JBUON 2018; 23(1): 173-178
ISSN: 1107-0625, online ISSN: 2241-6293 • www.jbuon.com
E-mail: editorial_office@jbuon.com

ORIGINAL ARTICLE

Factors affecting the survival of patients with glioblastoma multiforme

Vesna Nikolov[1,2], Miodrag Stojanovic[2,3], Aleksandar Kostic[1,2], Misa Radisavljevic[1], Natasa Simonovic[4], Boban Jelenkovic[1], Luka Berilazic[1]

[1]Clinic of Neurosurgery, Clinical Center, Nis; [2]Faculty of Medicine, University of Nis, Nis; [3]Institute for Public Health Nis, Nis; [4]Clinic of Oncology, Clinical Center, Nis, Serbia

Summary

Purpose: *Glioblastoma multiforme (GBM) is the most aggressive malignant tumor in the brain and no therapy can achieve full recovery/cure. The aim of this study was to identify which factors could improve the survival of operated patients, and to determine which kind of therapy was most successful.*

Methods: *The study was conducted at the Clinic for Neurosurgery in Nis, Clinical Centre Nis and the Oncology Institute, Clinical Center Nis. A cohort of patients who underwent surgery between January 2013 and December 2015 was studied and continuous monitoring of survival lasted until June 2017.*

Results: *Patients who underwent only biopsy have 3.82-fold greater chance of death than patients with complete tumor resection (HR 3,825; p=0.001). Karnofsky performance status score significantly affected survival (preoperatively and postoperatively; p<0.001). Apart from radiotherapy, three types of chemotherapy were applied: carmustine (BCNU) – 32.80% of the patients, procarbazine/lomustine/vincristine (PCV) – 38.80% and temozolomide – 28.40%. Kaplan-Meier overall survival showed that patients treated with temozolomide had the longest survival compared to patients treated with BCNU and/or PCV chemotherapy.*

Conclusion: *The best prognosis was seen in those patients who had complete tumor resection. Patients treated with temozolomide had the best survival compared with those treated with BCNU and PCV chemotherapy.*

Key words: *BCNU, glioblastoma, Karnofsky performance status, PCV, radiotherapy, temozolomide*

Introduction

GBM falls into the most common and most malignant tumors of the brain, representing 17% of all primary brain tumors [1]. It is characterized by rapid and infiltrative growth, which is histologically reflected in malignant morphology, tumor necrosis and vascular proliferation.

There are two subtypes of glioblastoma, primary and secondary. Primary GBM (pGBM) develops *de novo* in elderly patients and is characterized by shorter duration of symptoms (<3 months). Secondary or progressive GBM (sGBM) develops from glioma grade II and III. It has a longer duration of symptoms and often occurs in patients under 40 years of age [2,3]. Patients with GBM usually have a short medical history. Symptoms may vary from the appearance of seizures, headache, nausea, vomiting (resulting from increased intracranial pressure), to focal signs such as paralysis, speech disorder, which depend on the location of the tumor.

The diagnosis is based on magnetic resonance imaging (MRI) of the brain where the heterogeneous mass is seen, along with the hypointensity of the T1 sequences and the hyperintensity of the T2 sequences. GBM usually contains central necrosis, surrounded by large peripheral oedema [4,5].

Correspondence to: Vesna Nikolov, MD, PhD. Svetozara Miletica 7, Nis, Serbia.
Tel: +381 653094135, E-mail: v.novak@yahoo.com
Received: 25/08/2017; Accepted: 09/09/2017

Although MRI of the brain and clinical investigation can suggest presence of GBM, the pathological tissue study is mandatory for a definite diagnosis.

The cause of the GBM genesis is largely unknown. Despite advances in surgical techniques, radiation and chemotherapy, the prognosis of GBM is still very poor, and the median survival is 12.1-14.6 months after diagnosis [6,7].

One in 20 patients has a genetic predisposition [8]. Only 3-5% of patients live more than 36 months, and the 5-year survival rate is less than 5% [9].

Important prognostic factors for survival are age, the patient preoperative status, and extent of resection [10]. Lately, the psychological status of the patient is taken as an important factor of prognosis. The purpose of this study was to investigate clinical characteristics and kinds of therapy that were significantly connected with longer survival.

Methods

This study was conducted at the Clinic for Neurosurgery and the Institute of Oncology Nis. The analyzed patients were operated between January 2013 and December 2015 and were monitored up until June 2017. During this period, a total of 67 patients with GBM diagnosis were registered.

All patients were informed about the proposed therapy and signed informed consent. The study was approved by the ethics committees of the participating centres.

The analysis included gender, age, preoperative Karnofsky performance status score, tumor localization, type of surgery (complete/partial resection or biopsy only), the time to the initiation of oncologic therapy, the kind of therapy (temozolomide/BCNU/PCV) and survival duration.

All patients were treated with radiotherapy with 60 Gy in 30 fractions (2 Gy per day, 5 days a week). Patients were irradiated by 3D conformal radiotherapy on a linear accelerator (ONCOR", Siemens, Nis, Serbia), with 6 MeV energy.

Depending on the chemotherapy administered, the patients were classified into three groups:

Group 1: 6 cycles of temozolomide. The first cycle at a dose of 150 mg/m^2 for 5 days; the next 5 cycles at a dose of 200 mg/m^2. Cycles were repeated every 3 weeks.

Group 2: procarbazine, lomustine-CCNU, vincristine (PCV). CCNU 110 mg/m^2 p.o. day 1. Procarbazine 60 mg/m^2 p.o. days 8-21. Vincristine 1.4 mg/m^2 (maximum 2 mg) i.v., days 8 and 21. Cycles were repeated every 6 to 8 weeks for a total of 6 cycles.

Group 3: Carmustine (BCNU). BCNU 200 mg/m^2 i.v., day 1. Cycles were repeated every 8 weeks, for a total of 6 cycles.

Statistics

Data were presented as mean±standard deviation or frequencies (%) as appropriate. Kaplan-Meier survival was used for patients with GBM in relation to the applied oncological therapy, localisation, type of surgery and other clinical and demographic parameters. Univariate Cox regression analysis was used to test the predictive potential of death. Significance was set at $p<0.05$ and data analysis was preformed using the SPSS 16.0 software package.

Results

The patient average age was 50.49±14.69 years (Min 22, Max 79). There were 58.20% males and 41.80% females (Table 1).

Two groups were compared based on elapsed time for radiotherapy delivery: One and 2 months after surgery.

No statistically significant difference was noted between the 2 groups in terms of survival ($p=0.269$) (Table 2).

The preoperative hazard ratio (HR) of the Karnofsky performance status was 0.950, indicating

Table 1. Patient demographic and clinical characteristics

Characteristics	*n*	*%*
Gender		
Male	39	58.20
Female	28	41.80
Age, years (mean±SD)	50.49±14.69	
Location		
Frontal	14	20.90
Temporal	23	34.30
Parietal	19	28.40
Occipital	10	14.90
Cerebral	1	1.50
Type of surgical intervention		
Complete resection	35	52.20
Partial resection	24	35.80
Biopsy only	8	11.90
Time to oncological therapy		
1 month	38	56.70
2 months	29	43.30
Therapy		
BCNU	22	32.80
PCV	26	38.80
Temozolomide	19	28.40
Preoperative Karnofsky score (mean±SD)	81.64±12.01	
Postoperative Karnofsky score (mean±SD)	80.00±12.06	

that decrease of one unit of this index increased the chance of death by 5.2%. The postoperative HR of the Karnofsky performance status was 0.956, indicating that decrease of one unit of this index increased the chance of death by 4.6% (Table 3).

Better prognosis was seen in those patients in whom maximal tumor resection was achieved compared with those with biopsy only. Patients with a biopsy had a 3.82-fold greater chance of death than patients with complete resection (HR 3.825, p=0.001; Figure 1).

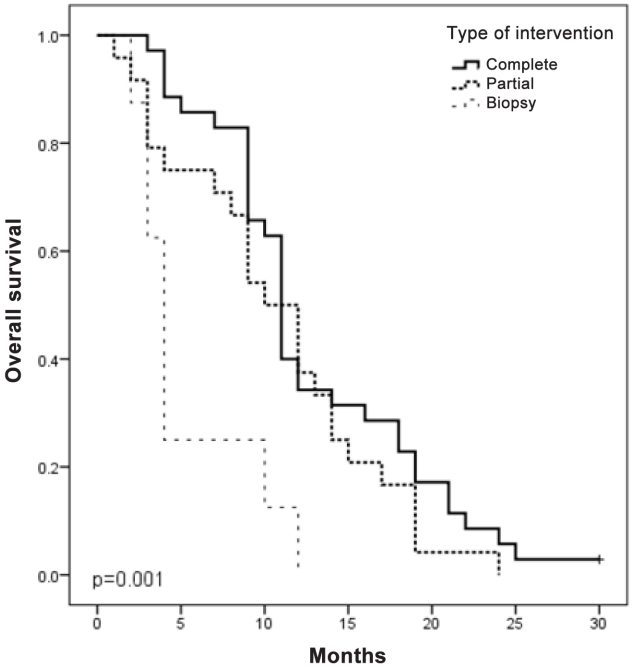

Figure 1. Kaplan-Meier overall survival according to the type of intervention.

The most frequent localization was the temporal area - 34.30%, but the statistics showed that it has no effect on survival (p=0.615; Figure 2).

Kaplan-Meier overall survival showed that patients treated with temozolomide had the best survival, compared with patients treated with BCNU and PCV chemotherapy (p=0.013; Figure 3).

Discussion

By analysing our data, we came to the conclusion that age affects significantly the duration of survival (HR 1.025; p=0.01; Table 3). Similar results have been achieved by Shinoim et al. who have suggested that younger patients have a longer survival compared to the elderly [11], whereas no such statistically significant difference was noted in our analysis concerning gender.

For the general assessment of the patient condition the Karnofsky score was used, which was determined before and after the surgical intervention. According to Cambless et al. candidates for surgical tumor removal should have a Karnofsky score higher than 70 [12]. It was shown that the values of the Karnofsky score, both preoperatively and postoperatively, affected significantly survival (p<0.001 ; Table 3). Reducing the Karnofsky score preoperatively by one unit led to an increase in mortality by 5.2% (HR 0.950), and also reducing the Karnofsky score postoperatively by one unit led to an increase in fatal outcome by 4.6% (HR 0.956 ; Table 3). Lacroix and colleagues have shown that the presurgical Karnofsky score and type of

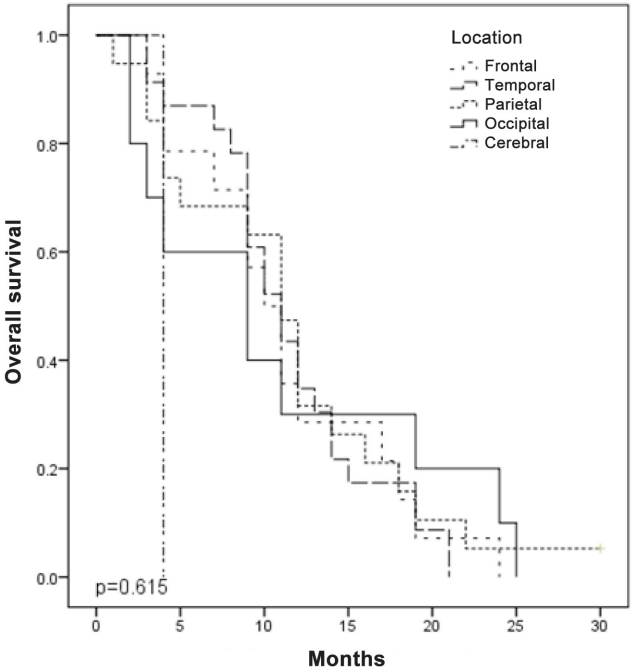

Figure 2. Kaplan-Meier overall survival according to the tumor location.

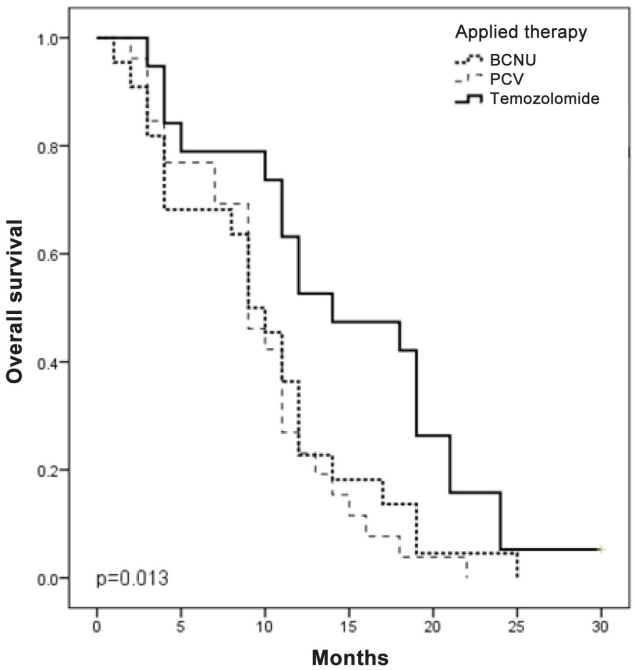

Figure 3. Kaplan-Meier overall survival according to performed therapy.

Table 2. Analysis of survival parameters according to different therapies, types of intervention, locations, and time to oncological therapy

Parameters	*Mean survival (months)*	*SE*	*p value**
Applied therapy			0.013
BCNU	9.91	1.34	
PCV	9.65	0.97	
Temozolomide	14.79	1.73	
Type of intervention			0.001
Complete resection	12.86	1.10	
Partial resection	10.75	1.27	
Biopsy only	5.25	1.29	
Location			0.615
Frontal	11.29	1.67	
Temporal	11.44	1.07	
Parietal	11.42	1.66	
Occipital	10.80	2.81	
Cerebral	4.00	0.00	
Time to oncological therapy			0.269
1 month	12.18	1.02	
2 months	9.90	1.25	

* log-rank test, SE: standard error

Table 3. Predictive potential for death of the tested demographic and clinical characteristics (univariate Cox regression analysis)

Predictors	*HR*	*95%CI*	*p value*
Gender – male	1.455	0.884-2.393	0.140
Age	1.025	1.006-1.045	0.010
Location			
Frontal	Reference group		
Temporal	1.011	0.518-1.972	0.975
Parietal	0.880	0.436-1.775	0.721
Occipital	0.870	0.380-1.992	0.741
Cerebral	3.852	0.484-30.676	0.203
Applied therapy			
BCNU	Reference group		
PCV	1.210	0.678-2.156	0.519
Temozolomide	0.516	0.273-0.973	0.041
Type of intervention			
Complete resection	Reference group		
Partial resection	1.331	0.783-2.263	0.292
Biopsy only	3.825	1.694-8.639	0.001
Time to oncological therapy			
1 month	Reference group		
2 months	1.291	0.791-2.111	0.307
Preoperative Karnofsky score	0.950	929-0.972	<0.001
Postoperative Karnofsky score	0.956	0.934-0.979	<0.001

HR: hazard ratio, 95%CI: 95% confidence interval

surgical resection are the most important factors related to survival after operation or reoperation. Longer survival had a group in which complete resection was achieved [13].

In this study, comparison of the type of surgical intervention with respect to survival has shown that the best prognosis was achieved in patients with maximal tumor reduction compared with those in whom only a biopsy was made (Figure 1). Patients with biopsy alone had 3.82-fold greater chance of death than patients with complete resection (HR 3,825, p=0.001). Sanai and Young [14,15] reported similar results in their works. Nevertheless, for recurrent GBM, survival benefit must be balanced against the risk of neurological morbidity, as more aggressive cytoreduction is usually connected with significant postoperative neurological deterioration [16].

Temporal localization was the most frequently encountered (34.30%), however it had no effect on survival (p=0.615) (Figure 2).

As for postoperative therapy, all patients had three-dimensional conformal radiotherapy with a tumor dose of 60 Gy in 30 fractions, 2 Gy daily, 5 days a week, today's standard external beam radiotherapy [17]. The target volume was 2-3cm around the lesion. Various regimes for increasing the radiation dose did not offer significant improvement in the local GBM control [18]. Niranian and coworkers stressed the need of financing clinical researches that will provide a higher level of evidence of the future role of radiotherapy for GBM patients in whom the disease progressed despite the applied therapy [19].

In addition to the radiotherapy delivered, three types of chemotherapy were used in GBM patients: BCNU-32.80%, PCV-38.80%, and temozolomide-28.40%. The chemotherapeutic agents were administered adjuvantly or separately in relation to radiotherapy. One metaanalysis has shown that postoperative chemotherapy extends the survival of patients with GBM [20].

The standard management for most GBM patients includes temozolomide, either concurrent with radiotherapy or as adjuvant. Focal radiation remains keystone of radiation therapy for most high grade gliomas [21].

In our study, PCV was used in 38.80% of the patients. The Karnofsky performance status of all patients in the PCV therapy group was satisfactory (median 80%). Total resection was achieved in 42.30% and biopsy in 15.38%. As in the study of Stupp et al., our study has also shown that adjuvant therapy with PCV prolonged the disease-free interval, but had no effect on total survival [22].

Patients on temozolomide had the best overall survival compared to patients treated with BCNU and PCV chemotherapy (p=0.013; Figure 3). In a randomized phase III European and Canadian trial, it was clearly demonstrated that the addition of 6 cycles of adjuvant temozolomide offered a significant survival benefit [23]. The final results of this study showed that the total survival was 27.2% after 2 years, 16.0% after 3 years, 12.1% after 4 years and 9.8% after 5 years in the group of radiotherapy and temozolomide, compared to 10.9%, 4.4%, 3.0% and 1.9% in the radiotherapy group [24].

Concerning the time of postoperative radiotherapy initiation (1 month vs 2 months) no significant difference in survival (p=0.269) was noted between the 2 groups (Table 2). In contrast, negative effect of delaying the initiation of radiotherapy for more than 6 weeks was shown in the study by Irwin et al. [25]. This study showed that each week of delay increased the risk of death by 8.9%. However, in many countries there is a waiting list problem for beginning radiotherapy [26-29].

Patients with GBM continue to represent a major problem in terms of treatment and survival. Unfortunately, none of the mentioned therapeutic methods offer a satisfactory solution.

Clinical and molecular factors that could contribute to improved survival of a patient with GBM are still being searched. Some karyometric variables that represent nuclear polymorphism and larger nuclear size are associated with larger tumors and, therefore, with decreased survival [30]. Genetic markers of hypermethylation of O^6-methylguanine-DNA methyltransferase (*MGMT*) and gene mutations for cytosolic $NADP^+$ dependent - isocitrate dehydrogenase (*IDH1*) have been proven as prognostically significant [31,32]. Research on the genetic level will enlighten and pave the way to more effective treatments for this devastating disease.

Conflict of interests

The authors declare no conflict of interests.

References

1. Khwaja FW, Nolen JD, Mendrinos SE et al. Proteomic analysis of cerebrospinal fluid discriminates malignant and nonmalignant disease of the central nervous system and identifies specific protein markers. Proteomics 2006;6:6277-87.
2. Brandes AA, Franceschi E, Tosoni A et al. Temozolomide concomitant and adjuvant to radiotherapy in elderly patients with glioblastoma: correlation with MGMT promoter methylation status. Cancer 2009;115:3512-8.
3. Louis DN and International Agency for Research on Cancer. WHO classification of tumours of the central nervous system. International Agency for Research on Cancer, Lyon, 2007.
4. Cha S, Lupo JM, Chen MH et al. Differentiation of glioblastoma multiforme and single brain metastasis by peak height and percentage of signal intensity recovery derived from dynamic susceptibility-weighted contrast-enhanced perfusion MR imaging. Am J Neuroradiol 2007;28:1078-84.
5. Grunwald I, Dillmann K, Roth C, Backens M, Reith W. Supratentorial tumors. Radiologe 2007;47:471-85.
6. Vecht CJ, Mokhtari K, Wesseling P et al. Effects of radiotherapy with concomitant and adjuvant temozolomide versus radiotherapy alone on survival in glioblastoma in a randomised phase III study: 5-year analysis of the EORTC-NCIC trial. Lancet Oncol 2009;10:459-66.
7. CBTRUS. Statistical Report: Primary Brain and Central Nervous Tumors Diagnosed in the United States in 2004-2006. Neurooncology 2012;14:1-49.
8. Gerson SL. MGMT: its role in cancer aetiology and cancer therapeutics. Nat Rev Cancer 2004;4:296-307.
9. Stupp R, Weber DC. The role of radio- and chemotherapy in glioblastoma. Onkologie 2005;28:315-7.
10. Curran J, Scott CB, Horton J et al. Recursive partitioning analysis of prognostic factors in three Radiation Therapy Oncology Group malignant glioma trials. J Natl Cancer Inst 1993;85;707-10.
11. Shinoima N, Kochi M, Hamada J et al. The influence of sex and presence of giant cells on postoperative long-term survival in adult patients with supratentorial glioblastoma multiforme. J Neurosurg 2004;101:219-26.
12. Chambless LB, Kistka HM,Parker SL et al. The relative value of postoperative versus preoperative Karnofsky Performance Scale scores as a predictor of survival after surgical resection of glioblastoma multiforme. J Neurooncol 2015;121:359-64.
13. Lacroix M, Abi-Said D, Fourney DR et al. A multivariate analysis of 416 patients with glioblastoma multiforme: prognosis,extent of resection and survival. J Neurosurg 2001;95:190-8.
14. Sanai N, Polley MY, McDermott MW et al. An extent of resection threshold for newly diagnosed glioblastomas. J Neurosurg 2011;115:3-8.
15. Young RM, Jamshidi A, Sherman JH. Current trends in the surgical management and treatment of adult glioblastoma. Ann Transl Med 2015;3:121-32.
16. Oppenlander ME, Wolf AB, Snyder LA et al. An extent of resection threshold for recurrent glioblastoma and its risk for neurological morbidity. J Neurosurg 2014;120:846-53.
17. Laperriener N, Zaura L, Cairncroos G. Cancer Care Ontario Practice Guidelines Initiative's Neuro-Oncology Disease Site Group. Radiotherapy for newly diagnosed malignant glioma in adults: a systematic review. Radiother Oncol 2002;64:259-73.
18. Chan JL, Lee SV, Fraass BA et al. Survival and failure patterns of high-grade gliomas after three-dimensional conformal radiotherapy. J Clin Oncol 2002;20:1635-42.
19. Niranjan A, Kano H, Iyer A, Kondziolka D, Flickinger JC, Lunsford LD. Role of adjuvant or salvage radiosurgery in the management of unresected residual or progressive glioblastoma multiforme in the pre-bevacizumab era. J Neurosurg 2015;122:757-65.
20. Sterwart LA. Chemotherapy in adult high-grade glioma: a systematic review and analysis of individual patient data from 12 randomised trials. Lancet 2002;359:1011-8.
21. Chao ST, Hunter GK, Khan MK, Suh JH, Vogelbaum M. Evidence-based adjuvant therapy for gliomas: Current concept and newer developments. Indian J Cancer 2009;46:96-107.
22. Stupp R, Hegib ME, van den Bentc MJ et al. Changing Paradigms-An Update on the Multidisciplinary Management of malignant Glioma. The Oncologist 2006;11:165-80.
23. Stupp R, Mason VP, van den Bentc MJ et al. Radiotherapy plus Concomitant and Adjuvant Temozolomide for Glioblastoma. N Engl J Med 2005;352:987-96.
24. Stupp R, Hegib ME, Wanner P et al. Effect of radiotherapy with concomitant and adjuvant temozolomide versus radiotherapy alone on survival in glioblastoma in a randomised phase III study:5-year analysis of the EORTC-NCIC trial. Lancet Oncol 2009;10:459-66.
25. Irwin C, Hunn M, Purdie G, Hamilton G. Delay in radiotherapy shortens survival in patients with high grade glioma. J Neurooncol 2007;85:339-43.
26. Bauchet L, Mathieu-Daude H, Fabbo-Peray P et al. Oncological patterns of care and outcome for 952 patients with newly diagnosed glioblastoma in 2004. Neurooncology 2004;12:725-35.
27. Ash D, Barrett A, Hinsh A. Re-adult of radiotherapy waiting times. Clin Oncol 2010;16:387-94.
28. Esco R, Palacios J, Pardo J et al. Infrastructure of radiotherapy in spine: a minimal standard of radiotherapy resources. Int J Radiat Oncol Biol Phys 2003;56:319-24.
29. Lourelio LVM, Pontes LB, Carceller Filho D et al. Initial care and outcomes of glioblastoma patients in 2 diverse health care scenarios in Brazil: does public versus private health care matter? Neurooncology 2014;16:999-1005.
30. Kostic A, Mihailovic D, Veselinovic S et al. Tumor size and karyometric variables in brain astrocytomas. JBUON 2009;14:473-7.
31. Olar A, Aldape KD. Using the molecular classification of glioblastoma to inform personalized treatment. J Pathol 2014;232:165-77.
32. Li QJ, Cai JQ, Liu CY. Evolving Molecular Genetics of Glioblastoma. Chin Med J 2016;129:464-71.