JOURNAL OF ONCOLOGY PHARMACY PRACTICE

Original Article

J Oncol Pharm Practice
0(0) 1–11

DOI: 10.1177/1078155220920684
journals.sagepub.com/home/opp
SAGE

Prognostic factors in progressive high-grade glial tumors treated with systemic approach: A single center experience

Ozkan Alan[1], Tugba Akin Telli[1], Tugba Basoglu Tuylu[1], Rukiye Arikan[1], Nazım Can Demircan[1], Ozlem Ercelep[2], Serap Kaya[2], Nalan Akgul Babacan[2], Beste M Atasoy[3], Suheyla Bozkurt[4], Yasar Bayri[5], Dilek Gul[6], Gazanfer Ekinci[7], Ibrahim Ziyal[5], Faysal Dane[1] and P Fulden Yumuk[1]

Abstract

Purpose: Malignant high-grade gliomas are the most common and aggressive type of primary brain tumor, and the prognosis is generally extremely poor. In this retrospective study, we analyzed the outcome of systemic treatment in recurrent high-grade glioma patients and the impact of prognostic factors on survivals.

Methods: Data from 114 patients with recurrent high-grade glioma who received systemic treatment and followed in our clinic between 2012 and 2018 were retrospectively analyzed. Eastern Cooperative Oncology Group (ECOG) performance status, age, gender, histology, type of surgical resection, side effects after systemic treatment (deep vein thrombosis, hypertension, proteinuria), IDH1 and alpha thalassemia/mental retardation syndrome X-linked (ATRX) mutation status were investigated as prognostic factors for progression-free survival and overall survival.

Results: At the time of diagnosis, the median age was 48 (17–77) and 68% of the patients were male. Most common pathologic subtype was glioblastoma multiforme (68%). Median follow-up duration was 9.1 months (1–68 months). Median progression-free survival and overall survival were 6.2 months and 8 months, respectively. In multivariate analysis, ECOG PS, deep venous thrombosis and the presence of ATRX and IDH1 mutation were found to be independent prognostic factors for progression-free survival ($p < 0.05$) and, ECOG PS, the presence of ATRX and IDH1 mutation for overall survival ($p < 0.05$).

Conclusion: Our study is real life data and the median progression-free survival and overall survival rates are similar to the literature. We have found ECOG PS, presence of ATRX and IDH1 mutation to be independent prognostic factors for both progression-free survival and overall survival.

Keywords

High-grade gliomas, glioblastoma multiforme, ATRX status, IDH status, thrombosis

Date received: 5 November 2019; revised: 29 March 2020; accepted: 30 March 2020

[1]Division of Medical Oncology, Department of Internal Medicine, Marmara University Faculty of Medicine, Istanbul, Turkey
[2]Marmara University Pendik Education and Research Hospital, Medical Oncology Clinic, Istanbul, Turkey
[3]Department of Radiation Oncology, Marmara University Faculty of Medicine, Istanbul, Turkey
[4]Department of Pathology, Marmara University Faculty of Medicine, Istanbul, Turkey
[5]Department of Neurosurgery, Marmara University Faculty of Medicine, Istanbul, Turkey
[6]Marmara University Pendik Education and Research Hospital, Radiation Oncology Clinic, Istanbul, Turkey
[7]Department of Radiology, Marmara University Faculty of Medicine, Istanbul, Turkey

Corresponding author:
Ozkan Alan, Pendik Education and Research Hospital, Marmara University, Fevzi Cakmak Mahallesi, Muhsin Yazicioğlu Cd No: 10, 34899 Pendik/Istanbul, Turkey.
Email: ozkan.alan@hotmail.com

Introduction

Malignant high-grade gliomas (HGGs) are the most common and aggressive type of primary brain tumors, and their prognosis is generally extremely poor. HGG is divided into two groups; anaplastic glioma (anaplastic astrocytoma/anaplastic oligodendroglioma) and glioblastoma multiforme (GBM).[1] Median age at diagnosis is 64 years and it is more common in men than women (ratio 1.3–1.6:1). Annual incidence is three to five new cases per 100,000 population.[2,3] Median expected survival time in patients with glioblastoma is 15 months. Survival increases with decreasing tumor grade, and grade 2–3 gliomas have a median survival range from approximately 2 to 12 years according to the 2016 World Health Organization (WHO) classification schema.[4] Initial therapeutic approach for HGG is surgery. Gross total tumor resection with preservation of neurological functions is recommended for debulking, tissue diagnosis, and also is prognostic.[5] When tumor resection is not safely feasible (e.g. location of the tumor or impaired clinical condition of the patient), a biopsy should be done. Fractionated localized radiotherapy (60 Gy, 30–33 fraction) is part of standard treatment after diagnosis (after biopsy or surgery).[6] In a large randomized trial, concomitant and adjuvant temozolomide chemotherapy with radiotherapy significantly improved median, two- and five-year survival in GBM patients. Therefore, it is the current standard of care for GBM.[7,8]

Progression is nearly always fatal and treatment options are limitedly effective. Treatment options for progressive HGG include re-resection, re-irradiation, stereotactic radiosurgery, temozolomide rechallenge, lomustine, carmustine, bevacizumab alone or with irinotecan.[9]

Bevacizumab is a humanized IgG1 directed against vascular endothelial growth factor (VEGF). It has been shown to inhibit new blood vessel formation.[10] In randomized controlled phase studies, it was first approved for the treatment of metastatic colorectal patients. Phase I and II studies reported that bevacizumab, alone or in combination with cytotoxic agents, had promising results in terms of treatment for recurrent GBM.[11,12] However, two randomized and placebo-controlled phase III studies on first-line bevacizumab treatment did not show progression-free survival (PFS) benefit.[13,14] Some patients seem to benefit from bevacizumab but there are no established biomarker available to identify this subgroup with improved progression-free and/or overall survival (OS).

Isocitrate dehydrogenase (IDH) mutations and 1p/19q codeletions are well-established prognostic factors for gliomas.[15] These two markers separated gliomas into more biologically distinct entities than histological classification alone. Therefore, WHO incorporated IDH mutation and 1p/19q codeletion into an "integrated diagnosis" in 2016 revised 4th edition of the classification of tumors of the central nervous system.[3] IDH1 mutations have been reported by approximately 12% in glioblastoma, are associated with younger age and better survival and rarely seen in older patients.[16,17]

Role of alpha thalassemia/mental retardation syndrome X-linked (ATRX) mutation has been discussed briefly in glioma classification and prognosis. ATRX mutations occur in almost 75% of grade 2–3 astrocytomas and secondary GBM, and in 12.7% of primary GBM. These mutations are widely distributed across the gene and are mostly truncating and less commonly missense mutations. Loss of ATRX protein expression by immunohistochemistry could be used as a surrogate marker of ATRX mutations with high sensitivity and specificity.[18–20]

Beside these molecular markers, several clinical prognostic factors were reported in the literature. Most important prognostic factors affecting survival outcome with HGG are age, and Karnofsky (KPS) or ECOG performance status (PS).[21,22]

Although IDH1 mutation and ATRX mutation have been well known as prognostic factors in newly diagnosed GBM, the prognostic significance of these mutations in progressive HGG patients have not been clearly defined. Based on this fact, In the current study, we aimed to evaluate prognostic factors in progressive HGG patients who were treated with systemic approach (bevacizumab alone or combined with chemotherapy).

Patients and methods

Patients

Charts of a total of 125 patients with diagnosis of HGGs treated in Marmara University Hospital Medical Oncology Outpatient Clinic between 2012 and 2018 were reviewed. Data of 114 progressive HGG patients who were treated with systemic treatment were collected retrospectively. Inclusion criteria were histological/cytological diagnosis of HGG, having progresive disease after current standard of care treatment, treated with systemic treatment (bevacizumab alone or with irinotecan) and having complete medical records. Patients who did not have high-grade or progressive disease, who did not received standard first-line therapy and was not treated with bevacizumab alone or with irinotecan were excluded from the study.

Systemic second-line treatment was bevacizumab plus irinotecan in 58% of patients, and only

bevacizumab in 42%. Bevacizumab (10 mg/kg) (in combination or alone) and irinotecan (125 mg/m^2) were administered in every two weeks. All patients were taking levetiracetam which is a non-enzyme-induced anticonvulsant drug. Treatment responses were evaluated every 12 weeks by magnetic resonance imaging.

Side effects

Side effects were recorded in patients receiving systemic treatment at least once. Deep vein thrombosis (DVT) was accepted in patients who were diagnosed by Doppler ultrasonography. Posttreatment hypertension was defined as blood pressure higher than 140/90 mm/Hg for measured in at least once during outpatient visit. Proteinuria was performed and confirmed on a spot urine examination by dipstick test. The Common Terminology Criteria for adverse events (CTCAE), version 5.0, was used to evaluate toxicities. Follow-up monitoring of all patients was performed until 25 November 2018.

Prognostic factors

ECOG PS, age, gender, histology, type of surgical resection, side effects after systemic treatment (DVT, hypertension, proteinuria, etc.), IDH1 and ATRX mutation status were investigated as prognostic factors for PFS and OS.

ATRX and IDH status were evaluated by immunohistochemical method.

PFS was defined as the time starting from the date of first dose of second-line systemic treatment (bevacizumab or bevacizumab plus irinotecan) till radiological progression, death or last visit date.

We also defined OS as the time starting from the date of first dose of second-line systemic treatment until death due to any reason or last visit date.

Statistical analysis

OS and PFS were calculated using the Kaplan–Meier method. Prognostic factors were compared using the log-rank test in univariate analysis. Hazard ratios with 95% confidence intervals (CI) were also calculated. All p-values were two-sided in the tests, and p-values of 0.05 were considered statistically significant. Multivariate analysis was carried out using the Cox proportional hazards model to assess the effect of prognostic factors on PFS and OS. SPSS 22 program was used for statistical analysis.

Results

Patients demographic and clinical characteristics outcomes

Seventy-eight of 114 patients were male (68%) and median age was 49 (range 17–77 years). Forty-six percent of patients had maximal surgical resection. Most common pathologic subtype was GBM (69%). Ninety-four percent of patients received concurrent chemoradiotherapy and followed adjuvant temozolomide after surgery or steoratactic biopsy. Six percent of patients received only adjuvant radiotherapy because of temozolomide intolerance. Median recurrence time (time from the start of adjuvant treatment to the date of radiological recurrence) was 10 months for all group and 9 months in GBM. After recurrence, 47 patients were treated with local approach, either with surgery or radiotherapy. Bevacizumab and irinotecan combination was given in 61% of patients. Both groups received median of 10 treatments (range 1–31 in bevacizumab only group and 1–55 cycles in combination with irinotecan group). Data for demographic and clinicopathologic findings reviewed in Table 1.

ATRX status was assessed in 90 patients, 19 (21%) patients had ATRX mutation (12 out of 65 patients with GBM and 7 out of 25 patients with anaplastic glioma). IDH1 status was studied in 89 patients, including 64 patients with GBM and 25 patients with anaplastic glioma. Thirteen (15%) patients had IDH1

Table 1. Demographic and clinicopathological findings.

	n = 114 (%)
Gender	
Male	78 (68)
Female	36 (32)
ECOG	
ECOG (0–1)	84 (74)
ECOG (2–4)	30 (26)
Surgery	
No	3 (2)
Stereotactic biopsy	22 (19)
Incomplete surgical resection	37 (33)
Maximal surgical resection	52 (46)
Pathology	
GBM	79 (69)
Anaplastic glioma	35 (31)
IDH1 mutation (n = 89)	
Mutant	13 (15)
Wild	76 (85)
ATRX mutation (n = 90)	
Mutant	19 (21)
Wild	71 (79)
Ki 67 expression (%) (median)	25 (range 2–90)

GBM: glioblastoma multiforme.

mutation (seven patients with GBM and six patients with anaplastic glioma). IDH1 mutant patients were younger compared to IDH1 wild patients (Median age was 35 (range 27–65 years) versus 52 (range 18–77 years)/p = 0.007, respectively). According to the ATRX status, there was no difference between the patients in terms of age distribution (p = 0.7). Age, sex, WHO classification, Ki 67 level expression and IDH mutation have been assessed for the effects on ATRX status by the Logistic Regression. Only IDH mutation was detected to be significantly associated with ATRX status. We found that the probability of ATRX mutation in IDH mutant samples was 4.1 times higher than that in IDH wild-type samples (odds ratio: 4.1 95% CI: (1.7–16.3)/p = 0.04).

Survival outcomes

Median follow-up time was 9.1 months (range 1–68 months). During the follow-up, 78% of the patients progressed. After the progression, third-line treatment was given to 17 patients. Median PFS and OS were 6.2 months and 8 months, respectively (Figure 1(a,b)). Six-month PFS rate was 51% and 12-month OS rate was 37%. Median PFS in only bevacizumab and combination treatment groups were 6.7 months and 5.6 months, respectively. Median OS in only bevacizumab and combination groups were 7.6 months and 7.9 months, respectively. There were no difference between the two treatment groups in terms of PFS and OS (p > 0.05). Initial and salvage treatment characteristics and overall clinical outcomes are outlined in Table 2. Effect of clinical and demographic characteristics of OS and PFS are shown Table 3.

Table 2. Treatment characteristics and clinical outcomes.

Characterestic n (%)	
Systemic treatment	
Bevacizumab	44 (39)
Bevacizumab + irinotecan	70 (61)
Deep vein thrombosis	
No	94 (83)
Yes	20 (17)
Proteinuria	
Grade 0	64 (56)
Grades 1–3	50 (64)
Hypertension	
Grade 0	91(80)
Grades 1–3	23 (20)
Progression	
Yes	89 (78)
No	25 (22)
Second-line treatment	
Best supportive care	72 (81)
Carmustine	3 (4)
Bevacizumab	12 (13)
Reoperation	2 (2)
Status	
Exitus	89 (78)
Alive	25 (22)
PFS (95% CI)	
Median (mo)	6.2 (4.8–7.6)
1 year (%)	25
2 years (%)	11
5 years (%)	0
OS (95% CI)	
Median mo	8 (5.7–10.2)
1 year (%)	37
2 years (%)	21
5 years (%)	9

PFS: progression-free survival; OS: overall survival; CI: confidence interval.

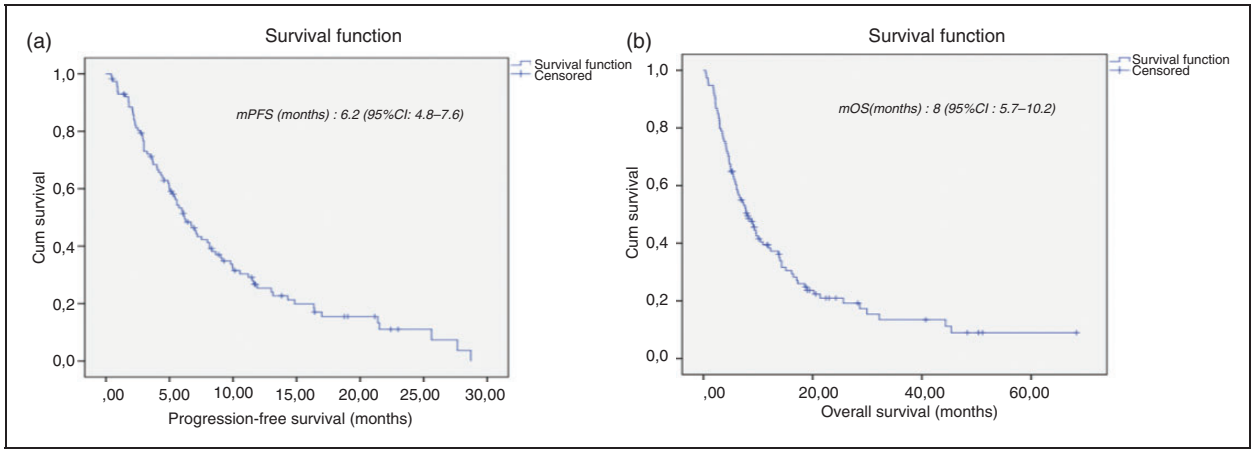

Figure 1. Survival outcomes graphic for whole cohort by Kaplan–Meier. (a) Progression-free survival for whole cohort. (b) Overall survival for whole cohort.

Table 3. Effect of clinical and demographic characteristics of overall survival and progression-free survival.

	Median PFS				Median OS			
		95% CI				95% CI		
	Months	Lower	Upper	p	Months	Lower	Upper	p
Age								
<40	5.4	2.2	8.7	0.4	9.6	6.2	13.0	0.1
≥40	6.7	5.3	8.1		7.3	5.4	9.2	
ECOG PS								
0–1	8.1	6.2	10.0	**0.004**	9.6	6.2	13.0	**0.001**
2–4	3.2	1.1	5.3		4.7	3.6	5.7	
Gender								
Female	8.6	3.9	13.3	0.1	9.6	5.8	13.4	0.08
Male	5.7	4.0	7.4		7.1	5.2	9.1	
Maximal surgical debulking								
Yes	6.7	3.3	9.0	0.1	9.6	3.9	11.6	**0.02**
No	5.7	4.1	7.3		7.1	5.4	8.8	
Pathology								
GBM	6.9	5.4	8.5	0.8	7.9	5.6	10.3	0.9
A.Glioma	4.9	2.3	6.3		6.8	2.5	11.0	
Ki 67 expression								
<25%	7.1	4.9	9.2	0.08	9.6	5.8	13.4	0.2
≥25%	5.5	4.1	7.1		7.1	5.2	9.1	
IDH1 status								
Mutant	21.3	13.1	23.9	**0.007**	25.6	9.2	42.0	**0.01**
Wild	6.1	4.7	7.5		7.9	5.5	10.4	
ATRX status								
Intakt	8.6	6.4	10.7	**0.002**	13.7	9.3	18.1	**0.003**
Mutant	2.9	2.5	3.3		4.7	2.5	6.8	
Mutational status combinaiton (n = 81)								
IDH1 wild-ATRX wild (n = 56)	8.1	5.1	11.2	**0.000**	9.1	6.8	11.4	**0.001**
IDH1 wild-ATRX mutant (n = 14)	2.6	1.7	3.6		3.4	1.9	4.9	
IDH1 mutant–ATRX wild (n = 6)	16.3	12.1	20.6		45.4	0.00	103.1	
IDH1 mutant–ATRX mutant[a] (n = 5)	–	–	–		–	–	–	
Hypertension								
Grades 1–3	8.4	7.5	12.4	0.05	17.2	13.3	21.1	**0.01**
Grade 0	5.5	4.5	6.6		6.8	5.0	8.5	
Deep vein thrombosis								
Yes	11.8	6.8	16.9	**0.007**	16.4	8.5	24.3	**0.03**
No	5.5	4.4	6.7		7.3	5.0	9.6	
Proteinuria								
Grades 1–3	8.3	6.5	10.1	**0.04**	10.4	7.3	13.5	**0.02**
Grade 0	4.8	3.0	6.7		5.8	4.3	7.3	

[a]Median PFS and OS were not calculated in this subgroup by Kaplan–Meier methods.
$p \leq 0.05$ is statistically significant.

Prognostic factors for PFS

In univariate analysis, ECOG PS 0–1, presence of mutant IDH1, DVT and proteinuria predicted prolonged PFS ($p < 0.05$). But the presence of ATRX mutation foresaw worse PFS ($p = 0.003$). In multivariate analysis, ECOG PS, presence of IDH1 mutation and DVT were found to be independent good prognostic factors for PFS ($p = 0.003$, 0.01 and 0.005 respectively), whilst ATRX mutation continued to be a poor prognostic factor ($p = 0.001$) (Figure 2).

Prognostic factors for OS

In univariate analysis, ECOG PS 0–1, maximal surgical debulking, presence of IDH1 mutation, hypertension, deep venous thrombosis and proteinuria showed statistically significant OS benefit ($p < 0.05$). But the presence of ATRX mutation was a statistically significant worse factor on OS ($p < 0.007$). In multivariate analysis, ECOG PS 0–1 and the presence of IDH1 mutation were found to be independent good prognostic factors for OS ($p < 0.05$). Conversely, ATRX mutation was

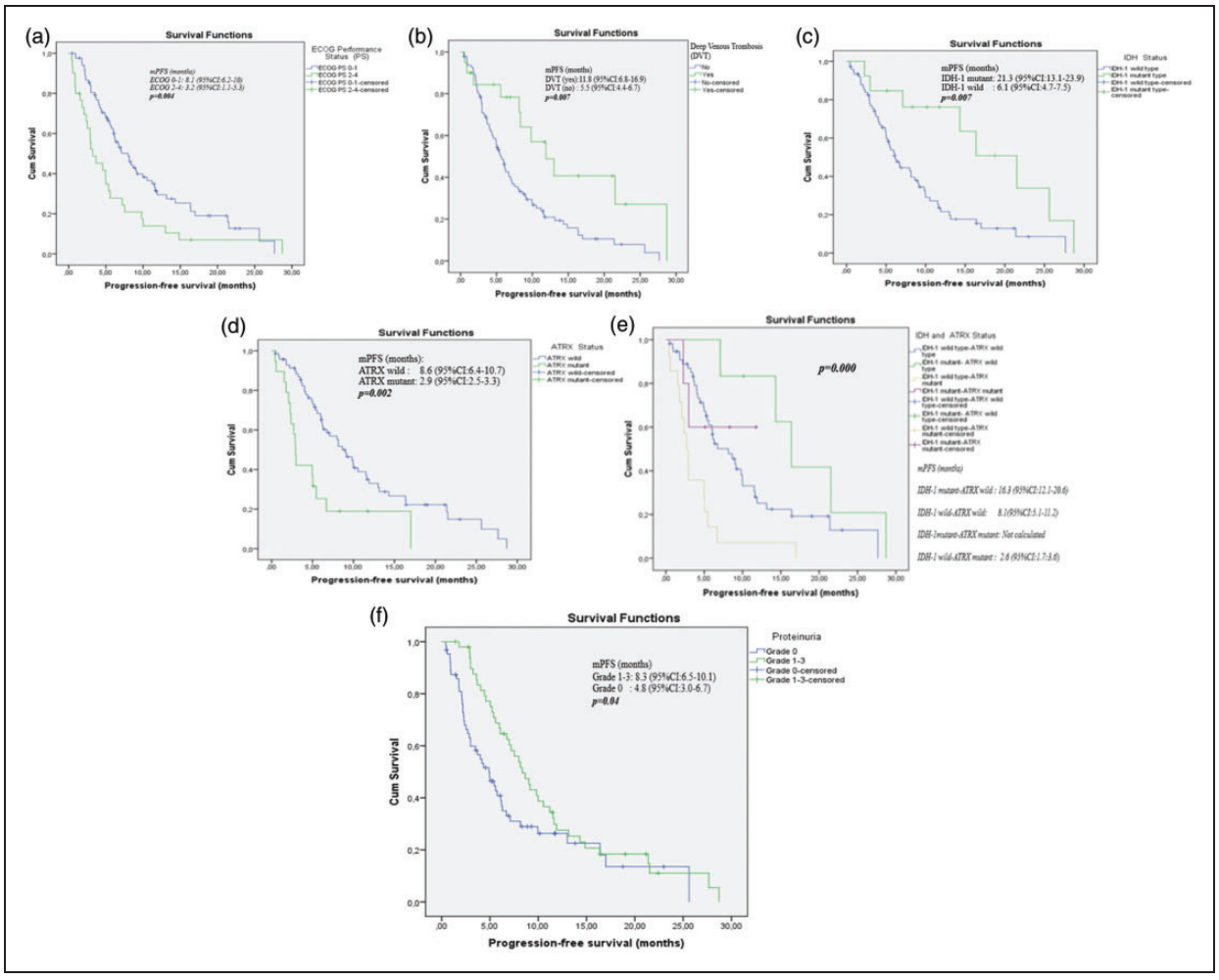

Figure 2. Survival outcomes graphic according to prognostic factors for progression-free survival by Kaplan–Meier: (a) ECOG PS groups, (b) deep venous thrombosis, (c,d) IDH1 and ATRX status, (e) IDH1 and ATRX status combination and (f) proteinuria.

poor prognostic factor for OS ($p = 0.007$) (Figure 3). Cox regression model of survival are outlined in Table 4.

Discussion

We reported true daily life data of patients diagnosed with progressive high-grade glial tumor treated with bevacizumab alone or in combination with irinotecan from a single institute. We achieve good objective results compared to previous phase trials in literature, especially in PFS.[12–23] Median PFS was 6.2 months in all group, and 6.7 months in only bevacizumab and 5.6 months in combination group. However, this was not projected to OS. Median OS in only bevacizumab was 7.6 months and combination group was 7.9 months. This could be explained by the lack of a central radiological assessment center and we may have overestimated the tumor response by the reason of initial response assessment which was done in 12th week. In clinical trials of bevacizumab, inclusion criteria are strictly defined and patients with ECOG PS 0–1 were included. Whereas 26% of the patients who we treat in our outpatient clinics had worse performance (ECOG PS 2-4), these patients died shortly after progression. This might be the reason for short OS. Therefore, our real life data could add valuable information to the literature on patients who were treated outside clinical trials.

Impact of prognostic factors has not been well defined in patients with recurrent HGGs. ECOG PS, gross total resection, unilateral tumor and adjuvant chemoradiotherapy are related with prolonged PFS or OS in patient with newly diagnosed HGGs. ECOG PS is considered to be an important component of clinical activity and treatment compliance in patients with recurrent GBM. In our study, ECOG PS to be an independent prognostic factor for both PFS and OS. Median PFS and OS are 8.1 months and 9.6 months, respectively, in patients with an ECOG 0–1. Our results

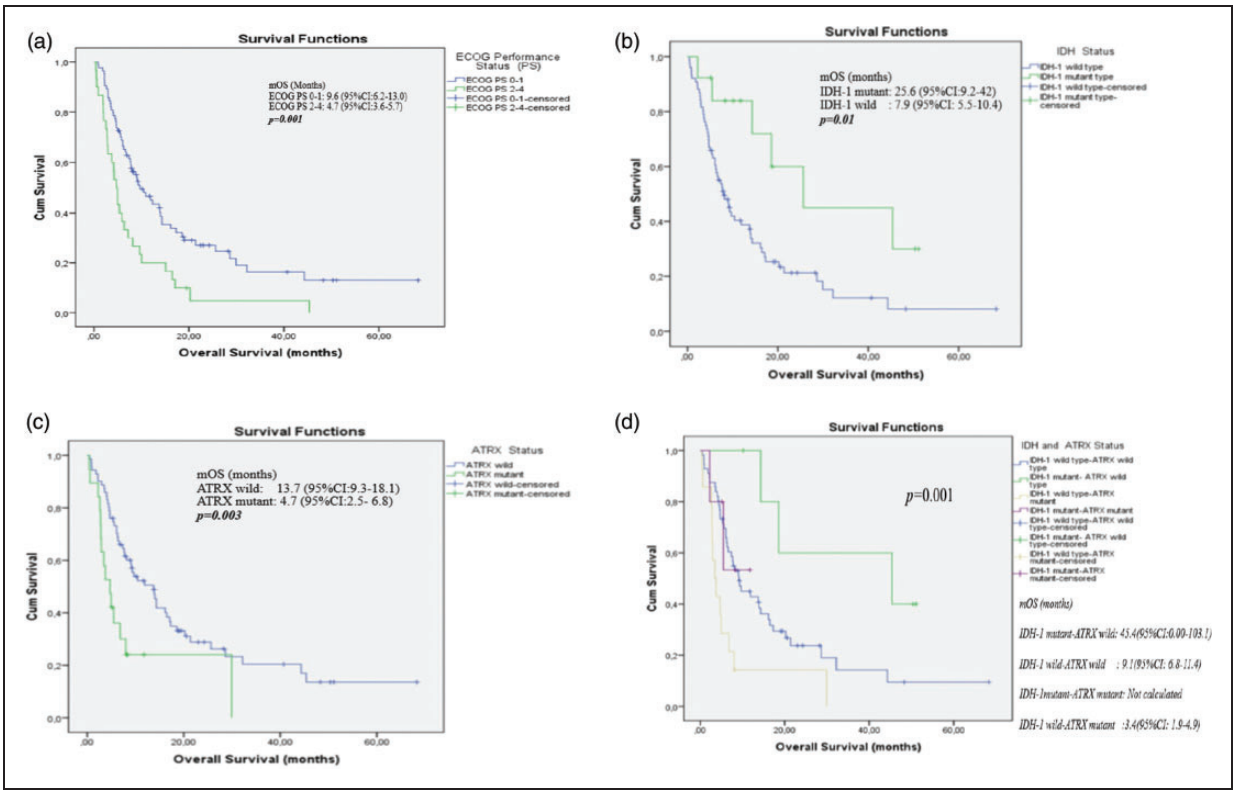

Figure 3. Survival outcomes graphic according to independent prognostic factors for overall survival by Kaplan–Meier: (a) ECOG PS groups, (b,c) IDH1 and ATRX status and (d) IDH1 and ATRX status combination.

are consistent with those obtained in previous studies.[24,25]

Proteinuria may develop as a side effect during treatment with VEGF inhibitors that inhibit angiogenesis. Whether development of proteinuria might also serve as a surrogate marker of on survival is unknown. A retrospective study found that development of proteinuria during antiangiogenic therapy tended to be related with poorer survival in patients with metastatic colorectal cancer. Median OS was 23.9 months for patients with grades 0 to 1 proteinuria and 4.2 months for those with ≥grade 2 proteinuria ($p = 0.028$).[26] Proteinuria was not found to be a predictive marker for PFS and OS in patients with recurrent GBM in another study.[27] Posttreatment hypertension also generally is related to angiogenesis inhibitors. In a study, in which paclitaxel versus paclitaxel plus bevacizumab was assessed in patients with metastatic breast cancer, association of bevacizumab-induced hypertension with OS was reported.[28] Patients with grade 3 or 4 hypertension had superior OS time compared with patients without hypertension (38.7 versus 25.3 months, $p = 0.002$) in this trial. In a retrospective study in which recurrent GBM patients treated with bevacizumab were evaluated, and posttreatment hypertension was reported as a predictive biomarker.[29] Median PFS and OS in patients who developed hypertension were, respectively, 6.7 months and 11.7 months. There was a statistically significant difference compared to normotensive patients ($p < 0.05$). Liau et al. reported that posttreatment hypertension to be prognostic for both PFS and OS in their retrospective study.[27] In the current study, we did not find proteinuria and hypertension as independent prognostic factors in both terms of PFS and OS in multivariate analysis.

The risk of venous thromboembolism (VTE) including DVT and pulmonary embolism is increased in cancer patients. For example, in population-based cohort studies, the risk of VTE is four- to seven-fold higher in patients with cancer compared with non-cancer patients were demonstrated.[30] Furthermore, the risk of VTE is particularly increased in patients with glial tumors. In a comprehensive meta-analysis, up to 20% of brain cancer patients develop VTE per year are reported.[31] Several factors such as older age, antiangiogenic treatment, glioblastoma subtype, IDH1 wild-type status, etc. have been defined as risk factors for VTE in brain tumor patients.[32] Deep venous thrombosis has been reported to be approximately 4% during the bevacizumab treatment in phase trials.[11–13] Two recent studies have reported the high risk of VTE in glioma patients with IDH1 wild

Table 4. Cox regression model of survival (univariate and multivariate analysis results).

	PFS				OS			
	Univariate analysis		Multivariate analysis		Univariate analysis		Multivariate analysis	
	HR (95% CI)	p	HR (95% CI)	p	HR (95% CI)	p	HR (95% CI)	p
Age								
<40	1.2	0.4			1.3	0.1		
≥40	(0.7–1.9)				(0.8–2.2)			
ECOG PS								
0–1	1.9	**0.001**	2.8	**0.003**	2.1	**0.01**	2.9	**0.001**
2–4	(1.2–3.02)		(1.4–5.7)		(1.3–3.3)		(1.5–5.5)	
Gender								
Female	1.3	0.1			1.4	0,08		
Male	(0.8–2.2)				(0.9–2.3)			
Maximal surgical debulking								
Yes	0.7	0,1			0.6	**0.02**		
No	(0.4–1.1)				(0.3–0.9)			
Pathology								
GBM	1.04	0.8			0.9	0.93		
A.Glioma	(0.6–1.6)				(0.6–1.5)			
IDH1 status								
Wild mutant	0,30	**0.009**	0.2	**0.01**	0.35	**0.01**	0.3	**0.01**
ATRX status	(0.1–0.8)		(0.08–0.7)		(0.1–0.8)		(0.1–0.8)	
Wild mutant	2.5	**0.01**	2.1	**0.01**	2.4	**0.004**	2.05	**0.03**
Ki 67	(1.4–4.6)		(1.1–3.9)		(1.3–4.3)		(1.07–3.9)	
<25%	0.9	0.9			1.2	0.2		
≥25%	(0.6–1.5)				(0.8–2.1)			
Hypertension								
Grades 1–3	0.6	0.05			0.5	**0.01**		
Grade 0	(0.3–1.01)				(0.2–0.8)			
Deep vein thrombosis								
Yes	0.4	**0.009**	0.2	**0.002**	0.5	**0.03**		
No	(0.2–0.8		(0.1–0.6)		(0.2–0.9			
Proteinuria								
Grades 1–3	0.6	**0.04**			0.62	**0.03**		
Grade 0	(0.4–0.9)				(0.4–0.9)			

HR: hazard ratios; CI: confidence intervals; PFS: progression-free survival; OS: overall survival; GBM: glioblastoma multiforme.

type.[33,34] VTE developed during treatment has been associated with poor OS.[35,36] However, the data of the prognostic value of VTE in patients with glial tumors are contradictory. Simanek et al. and Smith et al. showed that there was no statistically significant difference in survival between high-grade glial tumor patients who developed VTE compared with those without VTE in their studies.[37,38] Conversely, Semrad et al. in their studies which included 9489 patients with malignant glioma demonstrated that patients who experienced VTE had a 30% increase in the risk of death within two years.[39] In our study, 17% of the patients had DVT. According to IDH1 status, there was no statistical difference in developing VTE between the patients. We showed that patients who had experienced deep venous thrombosis, associated with prolonged PFS and OS. But it was found to be an independent prognostic factor for only PFS in multivariate analysis. Unlike other studies, the whole cohort consisted only of recurrent HGG patients, and we evaluated just DVT as a venous thromboembolic event. This situation may have affected our results and caused it to be different according to the literature.

Several trials have evaluated the role of IDH1 mutation as prognostic factor for survival in patients with high-grade glial tumors and it has been reported to be an independent predictive factor in these studies.[40–42] Also, in a meta-analysis, which includes nine studies including a total of 1669 patients, IDH1 mutation has also been demonstrated to be a prognostic factor in patients with GBM and was associated with improved OS.[43] In our study, IDH1 mutant patients had better survival for both PFS and OS, and it was an independent prognostic factor. Our findings were

consistent with the literature. Our IDH mutation cohort consisted of younger patients. Although we think that this situation may have affected our survival results, it was demonstrated in two retrospective studies that age was not a prognostic factor in recurrent glioblastoma.[24–27] Similarly, we did not find the prognostic significance of age in the present study.

ATRX mutation is seen in at least 15 types of human cancers, including neuroblastoma, osteosarcoma and pancreatic neuroendocrine tumors. However, the role of ATRX in tumorigenesis remains largely unknown.[15,44,45] ATRX has been evaluated in an animal model study in glioma. It has been shown that ATRX loss causes tumor growth and decreases median survival. Furthermore, the researcher showed that ARTX loss causes genetic instability in mouse GBM, including both microsatellite instability and impaired telomere maintenance.[46] In gliomas, ATRX mutation is primarily observed in adolescents and young adults. In adults (age >30 years), ATRX is mutated less frequently in primary GBM, but is frequently found in lower grade (WHO grade 2/3) and secondary GBM.[18] Liu et al. showed that ATRX mutations were positively associated with age and IDH mutations in glioma patients. Researchers concluded that the probability of ATRX mutation in IDH mutant patients was 14 times higher than that in IDH wild-type patients, and the probability of ATRX increased by 9% for each additional year of age.[47] The prognostic value of ATRX status has been reported in glioma patients who received postoperative adjuvant treatment. Cai et al. demonstrated that patients with ATRX wild-type/IDH1R132H mutation tended to have favorable survival in both low-grade gliomas and HGGs.[48] Chaurasia et al. in their study which included a total of 163 GBM patients who underwent surgery suggested that ATRX wild-type status was associated with a distinct and statistically significant increased survival rate regarding both OS and PFS.[49] Similarly, in another study, the ATRX mutation was associated with poor survival in WHO grade 2 glioma patients who were newly diagnosed.[50] Pekmezci et al. investigated the prognostic value of ATRX status in patients with WHO grades 2–3 and 4 in their study.[51] Conversely, researchers reported that the presence of ATRX mutation was only related to favorable survival in GBM patient with IDH1 wild type. They did not find any associated with ATRX status and survival in the other glial patient groups. In the current study, we evaluated the only recurrent WHO grades 3–4 glioma patients, unlike other studies. Twenty-one percent of patients had mutations and 16% of these patients had GBM. Similar to literature, we found an association between ATRX status and IDH1 status. And we reported that ATRX mutation as an independent poor prognostic factor in terms of both PFS and OS in recurrent HGG patients treated with systemic therapy. According to mutational status, the best survival was in the IDH1 mutant-ATRX wild group, while the worst survival was in the IDH1 wild-ATRX mutant group. To our knowledge, this is the first study in the literature that reports prognostic value of ATRX mutation in recurrent HGG patients who were treated with systemic approach.

There were many limitations of this study. First, the relatively low number of patients in a single center may cause selection bias. Second, there was no central radiologic center to assess treatment response, and unlike phase studies, response assessment was performed every 12 weeks, so we might have overestimated the tumor response. Lastly, ATRX status and IDH were evaluated in only 79% of patients immunohistochemically. Not all molecular markers could be evaluated as prognostic factors in all patients. More clinical trials are needed to identify clinical and molecular prognostic factors in recurrent HGG patients who were treated with systemic treatment (bevacizumab alone or with irinotecan).

Conclusion

Prognosis of progressive HGGs after standard chemoradiotherapy is poor and treatment options are limited. Hence, the identification of new prognostic markers for predicting the effectiveness of systemic treatment is very substantial in clinical practice. This study showed that ECOG PS, post-treatment deep venous thrombosis, IDH1 and ATRX status might be prognostic markers for predicting survival outcomes in these patients with recurrent HGGs. We suggest that these clinical (ECOG PS and DVT) and molecular (IDH1 and ATRX) prognostic markers could be used to select the patients who can tolerate and benefit from aggressive treatment strategies in clinical practice. Furthermore, we found that patients with ATRX mutations had a poor prognosis, and the effectiveness of systemic therapy was limited. Therefore, new treatment strategies are needed for these patients and should be recommended to participate in clinical trials. Further prospective and better-designed studies are necessary to confirm our results.

Ethics approval and consent to participate

All procedures performed were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Ethics/Institutional Review Board approval of research – Faculty of Medicine, Marmara University, Istanbul, Turkey. Number: 09.2018.410, 1 June 2018.

Informed consent

Written informed consent was obtained from the patients for publication of this original research. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

ORCID iDs

Ozkan Alan https://orcid.org/0000-0002-6635-2012
Tugba Akin Telli https://orcid.org/0000-0001-6535-6030
Tugba Basoglu Tuylu https://orcid.org/0000-0002-2059-5502
Nazım Can Demircan https://orcid.org/0000-0001-6630-5278
P Fulden Yumuk https://orcid.org/0000-0001-8650-299X

References

1. Louis DN, Ohgaki H, Wiestler OD, et al. (eds). *WHO classification of tumours of the central nervous system*. 4th ed. Lyon: IARC, 2016.
2. Ostrom QT, Gittleman H, Truitt G, et al. CBTRUS statistical report: primary brain and other central nervous system tumors diagnosed in the United States in 2011–2015. *Neuro Oncol* 2018; 20: iv1–iv86.
3. Louis DN, Perry A, Reifenberger G, et al. The 2016 World Health Organization classification of tumors of the central nervous system: a summary. *Acta Neuropathol* 2016; 131: 803–820.
4. van den Bent MJ, Weller M, Wen PY, et al. A clinical perspective on the 2016 WHO brain tumor classification and routine molecular diagnostics. *Neuro Oncol* 2017; 19: 614–624.
5. Nickel K, Renovanz M, König J, et al. The patients' view: impact of the extent of resection, intraoperative imaging, and awake surgery on health-related quality of life in high-grade glioma patients-results of a multicenter cross-sectional study. *Neurosurg Rev* 2018; 41: 207–219.
6. Corso CD, Bindra RS nd Mehta MP. The role of radiation in treating glioblastoma: here to stay. *J Neurooncol* 2017; 134: 479–485.
7. Stupp R, Mason WP, van den Bent MJ, et al. Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. *N Engl J Med* 2005; 352: 987–996.
8. Stupp R, Hegi ME, Mason WP, 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: 459–466.
9. Weller M, Cloughesy T, Perry JR, et al. Standards of care for treatment of recurrent glioblastoma – are we there yet? *Neuro Oncol* 2013; 15: 4–27.
10. Willett CG, Boucher Y, di Tomaso E, et al. Direct evidence that the VEGF-specific antibody bevacizumab has antivascular effects in human rectal cancer. *Nat Med* 2004; 10: 145–147 (published correction appears in *Nat Med* 2004; 10: 649).
11. Taal W, Oosterkamp HM, Walenkamp AM, et al. Single-agent bevacizumab or lomustine versus a combination of bevacizumab plus lomustine in patients with recurrent glioblastoma (BELOB trial): a randomised controlled phase 2 trial. *Lancet Oncol* 2014; 15: 943–953.
12. Friedman HS, Prados MD, Wen PY, et al. Bevacizumab alone and in combination with irinotecan in recurrent glioblastoma. *J Clin Oncol* 2009; 27: 4733–4740.
13. Chinot OL, Wick W, Mason W, et al. Bevacizumab plus radiotherapy-temozolomide for newly diagnosed glioblastoma. *N Engl J Med* 2014; 370: 709–722.
14. Gilbert MR, Dignam JJ, Armstrong TS, et al. A randomized trial of bevacizumab for newly diagnosed glioblastoma. *N Engl J Med* 2014;370(8):699–708. doi:10.1056/NEJMoa1308573
15. Eckel-Passow JE, Lachance DH, Molinaro AM, et al. Glioma groups based on 1p/19q, IDH, and TERT promoter mutations in tumors. *N Engl J Med* 2015; 372: 2499–2508.
16. Agarwal S, Sharma MC, Jha P, et al. Comparative study of IDH1 mutations in gliomas by immunohistochemistry and DNA sequencing. *Neuro Oncol* 2013; 15: 718–726.
17. Wirsching HG, Galanis E and Weller M. Glioblastoma. *Handb Clin Neurol* 2016; 134: 381–397.
18. Heaphy CM, de Wilde RF, Jiao Y, et al. Altered telomeres in tumors with ATRX and DAXX mutations. *Science* 2011; 333: 425.
19. Kannan K, Inagaki A, Silber J, et al. Whole-exome sequencing identifies ATRX mutation as a key molecular determinant in lower-grade glioma. *Oncotarget* 2012; 3: 1194–1203.
20. Ikemura M, Shibahara J, Mukasa A, et al. Utility of ATRX immunohistochemistry in diagnosis of adult diffuse gliomas. *Histopathology* 2016; 69: 260–267.
21. Reni M, Mazza E, Zanon S, et al. Central nervous system gliomas. *Crit Rev Oncol Hematol* 2017; 113: 213–234.
22. Zhang GB, Cui XL, Sui DL, et al. Differential molecular genetic analysis in glioblastoma multiforme of long- and short-term survivors: a clinical study in Chinese patients. *J Neurooncol* 2013; 113: 251–258.
23. Vredenburgh JJ, Desjardins A, Herndon JE 2nd, et al. Bevacizumab plus irinotecan in recurrent glioblastoma multiforme. *J Clin Oncol* 2007; 25: 4722–4729.
24. Schaub C, Tichy J, Schäfer N, et al. Prognostic factors in recurrent glioblastoma patients treated with bevacizumab. *J Neurooncol* 2016; 129: 93–100.
25. Stark AM, Stepper W and Mehdorn HM. Outcome evaluation in glioblastoma patients using different ranking scores: KPS, GOS, mRS and MRC. *Eur J Cancer Care (Engl)* 2010; 19: 39–44.

26. Khoja L, Kumaran G, Zee YK, et al. Evaluation of hypertension and proteinuria as markers of efficacy in antiangiogenic therapy for metastatic colorectal cancer. *J Clin Gastroenterol* 2014; 48: 430–434.
27. Liau CT, Chou WC, Wei KC, et al. Female sex, good performance status, and bevacizumab-induced hypertension associated with survival benefit in Asian patients with recurrent glioblastoma treated with bevacizumab. *Asia Pac J Clin Oncol* 2018; 14: e8–e14.
28. Schneider BP, Wang M, Radovich M, et al. Association of vascular endothelial growth factor and vascular endothelial growth factor receptor-2 genetic polymorphisms with outcome in a trial of paclitaxel compared with paclitaxel plus bevacizumab in advanced breast cancer: ECOG 2100. *J Clin Oncol* 2008; 26: 4672–4678 (published correction appears in *J Clin Oncol* 2009; 27: 3070].
29. Zhong J, Ali AN, Voloschin AD, et al. Bevacizumab-induced hypertension is a predictive marker for improved outcomes in patients with recurrent glioblastoma treated with bevacizumab. *Cancer* 2015; 121: 1456–1462.
30. Heit JA, Silverstein MD, Mohr DN, et al. Risk factors for deep vein thrombosis and pulmonary embolism: a population-based case-control study. *Arch Intern Med* 2000; 160: 809–815.
31. Horsted F, West J and Grainge MJ. Risk of venous thromboembolism in patients with cancer: a systematic review and meta-analysis. *PLoS Med* 2012; 9: e1001275.
32. Riedl J and Ay C. Venous thromboembolism in brain tumors: risk factors, molecular mechanisms, and clinical challenges. *Semin Thromb Hemost* 2019; 45: 334–341.
33. Unruh D, Schwarze SR, Khoury L, et al. Mutant IDH1 and thrombosis in gliomas. *Acta Neuropathol* 2016; 132: 917–930.
34. Mir Seyed Nazari P, Riedl J, Preusser M, et al. Combination of isocitrate dehydrogenase 1 (IDH1) mutation and podoplanin expression in brain tumors identifies patients at high or low risk of venous thromboembolism. *J Thromb Haemost* 2018; 16: 1121–1127.
35. Bozkaya Y, Özdemir N, Erdem GU, et al. Mortality risk analysis of asymptomatic and symptomatic venous thromboembolism in patients with metastatic colorectal cancer. *J Cancer Res Ther* 2018; 14: 1330–1335.
36. Alcalay A, Wun T, Khatri V, et al. Venous thromboembolism in patients with colorectal cancer: incidence and effect on survival. *J Clin Oncol* 2006; 24: 1112–1118.
37. Simanek R, Vormittag R, Hassler M, et al. Venous thromboembolism and survival in patients with high-grade glioma. *Neuro Oncol* 2007; 9: 89–95.
38. Smith TR, Lall RR, Graham RB, et al. Venous thromboembolism in high grade glioma among surgical patients: results from a single center over a 10 year period. *J Neurooncol* 2014; 120: 347–352.
39. Semrad TJ, O'Donnell R, Wun T, et al. Epidemiology of venous thromboembolism in 9489 patients with malignant glioma. *J Neurosurg* 2007; 106: 601–608.
40. Sanson M, Marie Y, Paris S, et al. Isocitrate dehydrogenase 1 codon 132 mutation is an important prognostic biomarker in gliomas. *J Clin Oncol* 2009; 27: 4150–4154.
41. Juratli TA, Kirsch M, Geiger K, et al. The prognostic value of IDH mutations and MGMT promoter status in secondary high-grade gliomas. *J Neurooncol* 2012; 110: 325–333 (published correction appears in *J Neurooncol* 2013; 111: 95. Schrok, E (corrected to Schrock, E)).
42. Mukasa A, Takayanagi S, Saito K, et al. Significance of IDH mutations varies with tumor histology, grade, and genetics in Japanese glioma patients. *Cancer Sci* 2012; 103: 587–592.
43. Cheng HB, Yue W, Xie C, et al. IDH1 mutation is associated with improved overall survival in patients with glioblastoma: a meta-analysis. *Tumour Biol* 2013; 34: 3555–3559.
44. Schwartzentruber J, Korshunov A, Liu XY, et al. Driver mutations in histone H3.3 and chromatin remodelling genes in paediatric glioblastoma. *Nature* 2012; 482: 226–231 (published correction appears in *Nature* 2012; 484: 130).
45. Cerami E, Gao J, Dogrusoz U, et al. The cBio cancer genomics portal: an open platform for exploring multidimensional cancer genomics data. *Cancer Discov* 2012; 2: 401–404 (published correction appears in *Cancer Discov* 2012; 2: 960).
46. Koschmann C, Calinescu AA, Nunez FJ, et al. ATRX loss promotes tumor growth and impairs nonhomologous end joining DNA repair in glioma. *Sci Transl Med* 2016; 8: 328ra28.
47. Liu J, Zhang X, Yan X, et al. Significance of TERT and ATRX mutations in glioma. *Oncol Lett* 2019; 17: 95–102.
48. Cai HQ, Wang PF, Zhang HP, et al. Phosphorylated Hsp27 is mutually exclusive with ATRX loss and the IDH1R132H mutation and may predict better prognosis among glioblastomas without the IDH1 mutation and ATRX loss. *J Clin Pathol* 2018; 71: 702–707.
49. Chaurasia A, Park SH, Seo JW, et al. Immunohistochemical analysis of ATRX, IDH1 and p53 in glioblastoma and their correlations with patient survival. *J Korean Med Sci* 2016; 31: 1208–1214.
50. Leeper HE, Caron AA, Decker PA, et al. IDH mutation, 1p19q codeletion and ATRX loss in WHO grade II gliomas. *Oncotarget* 2015; 6: 30295–30305.
51. Pekmezci M, Rice T, Molinaro AM, et al. Adult infiltrating gliomas with WHO 2016 integrated diagnosis: additional prognostic roles of ATRX and TERT. *Acta Neuropathol* 2017; 133: 1001–1016.