Research Article

Jiancun Wang*, Guancheng Hu, Xingyun Quan

Analysis of the factors affecting the prognosis of glioma patients

https://doi.org/10.1515/med-2019-0031
received October 4, 2018; accepted January 29, 2019

Abstract: This retrospective study was carried out to investigate factors affecting the prognosis of gliomas for better management of treatment. Clinical data from 186 glioma patients treated in our hospital from January 2013 to June 2016 were analyzed. There was slightly more male than female patients in the cohort. The main clinical symptoms included sudden limb twitching, headache and fatigue, vomiting, vision reduction and speaking disorders. The malignancy was high and the prognosis was poor in the patients, with an overall survival rate of 54.84 % by October 2017. Univariate analysis showed that the prognosis was mainly affected by age, tumor grade, preoperative Karnofsky performance status (KPS), surgical method, postoperative radiotherapy and chemotherapy, and postoperative use of temozolomide (TMZ). Multivariate Cox regression analysis showed that the independent risk factors for the prognosis were old age (≥ 60), advanced tumor, partial tumor resection, KPS of < 70, no chemotherapy after operation and < 4 courses of postoperative TMZ. The prognosis is negatively affected by age, tumor grade, KPS, and partial tumor resection. Surgical resection combined with chemotherapy and multi-course use of TMZ prolongs the survival time of patients.

Keywords: Glioma; Prognosis; Malignancy; Factor analysis

1 Introduction

Glioma derived from the glial cells is the most common primary malignant tumor in the human central nervous system, accounting for about 65% of primary intracranial tumors [1]. The incidence of glioma has been sharply increasing worldwide in recent years [2]. Gliomas have many different types and the prognosis of gliomas of different grades is affected by many factors. According to the World Health Organization classification scheme, gliomas are morphologically diagnosed as astrocytic, oligodendroglial, and mixed oligoastrocytic tumors, and are further subdivided into I to IV malignant grades based on the extent of cell proliferation, angiogenesis and necrosis [3]. Surgery remains the main therapeutic method, although other therapies, such as radiotherapy and chemotherapy and/or immunotherapy, are also used to treat the patients [4, 5]. However, even if treated with surgery combined with postoperative chemotherapy and radiotherapy, the prognosis is still poor and the recurrence is high [6-8]. Individual heterogeneity in the survival rates is undoubtedly observed and several prognostic factors that have been found in the recent years, such as age, Karnofsky performance status (KPS) and tumor locality [9, 10]. Recently, several studies have categorized glioblastoma into multiple molecular classes based upon molecular markers for better prognosis, survival time, and response to treatment [11]. Our experience shows that the survival time of glioma patients is not only related to the grade of the tumor. For example, many patients with grade II glioma had a longer survival time, and a few of them recurred within a few months even after surgery. To better understand the factors affecting the prognosis of glioma, we performed this retrospective study on patients that underwent surgical resection followed by radiotherapy and chemotherapy. The results show that age, tumor grade, KPS, and surgery methods affect the prognosis of glioma. The outcomes would help develop better treatment and care plans for these patients.

***Corresponding author: Jiancun Wang,** Department of Neurosurgery, Zhangjiajie People's Hospital, 192 Guyong road, Zhangjiajie, Hunan, China 427000. Tel:861397442406; email: Jiancunwang836@yeah.net

Guancheng Hu, Xingyun Quan, Department of Neurosurgery, Zhangjiajie People's Hospital, Zhangjiajie, China

2 Subjects and methods

2.1 Subjects

186 glioma patients treated between January 2013 and June 2016 in our hospital were included in this retrospective study. Patients were included if they were diagnosed with glioma [12] and were confirmed by postoperative pathological examination and had complete clinical data. Patients were excluded if they had other brain tumors and incomplete follow-ups. This study was approved by the ethical committee of Zhangjiajie People's Hospital. Informed consent was obtained from every participant.

2.2 Surgery, radiotherapy and chemotherapy

Craniotomy was performed to remove the tumor on the patients under general anesthesia. After the surgery, patients were given radiotherapy with a total dose of 45 to 65 Gy and chemotherapy with temozolomide (TMZ) for various cycles as previously reported [13].

2.3 Data collection

Clinical data were collected from patient's medical records, including laboratory tests, radiological examinations, medication and surgical records. The data collected included gender, age, medical history, type, clinical stage and diameter of tumor, imaging findings, surgical procedures, radiotherapy and chemotherapy plans and outcomes, last follow-up time and survival time. All patients were followed up until October 2017. Survival rates were calculated and the factors affecting the prognosis were analyzed.

2.4 Statistical analysis here

Data were analyzed using SPSS v18.0 (SPSS, Chicago, IL, USA). Categorical data were expressed as percent. Single factor analysis was performed using χ^2 test and multivariate analysis was performed using stepwise Cox regression. Values with $p < 0.05$ were considered statistically significant.

3 Results

3.1 The clinical manifestations

Among the 186 patients, 118 were males (63.44%) and 68 females (36.56%). They aged from 48 to 72 years and 77.42% were < 60 years old. The manifestations at admission included vomiting (n = 134), limb twitching (n = 104), headache and fatigue (n = 104), sudden limb twitching (n = 96), speaking disorders (n = 64), vision change (n = 40). Among them, 124 (66.67%) patients showed typical symptoms such as headache and fatigue and 62 (33. 33 %) patients had no typical symptoms.

3.2 Tumor assessments

We classified gliomas into low-grade (I and II) and high-grade based on 2007 World Health Organization Classification of the Central Nervous System [14]. Pathological analysis showed that 6 (3.23%) patients had grade I fibrous astrocytoma, 40 (21.51%) patients had grade II low malignant astrocytoma (21.51%), 80 (43. 01 %) cases had grade III degenerative astrocytoma and 60 cases (32.26%) had grade IV malignant astrocytoma (32.26%). The diameter of tumors ranged from 3.1 to 8.6 cm, among them 70 cases were < 5 cm (37. 63 %) and others were ≥ 5. 0 cm. KPS was between 53 and 87, with 146 (78. 49%) cases being ≥ 70.

3.3 Surgical resection

Complete resection was performed in 134 (72.04%) cases and partial resection in 52 (27.96%) patients. Postoperative radiotherapy was performed in 86 (46.24%) cases and chemotherapy in 144 (77.42%) cases. Temozolomide (TMZ) was used for 2 to 7 courses after operation.

3.4 Univariate analysis

The patients were followed up until October 2017 and 102 patients survived and 84 died. The overall survival rate was 54.84%. Univariate analysis showed that age, tumor grade, preoperative KPS, surgical method, postoperative radiotherapy and chemotherapy, and postoperative TMZ treatment were the factors affecting prognosis (Table 1). Among them, the course of TMZ, chemotherapy and age survival rate were highly influential on survival rate (>20%), while radiotherapy, KPS and surgical method

Table 1: Univariate analysis of prognostic factors in 186 glioma patients

Clinical factor		Number of case	Survival (n/%)	Difference in survival	X^2	P
Gender				6.28	0.875	1.232
	Male	118	62 (52.54)			
	Female	68	40 (58.82)			
Age (year)				21.53	5.271	0.021
	<60	42	30 (71.53)			
	>= 60	144	72 (50.00)			
Tumor diameter (cm)				0.88	0.315	0.575
	< 5	70	38 (54.29)			
	>= 5	116	64 (55.17)			
Tumor grade				8.63	5.941	0.015
	I-II	46	25 (54.34)			
	III-IV	140	64 (45.71)			
KPS				17.77	14.150	< 0.001
	>= 70	146	88 (60.27)			
	< 70	40	17 (42.50)			
Surgical method				17.39	5.102	0.036
	Complete resection	134	80 (59.70)			
	Partial resection	52	22 (42.31)			
Radiotherapy				19.00	3.941	0.011
	Yes	86	43 (50.0)			
	No	100	31 (31.0)			
Chemotherapy				21.62	2.414	0.022
	Yes	144	86 (59.72)			
	No	42	16 (38.10)			
Course of TMZ				46.21	5.301	0.012
	< 4	42	16 (38.10)			
	>= 4	102	86 (84.31)			

were also substantially influential (>15%). On other hand, tumor grade, gender and tumor size were less important on the survival rate (<10%).

3.5 Multivariate analysis

Multivariate analysis indicated that elderly (age ≥ 60 years), high-grade, partial resection, low preoperative KPS (< 70), no postoperative radiotherapy and chemotherapy, and shorter course of postoperative TMZ (< 4 courses) were independent risk factors for prognosis of glioma patients (Table 2).

4 Discussion

Gliomas are often highly aggressive and the prognosis is poor and the survival time is short [15]. Some risk factors

Table 2: Multivariate analysis of prognostic factors in 186 glioma patients

Independent variable	Regression coefficient	Standard error	Wald χ2	p	RR(95% CI)
Age (>=60 years)	1.467	0. 745	6.755	0.002	4.336 (1. 006, 18.675)
Advanced tumor	1.746	0.535	5.701	0.028	5.731 (2. 008, 16.356)
PKS < 70	1.121	0.295	20.111	0.011	3.547 (1. 983, 9.182)
Partial resection	1.833	0.421	9.223	0.012	5.731 (2. 008, 16.356)
No radiotherapy	1.122	0.045	10.211	0.013	4.542 (2. 013, 14.128)
No chemotherapy	1.436	0.021	23.291	0.014	5.512 (2. 883, 16.178)
TMZ < 4 courses	1.124	0.323	10.213	0.001	3.642 (1. 016, 8.128)

have been found to contribute to the pathogenesis of gliomas, such as ionizing radiation, genetic syndromes, dietary and occupational exposures [16, 17]. Although surgical resection and postoperative radiotherapy and chemotherapy delay tumor progression, the overall cure rate is still low, the recurrence rate is high. This is consistent with our results. The reported median survival time of this disease is only 14 months, and the median survival time is only about 1 year [18-20]. In our cohort, the survival rate is 54.84% after followed-up for four years and nine months to one year and four months, which is higher than that in a previous report [21].

Previous studies have shown that many factors affect the prognosis of glioma patients but remain elusive in their effects [22, 23]. Pathological grading, age of onset, surgical methods, and use of postoperative adjuvant therapy are shown to be directly related to the prognosis of patients [24, 25]. High-grade (above III) tumors have greater invasive growth than low-grade (below III) gliomas, suggesting that tumor grade is an important prognostic factor [26]. Currently, surgery is considered to be the first choice for treatment. Complete removal of the tumor is crucial for successful treatment [27, 28]. Since some patients have large tumor, or small but deeply located tumor where it is complexed with the nerves, blood vessels with unclear tumor and normal tissue boundary, surgical recession is often very challenging even under microscopy, resulting in complications and high recurrence [28-30].

A number of studies have shown that the median survival time after postoperative radiotherapy and chemotherapy and TMZ (> 4 courses) is longer than that without radiotherapy and chemotherapy or with < 4 TMZ courses, suggesting that postoperative therapies are beneficial to remove residual tumor cells and improve efficacy [31-33].

Recent studies also show that preoperative KPS is a good prognosis indicator for glioma patients. For example, the median survival time of patients with KPS of >70 is longer than that of patients with KPS of < 70 (21.5 months vs 11.5 months), indicating that a higher KPS predicts better prognosis [34, 35]. Our study showed that gender and tumor diameter are not related to the prognosis, which are consistent with the previous results [34, 35].

Multivariate regression analysis showed that elderly (age < 60 years) patients, advanced tumors, partial resection, low preoperative KPS (< 70), no radiotherapy, no chemotherapy, and short TMZ course (< 4) are independent risk factors for the prognosis of glioma patients. Furthermore, based on the impact of these parameters on courses of TMZ, chemotherapy and age survival rate, are highly influential on survival rate (>20%), while radiotherapy, KPS and surgical method are also substantially influential (>15%). On other hand, tumor grade, gender and tumor size are less important on the survival rate (<10%). However, it was found that for grade II glioma patients, tumor size is negatively associated with prognosis [36]. It is not clear why the tumor size does not impact the survival rate significantly in our study. It is likely the size of tumors may be not correlated to the tumor grade. Consequently, to better treat glioma patients, it is necessary to take in consideration the above risk factors, and implement reasonable and comprehensive treatment plans accordingly.

Since this is a single center study, the sample size is relatively small. Furthermore, as a retrospective study, data were solely based on medical records. Therefore, the conclusion needs further validation with more data.

Acknowledgement: This study was supported by Health Department of Hunan Province, China (grant no. 201305)

Conflict of interest: The authors have declared no conflicts of interest.

References

[1] Weller, M., et al., Glioma. Nat Rev Dis Primers, 2015. 1: p. 15017

[2] Rees, J., et al., Volumes and growth rates of untreated adult low-grade gliomas indicate risk of early malignant transformation. Eur J Radiol, 2009. 72(1): p. 54-64

[3] Louis, D.N., et al., The 2007 WHO classification of tumours of the central nervous system. Acta Neuropathol, 2007. 114(2): p. 97-109

[4] Cheung, N.K. and Dyer M.A., Neuroblastoma: developmental biology, cancer genomics and immunotherapy. Nat Rev Cancer, 2013. 13(6): p. 397-411

[5] Hafazalla, K., et al., Procarbazine, CCNU and vincristine (PCV) versus temozolomide chemotherapy for patients with low-grade glioma: a systematic review. Oncotarget, 2018. 9(72): p. 33623-33633

[6] Sun, J., et al., Overexpression of microRNA-155 predicts poor prognosis in glioma patients. Med Oncol, 2014. 31(4): p. 911

[7] Fuller, G.N., The WHO Classification of Tumours of the Central Nervous System, 4th edition. Arch Pathol Lab Med, 2008. 132(6): p. 906

[8] Nieder, C., et al., Therapeutic options for recurrent high-grade glioma in adult patients: recent advances. Crit Rev Oncol Hematol, 2006. 60(3): p. 181-193

[9] Carrillo, J.A., et al., Relationship between tumor enhancement, edema, IDH1 mutational status, MGMT promoter methylation, and survival in glioblastoma. AJNR Am J Neuroradiol, 2012. 33(7): p. 1349-1355

[10] Patil, C.G., et al., Prognosis of patients with multifocal glioblastoma: a case-control study. J Neurosurg, 2012. 117(4): p. 705-711

[11] Parsons, D.W., et al., An integrated genomic analysis of human glioblastoma multiforme. Science, 2008. 321(5897): p. 1807-1812

[12] Ferguson, S.D., Malignant gliomas: diagnosis and treatment. Dis Mon, 2011. 57(10): p. 558-569

[13] Stupp, R., et al., Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. N Engl J Med, 2005. 352(10): p. 987-996

[14] Fuller, G.N. and Scheithauer B.W., The 2007 Revised World Health Organization (WHO) Classification of Tumours of the Central Nervous System: newly codified entities. Brain Pathol, 2007. 17(3): p. 304-307

[15] Walbert, T. and Mikkelsen T., Recurrent high-grade glioma: a diagnostic and therapeutic challenge. Expert Rev Neurother, 2011. 11(4): p. 509-518

[16] Schwartzbaum, J.A., et al., Epidemiology and molecular pathology of glioma. Nat Clin Pract Neurol, 2006. 2(9): p. 494-503; quiz 1 p following 516

[17] Ohgaki, H., Epidemiology of brain tumors. Methods Mol Biol, 2009. 472: p. 323-342

[18] Dodoo, E., et al., Increased survival using delayed gamma knife radiosurgery for recurrent high-grade glioma: a feasibility study. World Neurosurg, 2014. 82(5): p. e623-632

[19] Yang, P., et al., Management and survival rates in patients with glioma in China (2004-2010): a retrospective study from a single-institution. J Neurooncol, 2013. 113(2): p. 259-266

[20] Ho, V.K., et al., Changing incidence and improved survival of gliomas. Eur J Cancer, 2014. 50(13): p. 2309-2318

[21] Brodbelt, A., et al., Glioblastoma in England: 2007-2011. Eur J Cancer, 2015. 51(4): p. 533-542

[22] Sarbu, N., et al., Increased signal intensity in FLAIR sequences in the resection cavity can predict progression and progression-free survival in gliomas. Neurocirugia (Astur), 2016. 27(6): p. 269-276

[23] Reithmeier, T., et al., Retrospective analysis of 104 histologically proven adult brainstem gliomas: clinical symptoms, therapeutic approaches and prognostic factors. BMC Cancer, 2014. 14: p. 115

[24] Dahlrot, R.H., The prognostic value of clinical factors and cancer stem cell-related markers in gliomas. Dan Med J, 2014. 61(10): p. B4944

[25] Ampie, L., et al., Prognostic factors for recurrence and complications in the surgical management of primary chordoid gliomas: A systematic review of literature. Clin Neurol Neurosurg, 2015. 138: p. 129-136

[26] Nuno, M., et al., Survival and prognostic factors of anaplastic gliomas. Neurosurgery, 2013. 73(3): p. 458-65; quiz 465.

[27] Gerard, C.S., Straus D., and Byrne R.W., Surgical management of low-grade gliomas. Semin Oncol, 2014. 41(4): p. 458-467

[28] Hayashi, Y., et al., Surgical strategies for nonenhancing slow-growing gliomas with special reference to functional reorganization: review with own experience. Neurol Med Chir (Tokyo), 2013. 53(7): p. 438-446

[29] Yong, R.L., et al., Residual tumor volume and patient survival following reoperation for recurrent glioblastoma. J Neurosurg, 2014. 121(4): p. 802-809

[30] Eyupoglu, I.Y., Buchfelder M., and Savaskan N.E., Surgical resection of malignant gliomas-role in optimizing patient outcome. Nat Rev Neurol, 2013. 9(3): p. 141-151

[31] Golebiowski, A., et al., Is duration of surgery a risk factor for extracranial complications and surgical site infections after intracranial tumor operations? Acta Neurochir (Wien), 2015. 157(2): p. 235-40; discussion 240

[32] Fisher, B.J., et al., Phase 2 study of temozolomide-based chemoradiation therapy for high-risk low-grade gliomas: preliminary results of Radiation Therapy Oncology Group 0424. Int J Radiat Oncol Biol Phys, 2015. 91(3): p. 497-504

[33] Nanegrungsunk, D., et al., Current evidence of temozolomide and bevacizumab in treatment of gliomas. Neurol Res, 2015. 37(2): p. 167-183

[34] Bigner, D.D., et al., Iodine-131-labeled antitenascin monoclonal antibody 81C6 treatment of patients with recurrent malignant gliomas: phase I trial results. J Clin Oncol, 1998. 16(6): p. 2202-2212

[35] Shaw, E., et al., Prospective randomized trial of low- versus high-dose radiation therapy in adults with supratentorial low-grade glioma: initial report of a North Central Cancer Treatment Group/Radiation Therapy Oncology Group/Eastern Cooperative Oncology Group study. J Clin Oncol, 2002. 20(9): p. 2267-2276

[36] Peng, X., et al., Prognostic analysis of world health organization grade II gliomas. Chin J Clin Oncol 2018. 45(8): p. 402-406