Original article

Prognostic factors influencing clinical outcomes of glioblastoma multiforme

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Keywords: *glioblastoma multiforme; prognostic factor; disease progression; survival; chemotherapy*

Background Glioblastoma multiforme (GBM) is the most malignant kind of astrocytic tumors and is associated with a poor prognosis. In this retrospective study, we assessed the clinical, radiological, genetic molecular and treatment factors that influence clinical outcomes of patients with GBM.

Methods A total of 116 patients with GBM who received surgery and radiation between January 2006 and December 2007 were included in this study. Kaplan-Meier survival analysis and Cox regression analysis were used to find the factors independently influencing patients′ progression free survival (PFS) time and overall survival (OS) time.

Results Age, preoperative Karnofsky Performance Scale (KPS) score, KPS score change at 2 weeks after operation, neurological deficit symptoms, tumor resection extent, maximal tumor diameter, involvement of eloquent cortex or deep structure, involvement of brain lobe, Ki-67 expression level and adjuvant chemotherapy were statistically significant factors (P <0.05) for both PFS and OS in the univariate analysis. Cox proportional hazards modeling revealed that age ≤50 years, preoperative KPS score ≥80, KPS score change after operation ≥0, involvement of single frontal lobe, non-eloquent area or deep structure involvement, low Ki-67 expression and adjuvant chemotherapy were independent favorable factors (P <0.05) for patients′ clinical outcomes.

Conclusions Age at diagnosis, preoperative KPS score, KPS score change at 2 weeks postoperation, involvement of brain lobe, involvement of eloquent cortex or deep structure, Ki-67 expression level and adjuvant chemotherapy correlate significantly with the prognosis of patients with GBM.

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Glioblastoma multiforme (GBM) is the most malignant kind of primary neoplasm in the central nervous system. The median survival time is usually less than a year despite multimodal intensive treatments including maximum surgical resection, irradiation and chemotherapy.[1] Even receiving the same treatments, the clinical outcome of patients with GBM varies significantly. It is important for us to understand the factors that contribute positively or negatively to the prognosis of patients, which may guide treatment paradigms and therapeutic strategies aimed at prolonging survival. Some researchers[2-4] have analyzed the role of patients′ clinical characteristics and tumor imaging features. Tumor molecular alteration has been taken into consideration in few studies.[5,6] Few studies are based on Chinese patients.

In this retrospective study, we analyzed an institutional series of Chinese patients with GBM to identify clinical, radiological, genetic molecular and treatment factors influencing the clinical outcomes.

METHODS

Patients

We retrospectively identified all the patients with GBM, who had undergone surgical resection and radiation in the Glioma Treatment Center of Beijing Tiantan Hospital between January 2006 and December 2007. Both primary and secondary GBM patients were included. The histological diagnosis was reaffirmed by two independent neuropathologists and graded according to the World Health Organization (WHO) classification.[7] Patients who died of non-primary diseases were excluded.

Data collection

The following data were collected from the medical records of the patients: (1) Demographic data (age and gender), preoperative Karnofsky Performance Scale (KPS) scores and KPS scores at two weeks after operation. (2)

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Preoperative clinical symptoms: headache, seizure attack and presentation of neurological deficit symptoms. (3) Preoperative and postoperative contrast enhancing magnetic resonance imaging (MRI): tumor radiological characteristics (including surrounding edema, cyst formation, contrast enhancement, maximal diameter, midline shift, contralateral involvement, hemisphere involvement, involvement of eloquent cortex or deep structure and involvement of brain lobe) assessed by a neuroradiologist based on preoperative MRI, extent of resection assessed on the postoperative enhanced MR image within 24 hours and graded as total or subtotal resection. (4) Follow-up data: clinical outcomes including progression free survival (PFS) and overall survival (OS) time, which were mainly collected when patients visited the clinics or during phone interviews with patients and/or their relatives.

Treatment

Standard treatment was consisted of surgery and postoperative radiotherapy, with or without adjuvant chemotherapy. Maximal tumor bulk resection while preserving the key eloquent cortex was the principle of operation. Preoperative functional MRI and awake mapping were used if necessary. Postoperative limited-radiotherapy was routinely delivered to the patient within 1 month after surgery. The total dose was 60 Gy, which was divided into 30 daily fractions of 2 Gy each. For patients receiving adjuvant chemotherapy, the treatment was given 4 weeks after radiation and composed of at least two cycles of chemotherapy. Combined drugs were used and made according to the drug-resistant protein expression status. A total of six cycles were to be administered if no disease progression occurred and there were no irreversible hematological toxic effects.

Evaluation of genetic molecular alteration

Immunoperoxidase staining for Ki-67, phosphatase and tension homology deleted onchromosome ten (PTEN), matrix metallopeptidase 9 (MMP-9) and epidermal growth factor receptor (EGFR) (Invitrogen, USA) were performed on formalin-fixed paraffin-embedded tissue sections following the standard protocol recommended by the manufacturer. Two blinded observers independently evaluated the slides. In each case, at least 1000 cells were counted in 10 different areas using the 40×objective lens. In case of a discrepancy, the two observers simultaneously reviewed the slides to achieve a consensus. The expression of individual molecule was graded as high or low for the analysis.

Statistical analysis

The primary goals were to uncover which parameters were associated with the clinical outcomes of the patients. Tumor progression was defined according to the modified WHO criteria,[8] as an increase of tumor size by 25 percent or appearance of new lesions. All timing was referenced to the date of operation, e.g. PFS time as the interval between operation and radiographic progression, OS time as the period from operation to death. Survivor function curves were calculated with the Kaplan-Meier method and differences were evaluated with the log-rank test. Multivariate Cox models were used after univariate analysis. A *P* value less than 0.05 were considered as statistically significant. SPSS 13.0 (USA) was used for statistical analysis.

RESULTS

General data

Totally 116 patients were recruited in the study, including 95 primary and 21 secondary GBM. Of the 116 cases, 28 had total tumor resection and 88 had subtotal tumor resection. For treatment, 76 patients had surgery, radiation and adjuvant chemotherapy and the other 40 patients had surgery and radiation only. In a median follow-up of 14 months (range: 5–30 months), 76 cases suffered tumor progression and 43 cases died. The patients′ median PFS time was 274 days (95% *CI*: 196–352 days) and median OS time was 508 days (95% *CI*: 378–637 days) (Figure).

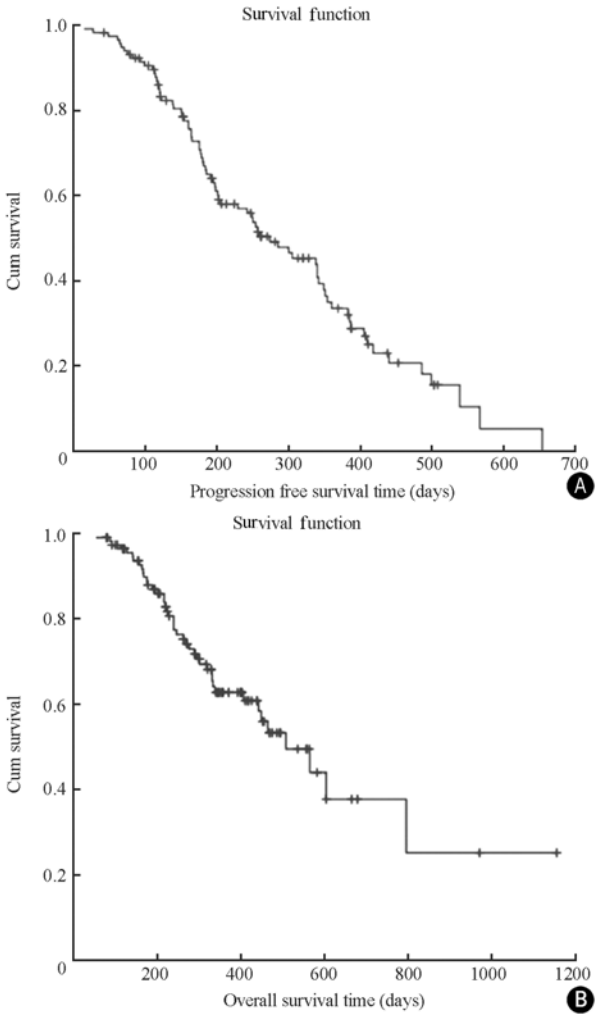

Figure. Kaplan-Meier estimates of PFS time (**A**) and OS time (**B**) for all the patients with GBM treated in our center.

Univariate analysis

According to the univariate analysis, clinical factors

Table 1. Clinical and treatment factors associated with PFS and OS in the univariate analysis

Variable	Cases (*n*)	Median PFS (days)	*P* values	Median OS (days)	*P* values
Gender					
Male	76	250	0.122	508	0.292
Female	40	340		604	
Age					
≤50	81	342	0.037	565	0.012
>50	35	191		331	
Headache					
Yes	69	257	0.094	508	0.638
No	30	229		449	
Seizure					
Yes	29	259	0.743	449	0.679
No	70	254		508	
Neurological deficit symptoms					
Yes	32	164	0.001	295	0.008
No	67	338		565	
Preoperative KPS score					
≥80	71	349	0.002	604	0.004
<80	45	204		319	
KPS score change at 2 weeks after operation					
≥0	100	339	0.000	565	0.000
<0	16	119		216	
GBM type					
Primary	95	285	0.598	565	0.243
Secondary	21	250		338	
Extent of resection					
Total	28	383	0.007	604	0.035
Subtotal	88	242		449	
Adjuvant chemotherapy					
Yes	76	340	0.011	604	0.002
No	40	184		331	

PFS: progression free survival; OS: overall survival; KPS: karnofsky performance scale; GBM: glioblastoma multiforme.

associated with PFS and OS are reported in Table 1. Age at diagnosis, preoperative KPS score, KPS score change at 2 weeks after operation and neurological deficit symptoms were statistically significant factors for PFS and OS. Both tumor resection extent and adjuvant chemotherapy were correlated with PFS and OS.

Radiological and molecular factors associated with PFS and OS are showed in Table 2. Tumor maximal diameter, involvement of eloquent cortex or deep structure and involvement of brain lobe were radiologically significant factors related to PFS and OS. Generous molecular changes were found in the GBM patients. Ki-67 was the only molecule statistically related to the patients′ PFS and OS.

Multivariate analysis

Factors with corresponding *P* values of less than 0.05 in the univariate analysis were introduced into multivariate model. Age at diagnosis (*P*=0.002), preoperative KPS score (*P*=0.001), KPS score change after operation (*P*=0.000), involvement of brain lobe (*P*=0.001), Ki-67 expression level (*P*=0.002) and adjuvant chemotherapy (*P*=0.001) were independent factors for PFS. In regards to OS, age at diagnosis (*P*=0.003), preoperative KPS score (*P*=0.000), KPS score change after operation (*P*=0.000), involvement of eloquent cortex or deep structure (*P*=0.009),

Table 2. Radiological and genetic factors associated with PFS and OS in the univariate analysis

Variable	Cases (*n*)	Median PFS (days)	*P* values	Median OS (days)	*P* values
Surrounding edema					
Yes	86	254	0.373	464	0.637
No	24	340		604	
Cyst formation					
Yes	31	349	0.230	508	0.390
No	79	242		565	
Contrast enhancement					
Yes	108	259	-	508	-
No	2	-		-	
Midline shift					
Yes	69	259	0.323	464	0.413
No	41	340		604	
Contralateral involvement					
Yes	27	198	0.141	333	0.107
No	83	338		565	
Maximal diameter					
<5 cm	48	349	0.030	565	0.032
≥5 cm	62	250		442	
Hemisphere involvement					
Left	42	259	0.821	565	0.980
Right	60	338		508	
Eloquent cortex or deep structure involvement					
Yes	54	181	0.000	331	0.000
No	56	383		604	
Involvement of brain lobe					
Single frontal lobe	25	567	0.000	-	0.000
Other single lobe	22	349		604	
Multiple lobe	61	185		406	
Ki-67					
Low	56	338	0.019	604	0.036
High	60	201		449	
PTEN					
Low	37	274	0.382	449	0.899
High	69	250		508	
MMP-9					
Low	35	305	0.447	464	0.905
High	73	259		508	
EGFR					
Low	34	340	0.505	565	0.144
High	74	259		508	

PFS: progression free survival; OS: overall survival.

Ki-67 expression level (*P*=0.009) and adjuvant chemotherapy (*P*=0.047) persisted as statistically independent prognostic factors. Among them, age ≤50, preoperative KPS ≥80, KPS score change after operation ≥0, involvement of single frontal lobe, non-eloquent area or deep structure involvement, low Ki-67 expression and adjuvant chemotherapy were favorable factors (Table 3).

DISCUSSION

For the dismal clinical outcomes of GBM, a full-scale knowledge of the prognostic factors from native patients is essential to the doctors in China. Age at diagnosis and preoperative KPS score have been the most well-documented predictors of survival.[6,9-11] We have reaffirmed them in the study as independent factors for PFS and OS. KPS score change at 2 weeks after operation is also identified as a prognostic predictor. The relative risk is even lower in the multivariate analysis, which may be attributed to the influence of surgery complication.

Table 3. Prognostic factors associated with PFS and OS in the multivariate analysis

Variable	Hazard ratio	95% *CI*	*P* values
PFS			
Age	2.827	1.443–5.539	0.002
Involvement of brain lobe	1.593	1.214–2.090	0.001
Preoperative KPS score	0.337	0.178–0.638	0.001
KPS score change at 2 weeks after operation	0.203	0.097–0.422	0.000
Ki-67	2.950	1.473–5.909	0.002
Adjuvant chemotherapy	0.294	0.146–0.593	0.001
OS			
Age	2.777	1.410–5.468	0.003
Eloquent cortex or deep structure involvement	2.234	1.219–4.096	0.009
Preoperative KPS score	0.283	0.140–0.571	0.000
KPS score change at 2 weeks after operation	0.254	0.118–0.546	0.000
Ki-67	2.439	1.247–4.769	0.009
Adjuvant chemotherapy	0.516	0.268–0.922	0.047

PFS: progression free survival; OS: overall survival; KPS: karnofsky performance scale.

The study revealed that tumor maximal diameter was a radiologically significant factor related to PFS and OS in the univariate analysis, not in the multivariate analysis. Single frontal lobe involvement was confirmed as a significant predictor of later progression and involvement of eloquent cortex or deep structure was independently associated with poor survival. All these indicate tumor location may be more important than tumor size for the prognosis of these patients.[12]

Ki-67 is a stable cell proliferation marker, which is only found in the active parts of the cell cycle: G1, G2, S, and M phases. The latest WHO classification of central nervous system tumors includes Ki-67 as an additional tool in histological typing and grading.[13] Our results showed Ki-67 was also a significant independent prognostic factor for GBM. Patients with low Ki-67 expression had much longer PFS and OS in comparison to those with high. Although some researches[14-16] have suggested that PTEN, MMP-9 and EGFR may influence the clinical outcomes of patients with glioma, no correlation was found in the analysis.

Tumor resection can relieve the symptoms of the patient and provides conclusive pathologic diagnosis. Advances in neurosurgical techniques have improved the safety of resection. In our center, preoperative functional MRI and awake mapping were routinely used for maximal resection while preserving key eloquent cortex if necessary. Only a quarter of patients achieved total resection, which was much lower than that reported by others in the country.[17] Judging by postoperative enhancing MRI rather than by operator himself may be the reason. Several data[6,9,10] have identified resection extent as an important predictor of clinical outcomes. It was not verified in our multivariate analysis. But we still think total resection is a favorable prognostic factor, since the independent radiological prognostic factors found in the study relate closely to the tumor resection extent.

Postoperative radiotherapy has been recognized as standard therapy for GBM for a long time.[18] The role of chemotherapy based on alkylating agent has been controversial[19-21] until the results of trial EORTC 26981 came out. The results showed temozolomide (TMZ) provided a statistically significant and clinically meaningful survival benefit, producing an increase in the median survival time from 12.1 to 14.6 months and in the two-year survival rate from 10% to 26%.[22] There are two kinds of patients receiving chemotherapy in our center. Patients with low O6-methylguanine-DNA methyl-transferase (MGMT) expression would take TMZ only and those with high MGMT expression would receive combined chemotherapy of cisplatin (DDP) and teniposide (VM-26), DDP and TMZ or VM-26 and TMZ. Our study confirmed adjuvant chemotherapy as an independent favorable prognostic factor for the clinical outcomes of GBM. Patients with adjuvant chemotherapy had a median PFS of 340 days and a median OS of 604 days, which were in accordance with the results from EORTC26981.

In conclusion, this is a valuable retrospective study with considerable number of GBM patients and full-scale analysis. Age at diagnosis, preoperative KPS score, KPS score change at 2 weeks postoperation, involvement of brain lobe, involvement of eloquent cortex or deep structure, Ki-67 expression level and adjuvant chemotherapy correlate significantly with the prognosis of these patients with GBM.

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