemotherapy, thus it can be used as an index for the evaluation of clinical prognosis of patients [15].

MMP-9 is one of the members of MMP family, and studies have shown that it can directly and indirectly degrade brain tumor cells and break through the extracellular matrix, resulting in the metastasis of tumor cells and invasion into adjacent normal tissues or distant metastasis, and directly participating in the process of cell infiltration. Glioma cells are characterized by tissue infiltration, so MMP-9 was selected as one of the relevant indexes in this study [16, 17]. p53, a tumor suppressor gene, is involved in the cell cycle regulation, differentiation and apoptosis, which is a negative regulator [18]. p53 can be found in a variety of tumor tissues, and studies have confirmed that abnormal expression of p53 protein is associated with tumor cell metastasis, recurrence and poor clinical prognosis of patients. Therefore, p53 protein expression was used as a prognostic index of elderly patients with glioma in this study [19, 20]. Moreover, results of this study demonstrated that MMP-9 had a certain impact on the prognosis of patients, but it was not included into the multi-factor model (this factor was not included into the multi-factor regression model in the multiple-factor analysis when $P > 0.05$), and p53 expression had no significant effect on the prognosis of patients. Considering that the sample size in this study was small, and this study was mainly aimed at elderly patients, it is necessary to further expand the sample size for in-depth research and analysis, so as to obtain more reliable conclusions.

In conclusion, cognitive function and quality of life of elderly patients can be effectively improved via glioma operation. Preoperative pathological grading, tumor diameter, preoper-

ative KPS score, and postoperative radiotherapy/chemotherapy are independent risk factors affecting the postoperative prognosis of patients.

Disclosure of conflict of interest

None.

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