Int J Clin Exp Med 2016;9(6):11883-11888
www.ijcem.com /ISSN:1940-5901/IJCEM0023783

Original Article

An analysis on the clinical characteristics of and prognostic factors for patients with glioma

Jie Zhu[1], Haiqing Li[2], Kefeng Gu[3], Guixiang Zhao[4], Chao Zhang[5], Hongsheng Yue[1]

[1]Department of Neurosurgery, Jinan Central Hospital Affiliated to Shandong University, Jinan 250013, P. R. China; Departments of [2]Nursing, [3]Interventional Radiology, [4]Rehabilitation Medicine, [5]Internal Medicine, The Sixth People's Hospital of Jinan, Jinan, P. R. China

Received January 11, 2016; Accepted May 19, 2016; Epub June 15, 2016; Published June 30, 2016

Abstract: Objective: To investigate the clinical characteristics of and prognostic factors for patients with glioma so as to provide a basis for improving its treatment and diagnosis. Methods: A retrospective analysis was made for the clinical characteristics and follow-up data of 216 patients with glioma admitted in the department of neurosurgery of our hospital from February 2009 to June 2014. A Cox proportional hazards regression model was used to investigate the prognostic factors for patients with glioma. Results: Among all included patients with glioma, 75.5% (163/216) patients had astrocytoma and their main symptoms included headache (77.8%, 164/216) and physical weakness (48.1%, 104/216) without specific clinical manifestations. The one-year and three-year survival rates of patients with glioma were 80.1% and 45.4% respectively and the median survival time was 30 months. Univariate analysis showed that the survival rates among patients with different age, tumor grade, tumor size, extent of tumor resection, KPS score and Ki-67 expression level were of statistically significant difference (P<0.05). Multivariate Cox regression showed that age >45 years (*RR*=1.75, 95% *CI*: 1.06-2.90) and pathological grading of III-IV (*RR*=3.39, 95% *CI*: 1.61-7.16) were independent prognostic factors and tumor total resection (*RR*=0.55, 95% *CI*: 0.37-0.84) and preoperative KPS score ≥70 points (*RR*=0.70, 95% *CI*: 0.51-0.95) protective prognostic factors (P<0.05). Conclusion: Patients with glioma have no specific clinical manifestation. Glioma patients with older age (>45 years), higher tumor grade, non-total resection and low preoperative KPS scores are more likely to undergo bad prognosis.

Keywords: Glioma, clinical characteristics, prognosis, influencing factors

Introduction

Glioma, a kind of tumor derived from neurogliocytes in the brain, was the most common primary encephalic tumor, accounting for about 45%~60%. Besides, in recent years, the incidence of glioma was increasing constantly [1, 2]. Based on the morphology of tumor cells, glioma could be classified into four groups-astrocytoma, oligodendroglioma, mixed glioma and ependymoma, among which astrocytoma was found most frequently [3]. Although along with advanced technology of diagnosis and treatment, the survival rate of patients with glioma had been improved, the prognosis was still poor overall, especially for patients with malignant glioma [4, 5]. Therefore, in order to improve the living condition of patients and extend their survival time, it was of great significance to investigate prognostic factors for patients with glioma [6]. This study was intended to explore clinical manifestations of and prognostic factors for patients with glioma through a retrospective analysis made for the clinical characteristics and follow-up data of 216 patients with glioma admitted in our department of neurosurgery from February 2009 to June 2014. It would provide a basis for improving the diagnosis and treatment of glioma and extending the survival time of patients.

Materials and methods

Object of study

The object of study was patients with glioma admitted in our hospital (the department of neurosurgery) from February 2009 to June 2014. Inclusion citeria were as follows: a. Pathologically diagnosed glioma; b. Complete

clinical and follow-up data. Exclusion citeria were as follows: a. Combined with tumors at other sites; b. Severe dysfunction of major organs like the heart, liver, spleen, lung and kidney. In total, 216 patients with glioma met the requirements and were included in this study, among which 126 were male (58.3%) and 90 were female (41.7%). Their age ranged from 11 to 78 years with a median age of 43 years, averaging (41.6±10.5) years.

Surgical treatment

It mainly included two methods: a. Total/Subtotal resection: According to the macroscopic/microscopic observation during operation and reexamination results of brain MRI, it was decided that the tumor body resected ≥90% (164, 75.9%); b. Partial resection: According to the macroscopic/microscopic observation during operation and reexamination results of brain MRI, it was decided that the tumor body resected <90% (52, 24.1%).

Postoperative radiotherapy and chemotherapy

(1) Radiotherapy: Whole brain radiotherapy + low-dose local radiotherapy was performed at a dose of 20 Gy/day for six weeks (5 days/week). The accumulated doses used for high-grade and low-grade tumors were 60 Gy and 54 Gy, respectively. (2) Chemotherapy: Temozolomide 150 mg/m^2·d was administered and one course of treatment lasted for 28 days.

Follow-up method

All patients were followed up for data collection every 3 months on average through methods like making telephone calls or out-patient review after operation. The follow-up visit did not finish until 1 December 2015 or patients died. The follow-up rate in this study was 100%. The survival time referred to the period starting from the beginning of treatment to the end of follow-up visit or the time when patients died. It was expressed in month.

Study methods

By looking up record data, including hospitalization notes, various auxiliary checklists and follow-up records, clinical and follow-up data of patients with glioma was collected. Relevant items were excerpted in a unified schedule of survey, mainly including sex, age, BMI, pathological pattern and grading of glioma[as per The 2007 WHO Classification of Tumours of the Central Nervous System [7], tumor size, preoperative KPS score, tumor marker Ki-67, therapeutic method, time of the last follow-up and survival time.

Statistical analysis

A statistical analysis was conducted by using software SPSS20.0. Measurement data was expressed as $\bar{x}\pm S$ and enumeration data was described by relative number such as rate and proportion. χ^2 test was used for deduction. Kaplan-Meier method was used to estimate the survival rate of patients with glioma with different characteristics and Log-rank test was used for comparison. A multivariate Cox proportional hazards regresssion model (factors were screen step by step, α_{in}=0.05, α_{out}=0.10) was used to investigate prognostic factors for patients with glioma. The inspection level was α=0.05. P<0.05 meant that there was statistically significant difference.

Results

Clinical characteristics

Among 216 patients with glioma, the male to female ratio was 1.20:1 (118:98). There were 138 cases (63.9%) with a single lesion and 163 cases (75.5%) with astrocytoma. 98, 74 and 44 cases had pathological gradings of II, III and IV, accounting for 45.4%, 34.3% and 20.4%, respectively. The surgical treatment mainly focused on total/subtotal resection, accounting for 75.9% (164/216). The preoperative KPS score ranged from 40 to 100, averaging 83.9. Major clinical manifestations included 168 cases (77.8%) of headache, 104 cases (48.1%) of physical weakness, 67 cases (31.0%) of alalia and 50 cases (23.1%) of epileptic seizure (**Table 1**).

Survival condition

216 patients with glioma had 3-68 months of follow-up survival time, 30 months of median survival time, 80.1% (173/216) of one-year survival rate and 45.4% (98/216) of three-year survival rate. The survival condition of patients receiving different surgical methods was as follows: a. 164 cases receiving total/subtotal

Table 1. Clinical characteristics of patients with glioma (n=216)

Clinical characteristics		No. (n)	Proportion (%)
Age (years)	≤45	118	54.6
	>45	98	45.4
Sex	Male	126	58.3
	Female	90	41.7
BMI (kg/m^2)	18.5~23.9	85	39.4
	24.0~27.9	91	42.1
	≥28.0	40	18.5
No. of lesions	Single	138	63.9
	Multiple	88	36.1
Histologic type	Astrocytoma	163	75.5
	Oligodendroglioma	18	8.3
	Mixed glioma	20	9.3
	Ependymoma	15	6.9
Pathological grading	II	98	45.4
	III	74	34.3
	IV	44	20.4
Diameter of tumor	≤5 cm	72	33.3
	>5 cm	144	66.7
Extent of tumor resection	Total/subtotal resection	164	75.9
	Partial resection	52	24.1
KPS score	<70	65	30.1
	≥70	151	69.9
Preoperative epilepsy	Yes	50	23.1
	No	166	76.9
Ki-67	<10%	43	19.9
	≥10%	173	80.1

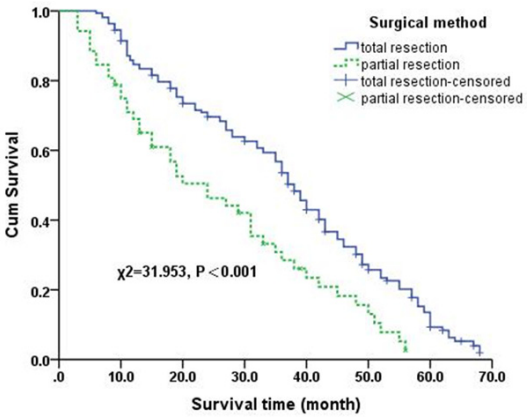

Figure 1. The survival curve of patients with glioma receiving different surgical methods.

resection had 6-68 months of follow-up survival time, 36 months of median survival time, as well as 84.1% and 50.0% of one-year and three-year survival rate, respectively; b. 52 cases receiving partial resection had 3-56 months of follow-up survival time, 19 months of median survival time, as well as 67.3% and 26.9% of one-year and three-year survival rate, respectively. The difference of patients' survival rate in two groups receiving these surgical methods was of statistical significance (χ^2= 31.953, P<0.001) (**Figure 1**).

Univariate analysis of prognosis

Univariate analysis by Log-rank test showed that the survival condition had no statistically significant difference for patients with glioma of different sex, BMI, No. of lesions, histologic type and preoperative epilepsy (P>0.05). Besides, the survival condition had statistically significant difference for patients with glioma of different age group, pathological grading, diameter of tumor, extent of tumor resection, KPS score and Ki-67 expression level (P<0.05) (**Table 2**).

Multivariate analysis of prognosis

Variables confirmed to be of significance in the above univariate analysis, including age group, pathological grading, diameter of tumor, extent of tumor resection, KPS score and Ki-67 expression level, were included in the multivariate Cox stepwise regression analysis as independent variables and survival time included as dependent variable. It was found that age >45 years (*RR*=1.75, 95% *CI*: 1.06-2.90) and pathological grading of III-IV (*RR*=3.39, 95% *CI*: 1.61-7.15) were independent risk factors for the prognosis of patients with glioma, while tumor total resection (RR=0.55, 95% CI: 0.37-0.84) and preoperative KPS score ≥70 points (RR=0.70, 95% CI: 0.51-0.95) were protective prognostic factors (P<0.05) (**Table 3**).

Discussion

Glioma, as the most common intracranial malignant tumor, was characterized by its high incidence, great difficulty in treatment, poor

Table 2. Univariate analysis of prognosis for patients with glioma (n=216)

Factors	No. [n (%)]	Median survival time (months)	χ^2	*P*
Age (years)				
≤45	118 (54.6)	34	9.342	0.002*
>45	98 (45.4)	23		
Sex				
Male	126 (58.3)	28	0.091	0.764
Female	90 (41.7)	32		
BMI (kg/m^2)				
18.5~23.9	85 (39.4)	34	4.764	0.092
24.0~27.9	91 (42.1)	28		
≥28.0	40 (18.5)	26		
No. of lesions				
Single	138 (63.9)	32	1.056	0.304
Multiple	88 (36.1)	27		
Hystologic type				
Astrocytoma	163 (75.5)	29	0.165	0.921
Non-astrocytoma	53 (24.5)	32		
Pathological grading				
I-II	98 (45.4)	37	23.571	<0.001*
III-IV	118 (54.6)	26		
Diameter of tumor				
≤5 cm	72 (33.3)	38	5.102	0.024*
>5 cm	144 (66.7)	23		
Extent of tumor resection				
Total/subtotal	164 (75.9)	36	31.953	<0.001*
Partial	52 (24.1)	19		
KPS score				
<70	65 (30.1)	20	8.452	0.015*
≥70	151 (69.9)	36		
Preoperative epilepsy				
Yes	50 (23.1)	28	1.385	0.500
No	166 (76.9)	31		
Ki-67				
<10%	43 (19.9)	36	8.345	0.004*
≥10%	173 (80.1)	27		

Note: *P<0.05.

prognosis and other features. Therefore, in recent years, researches on glioma had always been a key point in the field of neurosurgery [8]. This study indicated that the male to female ratio of patients with glioma was 1.20:1. Results of prognosis-influencing factor analysis showed that sex was not associated with the prognosis of patients with glioma. It was consistent with results of most previous studies [9, 10]. Major clinical manifestations of patients with glioma were symptoms of neurological impairment, including headache caused by increased intracranial pressure (77.8%) as well as physical weakness caused by tumor compression (48.1%) and epilepsy (23.1%). There were no specific manifestations. These results suggested that the diagnosis of glioma should take various examinations into account comprehensively [11, 12].

With the development of medical technology, the treatment of glioma was also constantly enriched and perfected. Currently, the major therapeutic regimen was comprehensive therapy based on surgery. Namely, tumors were resected by surgery and then treated by other adjuvant treatment measures like chemoradiotherapy and biological target therapy [13]. On the basis of retaining neurological function to the largest extent, total resection of tumor tissue to the best of our ability had always been the target for the surgical treatment of glioma [14]. Results of this study showed that the survival time of patients with glioma receiving total/subtotal resection was 36 months. At the same time, through exploring factors associated with the prognosis of patients with glioma by using a multivariate Cox model, we found that the mortality risk of patients receiving total/subtotal resection decreased significantly when compared with partial resection (*RR*=0.55, 95% *CI*: 0.37-0.84). This was similar to what was reported in previous studies [15, 16]. It suggested that total resection should be performed for patients with glioma as soon as possible. Besides, it was also found that patients with higher preoperative KPS score (≥70) had lower prognostic risk (*RR*=0.70, 95% *CI*: 0.51~0.95), which was also consistent with previous reports [17]. It was

Table 3. Multivariate Cox stepwise regression analysis on the prognosis factors for survival in patients with glioma (n=216)

Independent variable	Regression coefficient	Standard error	Wald χ^2	*P*	*RR* (95% *CI*)
Age >45 years (≤45 years as control)	0.562	0.257	6.311	0.012	1.75 (1.06~2.90)
Pathological grading of III-IV (I-II as control)	1.221	0.381	18.921	<0.001	3.39 (1.61~7.15)
Total resection (Control = partial resection)	-0.591	0.211	22.724	<0.001	0.55 (0.37~0.84)
KPS score ≥70 (Control<70)	-0.356	0.157	5.678	0.017	0.70 (0.51~0.95)

Note: adjusted independent variable include diameter of tumor and Ki-67 expression level.

possibly because KPS score was a measure reflecting patients' functional status. The higher KPS score was, the better patients' condition was. In this way, they would be able to bear side effects brought about by various treatments and accept comprehensive treatments. In addition, it was found that patients with older age (>45 years) and higher pathological grading (III-IV) had significantly higher prognostic risk (*RR* were 1.75 and 3.39, respectively). This was consistent with previous reports [18, 19]. It was possibly because there was invasive tumor growth. The higher the pathological grading was, the higher the grade of malignancy was and the stronger the invasiveness of tumor was. Therefore, it was very difficult to eliminate tumor thoroughly without damaging cerebral function. Furthermore, there tended to be recurrence after operation, which affected the prognosis of patients.

In conclusion, the histologic type of patients with glioma was mainly astrocytoma with no specific clinical symptoms, characterized by headache and physical weakness. Patients with older age (>45 years), higher pathological grading (III-IV) and low preoperative KPS score and receiving partial resection had poorer prognosis and shorter survival time. Therefore, for these patients, comprehensive measures should be taken and total resection should be conducted as early as possible when appropriate so as to improve the quality of life of patients and prolong their survival time.

Disclosure of conflict of interest

None.

Address correspondence to: Hongsheng Yue, Department of Neurosurgery, Jinan Central Hospital Affiliated to Shandong University, Jinan 250013, P. R. China. E-mail: yuehongshengjn@sina.com

References

[1] Wu CX, Lin GS, Lin ZX, Zhang JD, Chen L, Liu SY, Tang WL, Qiu XX, Zhou CF. Peritumoral edema on magnetic resonance imaging predicts a poor clinical outcome in malignant glioma. Oncol Lett 2015; 10: 2769-2776.

[2] Woo JY, Yang SH, Lee YS, Lee SY, Kim J, Hong YK. Continuous low-dose temozolomide chemotherapy and microvessel density in recurrent glioblastoma. J Korean Neurosurg Soc 2015; 58: 426-431.

[3] Seki T, Hida K, Yano S, Aoyama T, Koyanagi I, Houkin K. Surgical outcomes of high-grade spinal cord gliomas. Asian Spine J 2015; 9: 935-941.

[4] Draaisma K, Wijnenga MM, Weenink B, Gao Y, Smid M, Robe P, van den Bent MJ, French PJ. PI3 kinase mutations and mutational load as poor prognostic markers in diffuse glioma patients. Acta Neuropathol Commun 2015; 3: 88.

[5] Aktan M, Koc M, Kanyilmaz G. Survival following reirradiation using intensity-modulated radiation therapy with temozolomide in selected patients with recurrent high grade gliomas. Ann Transl Med 2015; 3: 304.

[6] Omuro A, DeAngelis LM. Glioblastoma and other malignant gliomas: a clinical review. JAMA 2013; 310: 1842-1850.

[7] Swerdllow SH, Campo E, Harris NL. WHO classification of tumours of haematopoietic and lymphoid tissues. France: IARC Press; 2008.

[8] Wen Q, Jalilian L, Lupo JM, Li Y, Roy R, Molinaro AM, Chang SM, Prados M, Butowski N, Clarke J, Nelson SJ. Association of diffusion and anatomic imaging parameters with survival for patients with newly diagnosed glioblastoma participating in two different clinical trials. Transl Oncol 2015; 8: 446-455.

[9] Stupp R, Taillibert S, Kanner AA. Maintenance therapy with tumor-treating fields plus temozolomide vs temozolomide alone for glioblastoma: a randomized clinical trial. JAMA 2015; 314: 2535-2543.

[10] Chen S, Tanaka S, Giannini C, Morris J, Yan ES, Buckner J, Lachance DH, Parney IF. Gliomatosis cerebri: clinical characteristics, management, and outcomes. J Neurooncol 2013; 112: 267-275.
[11] Annamalai AK, Dean AF, Kandasamy N, Kovacs K, Burton H, Halsall DJ, Shaw AS, Antoun NM, Cheow HK, Kirollos RW, Pickard JD, Simpson HL, Jefferies SJ, Burnet NG, Gurnell M. Temozolomide responsiveness in aggressive corticotroph tumours: a case report and review of the literature. Pituitary 2012; 15: 276-87.
[12] Shahar T, Ram Z, Kanner AA. Convection-enhanced delivery catheter placements for high-grade gliomas: complications and pitfalls. J Neurooncol 2012; 107: 373-378.
[13] Chowdhary SA, Ryken T, Newton HB. Survival outcomes and safety of carmustine wafers in the treatment of high-grade gliomas: a meta-analysis. J Neurooncol 2015; 122: 367-382.
[14] Mandonnet E, De Witt Hamer P, Poisson I, Whittle I, Bernat AL, Bresson D, Madadaki C, Bouazza S, Ursu R, Carpentier AF, George B, Froelich S. Initial experience using awake surgery for glioma: oncological, functional, and employment outcomes in a consecutive series of 25 cases. Neurosurgery 2015; 76: 382-389.
[15] Wong ET, Lok E, Swanson KD. Clinical benefit in recurrent glioblastoma from adjuvant NovoTTF-100A and TCCC after temozolomide and bevacizumab failure: a preliminary observation. Cancer Med 2015; 4: 383-391.
[16] Westphal M, Heese O, Steinbach JP, Schnell O, Schackert G, Mehdorn M, Schulz D, Simon M, Schlegel U, Senft C, Geletneky K, Braun C, Hartung JG, Reuter D, Metz MW, Bach F, Pietsch T. A randomised, open label phase III trial with nimotuzumab, an anti-epidermal growth factor receptor monoclonal antibody in the treatment of newly diagnosed adult glioblastoma. Eur J Cancer 2015; 51: 522-532.
[17] Trippa L, Wen PY, Parmigiani G, Berry DA, Alexander BM. Combining progression-free survival and overall survival as a novel composite endpoint for glioblastoma trials. Neuro Oncol 2015; 17: 1106-1113.
[18] Zhong J, Ali AN, Voloschin AD, Liu Y, Curran WJ Jr, Crocker IR, Shu HK. Bevacizumab-induced hypertension is a predictive marker for improved outcomes in patients with recurrent glioblastoma treated with bevacizumab. Cancer 2015; 121: 1456-1462.
[19] Tsang DS, Khan L, Perry JR, Soliman H, Sahgal A, Keith JL, Mainprize TG, Das S, Zhang L, Tsao MN. Survival outcomes in elderly patients with glioblastoma. Clin Oncol (R Coll Radiol) 2015; 27: 176-183.