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Original Article

NEIL3 variant rs12645561 is in association with the prognosis of glioma in Chinese Han population of Xi'an

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Abstract: *NEIL3* may affect the development of glioma. However, few previous studies evaluated the function of *NEIL3* in the prognosis of patients with glioma. The characteristics of age (≥40) had a significantly increased risk of death (HR: 1.302, 95% CI: 1.010-1.678, *P*=0.041), by contrast, the surgical operation (subtotal tumour resection, GTR) and chemotherapy were the protective factors which decreased risk of death (HR: 0.645, 95% CI: 0.492-0.845, *P*<0.05; HR: 0.755, 95% CI: 0.580-0.984, *P*<0.05). The genotype (T/T) of rs12645561 had a significantly increased risk of death (HR: 2.123, 95% CI: 1.099-4.104, *P*=0.043). After HR was adjusted with chemotherapy and surgical operation, the T/T genotype of rs12645561 increased risk of glioma death (HR: 1.808, 95% CI: 1.071-3.051, *P*=0.027). If HR was adjusted with chemotherapy, surgical operation, the minor allele T/T significantly increased risk of astrocytoma death (HR: 2.528, 95% CI: 1.292-4.947, *P*=0.007). Our results suggest that the polymorphisms of rs12645561 in *NEIL3* may predict overall survival of glioma.

Keywords: Glioma, prognosis, *NEIL3*, survival

Introduction

Glioma (astrocytoma, gliacytoma, oligodendroglioma, etc.) is the primary human brain tumor, which accounts for about 40% of all intracranial neural tumor [1, 2]. There was more than 0.39 million patients with brain glioma around the world, and the median survival time is only 12-18 months [3]. Glioma is the primary malignant tumor which is the fatal disease caused by the innate genetic factors and the environmental carcinogenic factors [4, 5]. For a long time, pathologist, immunologist and clinician were always trying to look for an optimal treatment on which can improve the glioma prognosis which increase the survival rate mortality decreased and median survival time extended [6-8]. The characteristic of glioma is to infiltrate and pinch the normal parenchyma and symptoms of patients may not appear for several years, not only diagnosis can be difficult but also the tumor can achieve massive size before medical treatment. Although the intensive treatment is given, most cases die of their extremely aggressive glioma [9]. The safe resection of elderly patients (≥40) are performed before receiving chemotherapy and radiotherapy and the survival outcomes are poorer compared with younger patients [10, 11], but the life survival of elderly is more than the younger. The reason is that the elderly patients may be courage therapeutic interventions and appropriate treatment [12-14].

Chemical instability of Deoxyribonucleic acid and single nucleotide polymorphisms (base transition, base transversion, base insertion and base deletion) are the characteristics of various human cancer cells [15]. Excessive oxidative stress is the most significant reason of nucleotide damage caused by free radicals and lead to oxidative stress and hyperinflammation resulting in the frequency of guanine appears to increase in the specific region of the chromo-

Table 1. Clinical data of patients with gliomas and astrocytoma

Characteristics	Gliomas			Astrocytoma		
	Frequency	Percent (%)	*P*-value[a]	Frequency	Percent (%)	*P*-value[a]
Gender			0.522			0.769
Male	145	53.9		88	55.0	
Female	124	46.1		72	45.0	
Total	269	100.0		160	100.0	
Age			0.025*			0.184
<40	116	43.1		66	41.3	
≥40	153	56.9		94	58.8	
Total	269	100.0		160	100.0	
WHO grading			0.127			0.612
I	18	6.7		18	11.3	
II	129	48		78	48.8	
III	72	26.8		64	40.0	
IV	50	18.6		0	0.0	
Total	269	100.0		160	100.0	
Surgical operation			*P*<0.001*			0.003*
STR or NTR	85	31.6		49	30.6	
GTR	184	68.4		111	69.4	
Total	269	100.0		160	100.0	
Radiotherapy			0.681			0.334
Gamma Knife	176	65.4		106	66.3	
Conformal therapy	69	25.7		41	25.6	
ND	24	8.9		13	8.1	
Total	269	100.0		160	100.0	
Chemotherapy			0.001*			0.029*
No	165	61.3		102	63.8	
Yes	104	38.7		58	36.3	
Total	269	100.0		160	100.0	
NEIL3 (rs12645561)			0.289			0.043*
C/C	144	53.5		92	57.5	
T/C	107	39.8		58	36.3	
T/T	18	6.7		10	6.3	
Total	269	100.0		160	100.0	
Survival status			-			-
Survival	11	4.1		6	3.8	
Loss to follow-up	9	3.3		7	4.4	
Death	249	92.6		147	91.9	
Total	269	100.0		160	100.0	
Infiltration condition			-			-
No	10	3.7		6	3.8	
Yes	255	94.8		152	95.0	
Total	265	98.5		158	98.8	
Missing	4	1.5		2	1.3	
Total	269	100.0		160	100.0	

STR, sub-total resection; NTR, near-total resection; GTR, gross-total resection. [a]*P* was calculated by Chi-square test. **P*<0.05 indicates statistical significance.

Table 2. Univariate analysis of glioma overall survival

Characteristics	Dead cases/ total cases	Median survival time (months)	1 year survival rate (%)	3 years survival rate (%)	*P*	HR (95% CI)
Gender						
Male	135/145	11	25.5	5.3		1
Female	114/124	11	35.5	7.9	0.559	0.928 (0.723-1.192)
Age						
<40	103/116	12	36.2	9.5		1
≥40	146/153	10	25.5	4.2	0.041*	1.302 (1.010-1.678)
WHO grading						
I-II	133/147	12	32.0	8.6		1
III-IV	116/122	10	27.9	4.6	0.164	1.194 (0.930-1.532)
Surgical operation						
STR or NTR	84/85	10	17.6	1.2		1
GTR	165/184	11	35.9	8.9	<0.05*	0.645 (0.492-0.845)
Radiotherapy						
ND	22/24	8	33.3	8.3		1
Conformal therapy	60/69	9	20.3	11.8		0.856 (0.523-1.402)
Gamma Knife	167/176	11	33.5	5.2	0.728	0.834 (0.534-1.303)
Chemotherapy						
No	158/165	9	24.1	2.7		1
Yes	91/104	12	39.4	12.7	<0.05*	0.755 (0.580-0.984)
NEIL3 (rs12645561)						
C/C	134/144	11	31.9	5.7		1
T/C	98/107	10	28.0	7.2		1.042 (0.803-1.352)
T/T	17/18	8	27.8	—	0.357	1.448 (0.873-2.400)

HR, Hazard Ratio; 95% CI, 95% confidence interval; STR, sub-total resection; NTR, near-total resection; GTR, gross-total resection. P<0.05 indicates statistical significance.

some [16]. Previous studies have reported that the SNPs of *NEIL3* play an important role in increasing glioma risk, what's more, the "C/T-T/T" genotype of rs12645561 in *NEIL3* significantly increase risk of glioma in dominant model [17]. Furthermore, *NEIL3* is highly expressed in certain areas of the brain, in addition, the expression of *NEIL3* is higher in tumor tissue compared with normal tissue [18], All in all, the highly expressed may relate to high proliferative potential and even lead the unlimited proliferation.

However, the association analysis between NEIL3 and glioma risk has been reported, few geneticists and clinicians assess the association between NEIL3 and the prognosis of glioma. In this study the association between various factors and prognosis of patients with glioma (especially Chinese) was investigated. 288 patients performed different treatment methods were recruited to analyze the statistical results of preoperative and postoperative promote glioma precise treatment, and association between retrospective survival and glioma.

Methods and materials

Patient selection and follow-up characteristics

We retrospectively reviewed 288 patients with signing the informed consent form that was confirmed glioma by histopathological analysis after surgery at neurosurgery of Shaanxi Province Tangdu Hospital of the Fourth Military Medical University between 2010 and 2014. We gleaned patient characteristic information (age, sex, race, residential region, and family history of cancer) were recorded using a standard epidemiologic questionnaire. December 1, 2010 was chose as the closing date of eligibility in order to have enough follow-up of patients with glioma. Not all cases were treated at Tangdu Hospital, so the information of cases treated at other hospital may be sparse, and the standard treatments were strictly performed. The data of follow-up were logged in

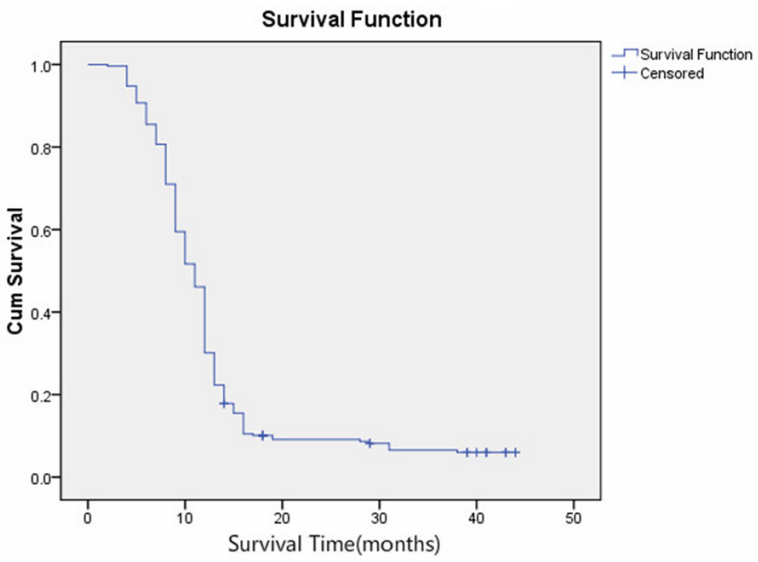

Figure 1. Kaplan-Meier curves of glioma overall. The graphs present 3 years of follow-up. The log-rank test was based on the full data.

EpiData 3.02 software. The blood samples with collected from each participant's venous blood about 5 ml were collected after signing the informed consent form and stored in accordance with our unified standards (-60°C). Because the survival of patients with neuroastrocytoma is longer compared with the others, 160 participants from all the patients were identified a subset. When the patient breathed one's last, the dates were recorded using at the following methods: in/out-patient records, Tangdu Hospital tumor registry and confirmation with family. The study was approved by the Clinical Research Ethics of Northwestern University.

SNP selection and genotyping

The rs12645561 located in *NEIL3* were selected to analyze in this study based on data for Asian subjects from the International HapMap Project (http://hapmap.ncbi.nlm.nih.gov/index.html.en). Minor allele frequencies of the SNP was >5% in the HapMap of the Chinese Han population. DNA from whole blood was extracted by using GoldMag-Mini Whole Blood Genomic DNA Purification Kits (GoldMag Co., Ltd., Hainan City, China), and quantified with a spectrophotometer (NanoDrop 2000; Thermo Fisher Scientific, Waltham, MA, United States). The SNPs were genotyped using the MassARRAY RS1000 system (Sequenom). Data management and analysis were performed using Sequenom Typer 4.0 Software.

Statistical analysis

The database was built with EpiData3.02 software and SPSS17.0 software was used to statistical analysis. Survivorship curve was drawn in Kaplan-Meier and the differentia of survival time was examined with Log-rank. $P<0.05$ was considered statistically significant and two-sided. The analysis of Single factor and multiple factors were used to calculate HR and 95% Confidence Interval (CI). Odds ratio (OR) and 95% CIs were determined by using unconditional logistic regression analysis with adjustments for age and sex which to estimate the association between polymorphic site and patients with glioma.

Results

The characteristics of patient with glioma were shown in **Table 1**. The cases totally achieves 269 that males accounted for 53.9% and the greater than or equal to 40 years old accounted for 56.9%, According to the 2007 WHO central nervous system tumor classification standard, to do pathological grading of gliomas, grade-I (18 cases), grade-II (129 cases), grade-III (72 cases), grade-IV (50 cases). WHO I-III was diagnosed with astrocytoma (160 cases) and don't contain glioblastoma. The C/C, T/C and T/T of rs12645561 accounted for 53.5%, 39.8% and 6.7%.

Univariate analysis of glioma overall survival was shown in **Table 2** and **Figure 1**. No significant associations were displayed between the prognosis of gliomas and gender, WHO grading, radiotherapy and *NEIL3* (rs12645561). The rs12645561 statistical results of prognostic showed in **Table 3**. However, the characteristics of age (≥40) had a significantly increased risk of death (HR: 1.302, 95% CI: 1.010-1.678, $P=0.041$), by contrast, the GTR and chemotherapy were the protective factors which decreased risk of death (HR: 0.645, 95% CI: 0.492-0.845,

Table 3. Univariate analysis of astrocytoma overall survival

Characteristics	Dead cases/total cases	Median survival time (months)	1 year survival rate (%)	3 years survival rate (%)	*P*	HR (95% CI)
Gender						
Male	80/88	11	26.1	6.8		1
Female	67/72	11	31.9	6.3	0.789	1.045 (0.755-1.447)
Age						
<40	58/66	11	31.8	8.6		1
≥40	89/94	10	26.6	-	0.227	1.227 (0.880-1.711)
WHO grading	WHO grading					
I-II	86/96	11	28.1	-		1
III-IV	61/64	11	29.7	3.9	0.612	1.081 (0.778-1.501)
Surgical operation	Surgical operation					
STR or NTR	49/49	9	16.3	-		1
GTR	98/111	11	34.2	9.6	0.007*	0.614 (0.431-0.875)
Radiotherapy	Radiotherapy					
ND	11/13	12	46.2	-		1
Conformal therapy	37/41	9	14.6	8.8		1.475 (0.749-2.905)
Gamma Knife	99/106	11	32.1	-	0.407	1.183 (0.634-2.209)
Chemotherapy	Chemotherapy					
No	96/102	9	23.5	-		1
Yes	51/58	12	37.9	11.4	0.048*	0.705 (0.498-0.997)
NEIL3 (rs12645561)						
C/C*	84/92	11	31.5	5.2		1
T/C*	53/58	11	25.9	-		1.028 (0.728-1.450)
T/T*	10/10	8	20	-	0.043*	2.123 (1,099-4.104)

HR, Hazard Ratio; 95% CI, 95% confidence interval; STR, sub-total resection; NTR, near-total resection; GTR, gross-total resection. *$P<0.05$ indicates statistical significance.

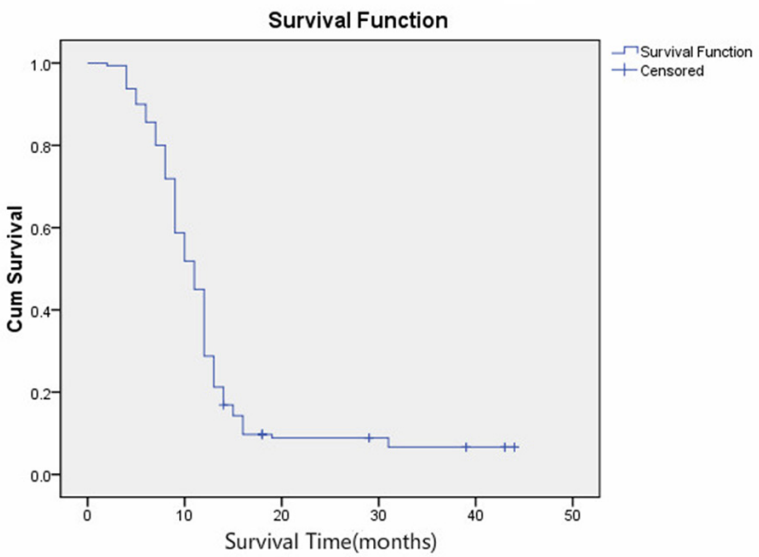

Figure 2. Kaplan-Meier curves of astrocytoma overall. The graphs present 3 years of follow-up. The log-rank test was based on the full data.

P<0.05; HR: 0.755, 95% CI: 0.580-0.984, *P*< 0.05). As shown in **Table 3** and **Figure 2** (astrocytoma) significant association was found that the GTR and chemotherapy can decreased risk of death (HR: 0.614, 95% CI: 0.431-0.875, *P*=0.07; HR: 0.705, 95% CI: 0.498-0.997, *P*=0.048). The minor allele (T/T) of rs12645561 had a significantly increased risk of death (HR: 2.123, 95% CI: 1.099-4.104, *P*=0.043). The rs12645561 affect the statistical results of prognostic shown in **Figure 3**. The results of multivariate analysis between gene polymorphism and the overall survival and free survival were shown in **Table 4**. After HR was adjusted with chemotherapy and surgical operation, the T/T allele of rs12645561 increased risk of glioma death (HR: 1.808, 95% CI: 1.071-3.051, *P*=0.027). If HR was adjusted

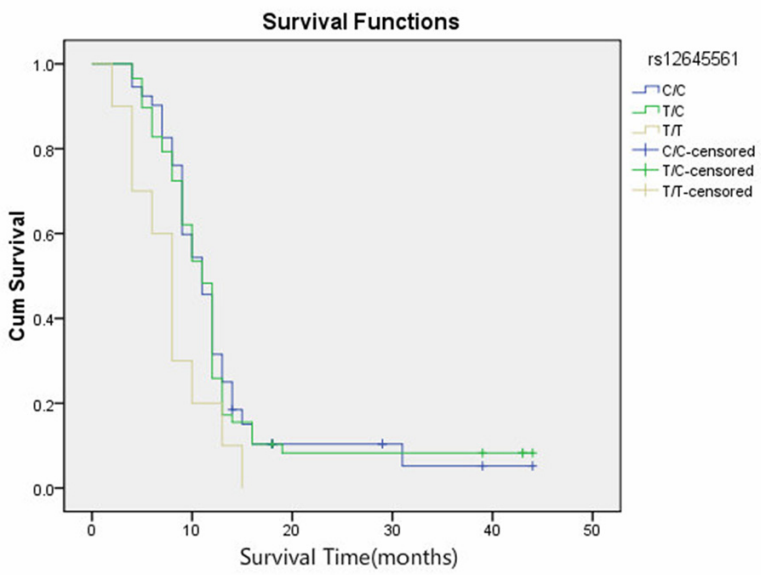

Figure 3. Kaplan-Meier curves of *NEIL3* rs12645561 genotypes by stage. (*P*=0.043, log-rank test); The graphs present 3 years of follow-up. The log-rank test was based on the full data.

Table 4. Multivariate analysis between gene polymorphism and the overall survival and free survival

	Gene	SNP	Genotype	*P*	HR (95% CI)[a]
Glioma	*NEIL3*	rs12645561	C/C	0.081	1
			T/C	0.389	1.123 (0.863-1.460)
			T/T	0.027	1.808 (1.071-3.051)
Astrocytoma	*NEIL3*	rs12645561	C/C	0.026	1
			T/C	0.594	1.099 (0.776-1.556)
			T/T	0.007	2.528 (1.292-4.947)

HR, Hazard Ratio; 95% CI, 95% confidence interval. P≤0.05 indicates statistical significance. [a]: HR was adjusted with chemotherapy and surgical operation.

with chemotherapy, surgical operation, the minor allele significantly increased risk of astrocytoma death (HR: 2.528, 95% CI: 1.292-4.947, *P*=0.007).

Discussion

In clinical practice, surgeons are willing to offer surgical treatment to patients with glioma because it can attenuate the tumor oppression of important tissue and diminish the burden of body, but there are a lot of concerns about tolerance relating to age and underlying complications. Resection has been confirmed that it is more effective than other treatments. Our experimental study showed that the 1 and 3 year(s) survival rate of patient with GTR (35.92% and 8.9%) were well above the subtotal tumor resection (STR) or no tumor resection (NTR) (17.6% and 1.2%). Stummer et al reported that the gross total resection of malignant tumor has higher survival than the STR or no tumor resection related to the size of residual tumor [19]. Hence, the size of residual tumor is smaller, the prognosis of patients with glioma is richer.

The data from many tumor centers around the world showed, the incidence rate of astrocytoma is very high in 40-50 years old and the incidence peak of glioblastoma in old age. As a result, the patients (≥40) have poorer prognosis compared with younger patients [20]. Our research showed that the age (≥40) of patients' 1 and 3 year(s) survival rate compared with the less than 40 years old has dropped by 10.7% and 5.3%. European Organization for Research and Treatment of Cancer (EORTC) has already confirmed that the prognosis evaluation of patients with glioma was barely satisfactory among the more than 40 years old of patients [21]. According to North Central Cancer Treatment Group (NCCTG) study, postoperative survival time of patients with glioma was negatively correlated with age of onset. Therefore, age is a crucial factor for the prognosis evaluation of patients with glioma.

According to our experimental results deduced that the chemotherapy may grow the survival time of patients with glioma. Stewart and coworkers collected 12 Case control studies performed in 304 patients after chemotherapy to analyze by fixed effects model, meta-analysis of evidence-based medicine (EBM). The results showed that the 1 year survival rate of patients receiving chemotherapy grows from 40% to 46% and the 2 years survival rate grows from 9% to 13% [22]. Because of drug resistance of glioma cell, blood-brain barrier (BBB) and arrest

of bone marrow, patients received chemotherapy has a poorer survival compared with the rest. With the development of precision medicine, individualized glioma chemotherapy will play a role in prognosis of glioma.

The *NEIL3* with 10 exons and 12 introns located on Chromosome 4q34.3 covers 53.25 kb from 178230990 to 178284237, and encoded by the direct strand according to Entrez Gene (http://www.ncbi.nlm.nih.gov/IEB/Research/Acembly/av.cgi). The Expression of NEIL3 gene being a cell cycle-regulated dependent was confirmed that the *NEIL3* is induced by mitogen stimulation in early S phase with the highest expression in the G2 phase under the control of the Ras dependent ERK-MAP kinase pathway [23]. In 2002, a DNA glycosylase (*NEIL3*) from colibacillary protein was discovered, which can repair DNA damaged by damaging agents and replicate errors that it also is capable of endonuclease. The role of the enzymes is excise and repair base which is to protect proliferating cells. However oxidative base lesions contribute to DNA damage, repaired by DNA glycosylases from the endonuclease III. *NEIL3* might be involved in the process of replicating genomes and provide a defense against oxidative base lesions from the S phase to the G2 phase. Reis' results suggested that RNA knockdown of the OGG1 and *NEIL3* decreased proliferation of neural stem cells (NSCs) but was secondary to an decreased death rate [24]. Similarly, in previous study, Perillo and co-workers demonstrated that DNA glycosylases has been shown to participate in the prothetic process of base lesions damaged by senses oxidative stress and exo-/endo-genous agents, then recruit transcription factors, which results in promoting survival cell specialization [25]. These results suggest that *NEIL3* might be involved in cell signaling pathways and play a role in the proliferative process of NSCs.

Human *NEIL3* is expressed in various cell lines with high proliferative, including unfertilised oocyte, marrow cells and keratinocytes [18]. Highest expression of human and mouse *NEIL3* has been demonstrated in liver, cerebrum and spleen [18, 26, 27]. Association between *NEIL3* expression and multiple human cancers has been also examined such as hepatocellular carcinoma, prostate cancer and colon cancer [26, 28, 29]. The developing mouse brain highly expressed *NEIL3* in various regions that are rich in progenitor cells [18]. Regnell demonstrated that proliferative capacity of NSCs from aged *NEIL3*$^{-/-}$ mouse was diminished and DNA repair activity is impaired [30]. Herein, the behavioral tests confirmed that the NSCs derived from adult *NEIL3*$^{-/-}$ mouse were deficient on learning and memory and reduced anxiety-like behavior. Our previous researches indicate that the "C/T-T/T" genotype of rs12645561 in *NEIL3* was associated with differential odds of developing glioma in the Chinese population [17], which might predict overall survival of glioma.

In conclusion, our result, combined with previous studies, showed that rs1264556 in *NEIL3* may be potentially valuable prognostic markers for glioma patients. The goal of our study is to generate the clinical data to move toward a brand period in which comprehensive therapy is individualized. Ultimately, through study in this field, we can inform a clearer understanding of various therapies.

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Disclosure of conflict of interest

None.

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References

[1] Furnari FB, Fenton T, Bachoo RM, Mukasa A, Stommel JM, Stegh A, Hahn WC, Ligon KL, Louis DN, Brennan C, Chin L, DePinho RA and Cavenee WK. Malignant astrocytic glioma: genetics, biology, and paths to treatment. Genes Dev 2007; 21: 2683-2710.

[2] Hess KR, Broglio KR and Bondy ML. Adult glioma incidence trends in the United States, 1977-2000. Cancer 2004; 101: 2293-2299.

[3] Das P, Puri T, Jha P, Pathak P, Joshi N, Suri V, Sharma MC, Sharma BS, Mahapatra AK, Suri A and Sarkar C. A clinicopathological and molecular analysis of glioblastoma multiforme with long-term survival. J Clin Neurosci 2011; 18: 66-70.

[4] Pereboeva L, Harkins L, Wong S and Lamb LS. The safety of allogeneic innate lymphocyte therapy for glioma patients with prior cranial irradiation. Cancer Immunol Immunother 2015; 64: 551-562.

[5] Amirian ES, Armstrong GN, Zhou R, Lau CC, Claus EB, Barnholtz-Sloan JS, Il'yasova D, Schildkraut J, Ali-Osman F, Sadetzki S, Johansen C, Houlston RS, Jenkins RB, Lachance D, Olson SH, Bernstein JL, Merrell RT, Wrensch MR, Davis FG, Lai R, Shete S, Amos CI, Scheurer ME, Aldape K, Alafuzoff I, Brannstrom T, Broholm H, Collins P, Giannini C, Rosenblum M, Tihan T, Melin BS and Bondy ML. The Glioma International Case-Control Study: A Report From the Genetic Epidemiology of Glioma International Consortium. Am J Epidemiol 2016; 183: 85-91.

[6] Chen JR, Yao Y, Xu HZ and Qin ZY. Isocitrate Dehydrogenase (IDH)1/2 Mutations as Prognostic Markers in Patients With Glioblastomas. Medicine (Baltimore) 2016; 95: e2583.

[7] Sun X, Li Z and Chen Y. The Potential Prognostic Value of MicroRNA-429 for Human Gliomas. Ann Clin Lab Sci 2016; 46: 44-48.

[8] Li MY, Yang P, Liu YW, Zhang CB, Wang KY, Wang YY, Yao K, Zhang W, Qiu XG, Li WB, Peng XX, Wang YZ and Jiang T. Low c-Met expression levels are prognostic for and predict the benefits of temozolomide chemotherapy in malignant gliomas. Sci Rep 2016; 6: 21141.

[9] Chaichana KL, Halthore AN, Parker SL, Olivi A, Weingart JD, Brem H and Quinones-Hinojosa A. Factors involved in maintaining prolonged functional independence following supratentorial glioblastoma resection. Clinical article. J Neurosurg 2011; 114: 604-612.

[10] McGirt MJ, Chaichana KL, Gathinji M, Attenello FJ, Than K, Olivi A, Weingart JD, Brem H and Quinones-Hinojosa AR. Independent association of extent of resection with survival in patients with malignant brain astrocytoma. J Neurosurg 2009; 110: 156-162.

[11] Alvarez de Eulate-Beramendi S, Alvarez-Vega MA, Balbin M, Sanchez-Pitiot A, Vallina-Alvarez A and Martino-Gonzalez J. Prognostic factors and survival study in high-grade glioma in the elderly. Br J Neurosurg 2016; 1-7.

[12] Marijnen CA, van den Berg SM, van Duinen SG, Voormolen JH and Noordijk EM. Radiotherapy is effective in patients with glioblastoma multiforme with a limited prognosis and in patients above 70 years of age: a retrospective single institution analysis. Radiother Oncol 2005; 75: 210-216.

[13] Bauman GS, Gaspar LE, Fisher BJ, Halperin EC, Macdonald DR and Cairncross JG. A prospective study of short-course radiotherapy in poor prognosis glioblastoma multiforme. Int J Radiat Oncol Biol Phys 1994; 29: 835-839.

[14] Laigle-Donadey F and Delattre JY. Glioma in the elderly. Curr Opin Oncol 2006; 18: 644-647.

[15] Negrini S, Gorgoulis VG and Halazonetis TD. Genomic instability--an evolving hallmark of cancer. Nat Rev Mol Cell Biol 2010; 11: 220-228.

[16] Mangerich A, Knutson CG, Parry NM, Muthupalani S, Ye W, Prestwich E, Cui L, McFaline JL, Mobley M, Ge Z, Taghizadeh K, Wishnok JS, Wogan GN, Fox JG, Tannenbaum SR and Dedon PC. Infection-induced colitis in mice causes dynamic and tissue-specific changes in stress response and DNA damage leading to colon cancer. Proc Natl Acad Sci U S A 2012; 109: E1820-1829.

[17] Jin TB, Li XL, Yang H, Jiri M, Shi XG, Yuan DY, Kang LL and Li SQ. Association of polymorphisms in FLT3, EGFR, ALOX5, and NEIL3 with glioblastoma in the Han Chinese population. Med Oncol 2013; 30: 718.

[18] Hildrestrand GA, Neurauter CG, Diep DB, Castellanos CG, Krauss S, Bjoras M and Luna L. Expression patterns of Neil3 during embryonic brain development and neoplasia. BMC Neurosci 2009; 10: 45.

[19] Stummer W, Meinel T, Ewelt C, Martus P, Jakobs O, Felsberg J and Reifenberger G. Prospective cohort study of radiotherapy with concomitant and adjuvant temozolomide chemotherapy for glioblastoma patients with no or minimal residual enhancing tumor load after surgery. J Neurooncol 2012; 108: 89-97.

[20] Konglund A, Helseth R, Lund-Johansen M, Helseth E and Meling TR. Surgery for high-grade gliomas in the aging. Acta Neurol Scand 2013; 128: 185-193.

[21] Gorlia T, Wu W, Wang M, Baumert BG, Mehta M, Buckner JC, Shaw E, Brown P, Stupp R, Galanis E, Lacombe D and van den Bent MJ. New validated prognostic models and prognostic calculators in patients with low-grade gliomas diagnosed by central pathology review: a pooled analysis of EORTC/RTOG/NCCTG phase III clinical trials. Neuro Oncol 2013; 15: 1568-1579.

[22] Stewart LA. Chemotherapy in adult high-grade glioma: a systematic review and meta-analysis of individual patient data from 12 randomised trials. Lancet 2002; 359: 1011-1018.

[23] Neurauter CG, Luna L and Bjoras M. Release from quiescence stimulates the expression of

human NEIL3 under the control of the Ras dependent ERK-MAP kinase pathway. DNA Repair (Amst) 2012; 11: 401-409.

[24] Reis A and Hermanson O. The DNA glycosylases OGG1 and NEIL3 influence differentiation potential, proliferation, and senescence-associated signs in neural stem cells. Biochem Biophys Res Commun 2012; 423: 621-626.

[25] Perillo B, Ombra MN, Bertoni A, Cuozzo C, Sacchetti S, Sasso A, Chiariotti L, Malorni A, Abbondanza C and Avvedimento EV. DNA oxidation as triggered by H3K9me2 demethylation drives estrogen-induced gene expression. Science 2008; 319: 202-206.

[26] Zhang H, Ma H, Wang Q, Chen M, Weng D, Wang H, Zhou J, Li Y, Sun J, Chen Y, Liang X, Zhao J, Pan K, Wang H and Xia J. Analysis of loss of heterozygosity on chromosome 4q in hepatocellular carcinoma using high-throughput SNP array. Oncol Rep 2010; 23: 445-455.

[27] Takao M, Kanno S, Kobayashi K, Zhang QM, Yonei S, van der Horst GT and Yasui A. A back-up glycosylase in Nth1 knock-out mice is a functional Nei (endonuclease VIII) homologue. J Biol Chem 2002; 277: 42205-42213.

[28] Barry KH, Koutros S, Berndt SI, Andreotti G, Hoppin JA, Sandler DP, Burdette LA, Yeager M, Freeman LE, Lubin JH, Ma X, Zheng T and Alavanja MC. Genetic variation in base excision repair pathway genes, pesticide exposure, and prostate cancer risk. Environ Health Perspect 2011; 119: 1726-1732.

[29] Farkas SA, Vymetalkova V, Vodickova L, Vodicka P and Nilsson TK. DNA methylation changes in genes frequently mutated in sporadic colorectal cancer and in the DNA repair and Wnt/beta-catenin signaling pathway genes. Epigenomics 2014; 6: 179-191.

[30] Regnell CE, Hildrestrand GA, Sejersted Y, Medin T, Moldestad O, Rolseth V, Krokeide SZ, Suganthan R, Luna L, Bjoras M and Bergersen LH. Hippocampal adult neurogenesis is maintained by Neil3-dependent repair of oxidative DNA lesions in neural progenitor cells. Cell Rep 2012; 2: 503-510.