The Prognostic Value of MRI Subventricular Zone Involvement and Tumor Genetics in Lower Grade Gliomas

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ABSTRACT

BACKGROUND AND PURPOSE: **Glioblastomas (GBMs) that involve the subventricular zone (SVZ) have a poor prognosis, possibly due to recruitment of neural stem cells. The purpose of this study was to evaluate whether SVZ involvement by lower grade gliomas (LGG), WHO grade II and III, similarly predicts poorer outcomes. We further assessed whether tumor genetics and cellularity are associated with SVZ involvement and outcomes.**

METHODS: **Forty-five consecutive LGG patients with preoperative imaging and next generation sequencing were included in this study. Regional SVZ involvement and whole tumor apparent diffusion coefficient (ADC) values, as a measure of cellularity, were assessed on magnetic resonance imaging. Progression was determined by RANO criteria. Kaplan-Meier curves and Cox regression analyses were used to determine the hazard ratios (HR) for progression and survival.**

RESULTS: **Frontal, parietal, temporal, and overall SVZ involvement and ADC values were not associated with progression or survival ($P \geq .05$). However, occipital SVZ involvement, seen in two patients, was associated with a higher risk of tumor progression (HR = 6.6, $P = .016$) and death (HR = 31.5, $P = .015$), CDKN2A/B mutations ($P = .03$), and lower ADC histogram values at the 5th ($P = .026$) and 10th percentiles ($P = .046$). Isocitrate dehydrogenase, phosphatase and tensin homolog, epidermal growth factor receptor, and cyclin-dependent kinase 4 mutations were also prognostic ($P \leq .05$).**

CONCLUSIONS: **Unlike in GBM, overall SVZ involvement was not found to strongly predict poor prognosis in LGGs. However, occipital SVZ involvement, though uncommon, was prognostic and found to be associated with CDKN2A/B mutations and tumor hypercellularity. Further investigation into these molecular mechanisms underlying occipital SVZ involvement in larger cohorts is warranted.**

Keywords: Genomics, glioma, isocitrate dehydrogenase, MRI, subventricular zone.

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Introduction

Involvement of the subventricular zone (SVZ) is a poor prognostic indicator in glioblastoma (GBM). GBMs that involve the SVZ have been shown to demonstrate more rapid progression, multifocal disease, increased risk of distant tumor recurrence, and poorer overall survival.[1-3] SVZ involvement may be detrimental because the SVZ serves as a source of tumor precursor stem cells that can promote resistance to chemotherapy and radiotherapy[4,5] and increase invasiveness and migratory potential.[6]

A few papers have investigated whether SVZ involvement is also a poor prognostic indicator in lower grade gliomas (LGG). Both SVZ involvement and a shorter distance between the tumor margin and the SVZ were found to be associated with more rapid growth and worse prognosis in grade II and III astrocytomas.[7-9] Furthermore, involvement of the occipital portion of the SVZ was associated with worse prognosis in grade III astrocytomas.[9]

Recently, tumor genetics has assumed a major role in glioma prognostication,[10,11] particularly mutations in isocitrate dehydrogenase (IDH1 or IDH2), which are found in more than 70% of LGGs.[12] Tumor cellularity, assessed with apparent diffusion coefficient (ADC) values, has also been shown to predict survival.[13-15] Some papers in GBMs have reported that imaging phenotypes, such as edema, necrosis, and SVZ involvement, may reflect biological characteristics of the tumors conferred by underlying gene mutations.[15-19] These papers suggest that alterations in specific genetic pathways may affect how GBMs infiltrate and spread throughout the brain. However, how tumor genetics and cellularity relate to SVZ involvement in LGGs is unclear.

The purpose of this study was therefore, in a cohort of LGGs, (1) to investigate whether SVZ involvement is associated with specific tumor mutations, (2) to investigate the relationship between SVZ involvement and tumor cellularity, measured by whole tumor ADC values, and (3) to investigate the roles of

SVZ involvement, tumor genetics, and tumor cellularity in predicting progression and overall survival.

Methods

Patient Population and Clinical Information

This health insurance portability and accountability act-compliant, retrospective study was approved by our institutional review board. We included 45 consecutive adult patients with pathologically confirmed LGGs (17 World Health Organization [WHO] grade II and 28 WHO grade III), who were resected between February 2006 and June 2018 and underwent both preoperative imaging and an assay to assess for tumor genetic mutations. Formalin-fixed paraffin embedded tumor samples were submitted for next-generation sequencing to FoundationOne™ (Foundation Medicine Inc., Cambridge, MA),[20] which tests for mutations in 324 genes. In addition, 1p19q codeletion status was assessed in 44 of the 45 subjects for the diagnosis of oligodendroglioma; the one patient for whom codeletion status was not available had an IDH-wild-type tumor and therefore was unlikely to be 1p19q-codeleted.

Magnetic Resonance Imaging Acquisition and Analysis

All patients underwent magnetic resonance imaging (MRI) of the brain on 1.5 or 3 Tesla clinical scanners (Skyra, Biograph mMR, Siemens Healthcare; Discovery 750w, Signa HDxt, GE Healthcare, Milwaukee, WI), which included axial T1-weighted (repetition time [TR]/echo time [TE] = 550-700 ms/7-10 ms; 3-5 mm slice thickness) or 3D T1 SPACE (TR/TE = 600-700 ms/11-19 ms; 120° flip; 1 mm slice thickness), axial T2 (TR/TE = 3,200-4,000 ms/93-98 ms; 5 mm slice thickness), and axial T2 fluid-attenuated inversion recovery (FLAIR) or 3D T2 FLAIR (TR/TE = 6,300-8,500 ms/394-446 ms; 120° flip; 1 mm slice thickness) sequences. Axial diffusion-weighted sequences were also obtained (TR/TE 6,280-9,000 ms/78-103 ms; 90° or 180° flip; 5 mm slice thickness) with ADC maps available for 41 of the 45 patients.

The volume of each tumor was calculated using FDA-approved software (Olea Medical 3.0; La Ciotat, France) by selecting a seed voxel at the center of the tumor on the T2 FLAIR magnetic resonance (MR) images and expanding the volume-of-interest (VOI) in three dimensions, across all slices, to include surrounding voxels of similar signal intensities. Manual editing was then performed to include or exclude voxels as necessary. The VOI was then copied onto the overlaid and spatially aligned ADC map to obtain histogram values across the entire T2-hyperintense tumor volume. The 5th percentile, 10th percentile, 25th percentile, median, and mean ADC values were included in the analyses and normalized by normal-appearing contralateral white matter

SVZ involvement and distance from the ependymal margin of the lateral ventricles, in millimeters, were determined by two neuroradiologists, each with over 12 years of experience evaluating MRI scans (GC and IK), who were blinded to other clinical information during this assessment. The SVZ was considered involved if the tumor contacted the ependymal margin.

Statistical Analysis

Statistical analysis was performed utilizing STATA 13 (StataCorp, College Station, TX). Progression-free survival was defined as the duration of time from initial surgery to MRI evidence of tumor progression by RANO criteria or last recorded date of follow-up without progression. Overall survival was defined as the duration of time from initial surgery to death or last recorded date of follow-up.

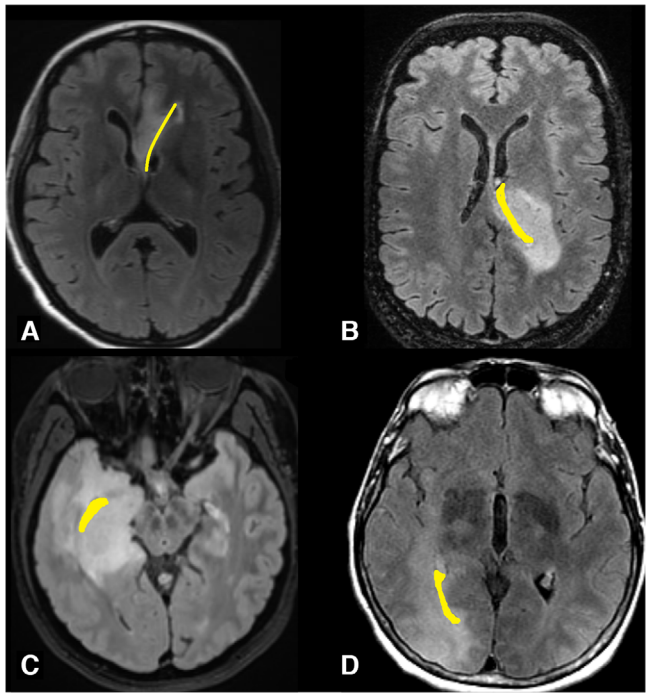

Fig 1. Subventricular zone (SVZ) involvement as assessed on fluid-attenuated inversion recovery MR images. Examples of frontal (A), parietal (B), temporal (C), and occipital (D) SVZ involvement (outlined in yellow).

The Fisher's exact test was used to determine whether any of the tumor mutations were associated with SVZ involvement. Post hoc, we also used the Fisher's exact test to assess whether any of the tumor mutations were specifically associated with occipital SVZ involvement. A logistic regression model was used to determine whether tumor ADC values were associated with SVZ involvement, with a dichotomous variable representing SVZ involvement as the outcome variable and whole tumor mean ADC value as the predictor.

Cox regression models were used to determine whether SVZ involvement, individual tumor mutations, and tumor ADC values were independently associated with progression or survival. Regional involvement of the SVZ was determined by anatomical landmarks and reported as frontal, parietal, temporal, and occipital regions (Fig 1), because occipital SVZ involvement was noted to be prognostic in a prior paper.[9] Distance from the SVZ in millimeters was also considered in the Cox regression models. Hazard ratios (HR) were assessed to determine risk of progression and death. *P*-values of less than .05 were considered significant.

Age, Karnofsky performance status (KPS), and gross total resection have been reported to be prognostic[21] and were considered in the Cox regression models. Sex, tumor grade, preoperative tumor volume, the use of radiation therapy, and the use of chemotherapy were also included in the Cox regression models as potential predictors.

Finally, post hoc, we performed subgroup analyses to determine whether occipital SVZ involvement and significant

Table 1. Demographics and Clinical Characteristics of the Cohort ($N = 45$ patients)

Age (years)	**48 ± 14 (range 21-77)**
Karnofsky Performance Scale[a]	
100	7
90	18
80	14
70	4
60	1
WHO[b] histological grade II: grade III	17: 28
Astrocytoma: oligodendroglioma[c]	35: 10
Female: male	20: 25
Preoperative tumor volume (cubic centimeters)	36 ± 48
Distance from ependymal margin (millimeters)	0 ± 8
Involvement of the subventricular zone (yes: no)	32: 13
Gross total: partial resection	10: 35
Received radiotherapy and chemotherapy during follow-up (yes: no)	41: 4

Data presented are medians ± standard deviation, or number of patients.
[a]The Karnofsky Performance Scale was available for 44 of 45 patients.
[b]WHO = World Health Organization.
[c]Oligodendroglioma as defined by a 1p19q codeletion.

Table 2. Distribution of Lower Grade Gliomas with Key Genetic Alterations, in Relation to Subventricular Zone Involvement

	IDH1 mutation ($N = 24$)	**IDH2 mutation ($N = 2$)**	**PTEN mutation ($N = 6$)**	**CDKN2A/B mutation ($N = 8$)**	**CDK4 mutation ($N = 4$)**	**EGFR alteration ($N = 10$)**	**1p19q codeletion ($N = 10$)**
WHO tumor grade II:III	13:11	1:1	0:6	1:7	0:4	2:8	7:3
Frontal subventricular zone involvement	8 [>.99]	1 [>.99]	0 [.16]	3 [>.99]	2 [.59]	5 [.26]	3 [>.99]
Parietal subventricular zone involvement	6 [.23]	0 [.55]	2 [>.99]	5 [.10]	1 [>.99]	5 [.26]	2 [.45]
Temporal subventricular zone involvement	10 [.56]	0 [.49]	5 [.08]	6 [.12]	2 [>.99]	8 [.029]*	2 [.072]
Occipital subventricular zone involvement	0 [.21]	0 [>.99]	1 [.25]	2 [.028]*	0 [>.99]	0 [>.99]	0 [>.99]
No subventricular zone involvement	8 [.53]	1 [.50]	1 [.66]	1 [.41]	1 [>.99]	9 [.24]	5 [.13]

Numbers shown in table represent the numbers of tumors with regional subventricular zone involvement and a genetic alteration. *P*-values for the association between subventricular zone involvement and the genetic alteration by Fisher's exact test are shown in brackets.
*$P < .05$
IDH = isocitrate dehydrogenase; PTEN = phosphatase and tensin homolog; CDKN2A/B = cyclin-dependent kinase inhibitor 2A/B; CDK4 = cyclin-dependent kinase 4; EGFR = epidermal growth factor receptor; 1p19q = short arm of chromosome 1 and long arm of chromosome 19; WHO = World Health Organization.

tumor mutations remained prognostic among patients with similar treatment regimens, including those who underwent partial rather than gross total initial resection and those who received chemotherapy and radiation during follow-up.

Results

Baseline Characteristics of the Cohort

Clinical and demographic characteristics of the study cohort are outlined in Table 1. The median patient age was 48 ± 14 (range: 21-77 years). Twenty (44%) patients were female and 25 (56%) were male. Ten (22%) had undergone gross total initial resection. Twenty-four (53%) patients progressed during the follow-up period (median = 2.3 ± 3.2 years; range: .3-12.6 years). For these 24 patients, the median time-to-progression was 1 year (standard deviation = 2.4; range: .2-8.1 years). There were five deaths (11%) during the time of follow-up. For these 5 patients, the median time-to-death was 1.7 years (standard deviation = 1.3; range: 1.1-4.3 years).

Relationship Between SVZ Involvement and Tumor Genetics and Cellularity

The median number of tumor mutations per patient was 3 ± 1 (range: 1-6 mutations). The most common mutations were IDH1, found in 24 (53%) of patients (13 grade II and 11 grade III), and TP53, found in 22 (49%) of patients (eight grade II and 14 grade III). A 1p19q codeletion was present in 10 of the 44 patients (24%) for which this could be assessed. None of the tumor mutations were associated with overall SVZ involvement ($P > .05$) (Table 2). However, occipital SVZ involvement was associated with having a cyclin-dependent kinase inhibitor 2A/B (CDKN2A/B) mutation ($P = .03$). In addition, occipital SVZ involvement was associated with lower ADC histogram values at the 5th ($P = .026$) and 10th percentile ($P = .046$) (Table 3).

Prognostic Utility of SVZ Involvement in LGGs

The SVZ was involved in 32 (71%) patients: the frontal region in 15 (33%), the parietal region in 15 (33%), the temporal region in 21 (47%), and the occipital region in 2 (4%) patients; more than one SVZ region was involved in 15 patients. The median distance from the ependymal margin was 0 ± 7.7 mm (range: 0-31 mm).

Occipital SVZ involvement was associated with a higher risk of progression (HR = 6.6; $P = .016$) (Fig 2), whereas frontal ($P = .95$), parietal ($P = .43$), and temporal SVZ ($P = .57$) involvement were not (Table 4). Occipital SVZ was also associated with a higher risk of death (HR = 31, $P = .015$) (Fig 3) (Table 5). In post

Table 3. Associations Between Subventricular Zone (SVZ) Involvement and Apparent Diffusion Coefficient (ADC) Values

	Overall SVZ involved	Frontal SVZ involved	Parietal SVZ involved	Temporal SVZ involved	Occipital SVZ involved
ADC, 5th percentile	−.06	.04	−.07	−.02	−.38
	[.50]	[.60]	[.37]	[.77]	[.026]*
ADC, 10th percentile	−.01	.05	−.09	.002	−.37
	[.88]	[.52]	[.27]	[.98]	[.046]*
ADC, 25th percentile	.03	.05	−.13	.05	−.42
	[.77]	[.66]	[.21]	[.63]	[.075]
ADC, median	.05	.02	−.16	.09	−.54
	[.72]	[.88]	[.23]	[.47]	[.067]
ADC, mean	.01	−.11	−.12	.20	−.46
	[.93]	[.41]	[.38]	[.12]	[.14]

Regression coefficients [*P*-values] shown in table.
*$P < .05$

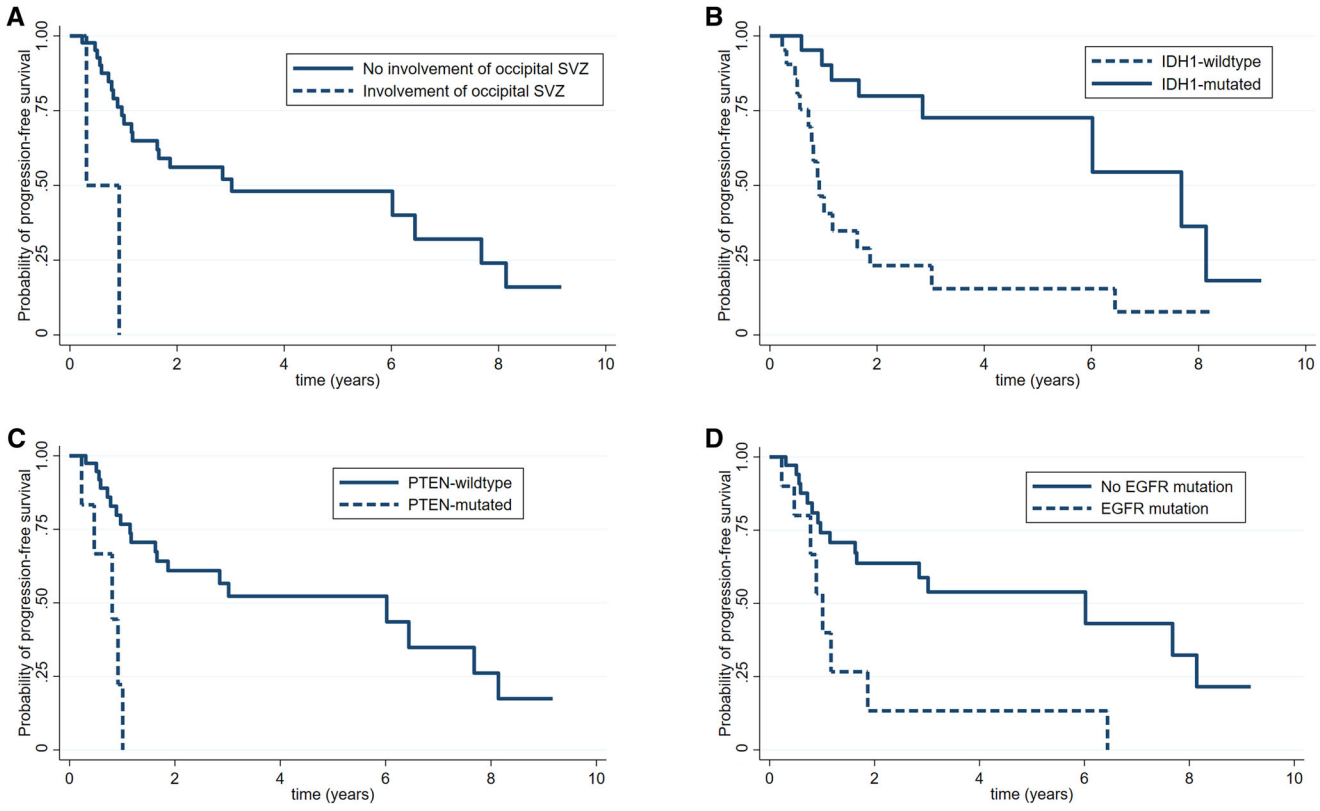

Fig 2. Kaplan-Meier curves for progression-free survival, stratified by occipital subventricular zone involvement (hazard ratio = 6.6, $P = .016$) (A), IDH1 mutation (hazard ratio = .25, $P = .001$) (B), PTEN mutation (hazard ratio = 6.6, $P = .001$) (C), and EGFR mutation (hazard ratio = 3.1, $P = .01$) (D).

hoc analyses, occipital SVZ involvement remained a significant predictor of progression and death in a subgroup that received both chemotherapy and radiation during follow-up ($P = .018$ and .023) and in a subgroup that underwent partial rather than gross total resection ($P = .047$ and .026).

However, the distance from the SVZ was not associated with progression or survival ($P > .05$).

Prognostic Utility of Tumor Genetics in LGGs

Harboring an IDH1 mutation was associated with a lower risk of tumor progression (HR = .25; $P = .001$) (Fig 2). Harboring either an IDH1 or IDH2 mutation was associated with an even lower risk of tumor progression (HR = .12; $P < .001$) (Table 4). Mutations in the phosphatase and tensin homolog (PTEN) gene and molecular alterations in the epidermal growth factor receptor (EGFR) gene were associated with an increased risk of tumor progression (HR = 6.6 [$P = .001$] and HR = 3.1 [$P = .01$], respectively). 1p19q codeletion status was not associated with tumor progression (HR = .43; $P = .11$). In a multivariate regression model, IDH1 (HR = .34; $P = .04$) and PTEN (HR = 3.4; $P = .04$) mutations were more strongly associated with tumor progression than EGFR alterations (HR = 1.3; $P = .59$).

In assessing overall survival, mutations in PTEN (HR = 33.2; $P = .005$), the cyclin-dependent kinase 4 (CDK4) (HR = 11.2; $P = .017$), and CDKN2A/B (HR = 13.0; $P = .006$) were associated with a higher risk of death (Fig 3) (Table 5). Both 1p19q-codeleted and *IDH*-mutated tumors had the lowest risk of death with a hazard ratio approaching 0, because none of these patients died during the time of follow-up.

Table 4. Risk of Tumor Progression Associated with Subventricular Zone Involvement, Tumor Genetics, and Apparent Diffusion Coefficient (ADC) Values

	Hazard ratio [95% confidence interval]	*P*-value
Tumor volume	1.00 [.99–1.01]	.59
Any subventricular zone involvement	1.30 [.52–3.29]	.58
Frontal subventricular zone involvement	.97 [.41–2.28]	.95
Parietal subventricular zone involvement	1.40 [.61–3.21]	.43
Temporal subventricular zone involvement	1.26 [.56–2.83]	.57
Occipital subventricular zone involvement	6.56 [1.31–30.52]	.016*
IDH1 mutation	.25 [.10–.58]	.001*
PTEN mutation	6.56 [2.11–20.47]	.001*
EGFR alteration	3.13 [1.29–7.57]	.01*
ADC, 5th percentile	.69 [.12–3.93]	.68
ADC, 10th percentile	.44 [.08–2.58]	.36
ADC, 25th percentile	.29 [.06–1.43]	.13
ADC, median	.31 [.09–1.10]	.07
ADC, mean	.44 [.18–1.07]	.07

*$P < .05$

Table 5. Risk of Death Associated with subventricular Zone Involvement, Tumor Genetics, and apparent Diffusion Coefficient (ADC) Values

	Hazard ratio [95% confidence interval]	*P*-value
Tumor volume	.97 [.93–1.02]	.21
Any subventricular zone involvement	.77 [.13–4.61]	.77
Frontal subventricular zone involvement	.48 [.05–4.34]	.52
Parietal subventricular zone involvement	.70 [.08–6.35]	.76
Temporal subventricular zone involvement	.82 [.14–4.95]	.83
Occipital subventricular zone involvement	31.50 [1.97–503.59]	.015*
PTEN mutation	33.21 [2.87–384.55]	.005*
CDKN2A/B mutation	13.03 [2.06–82.54]	.006*
CDK4 mutation	11.20 [1.54–81.37]	.017*
ADC, 5th percentile	.08 [.003–2.67]	.16
ADC, 10th percentile	.025 [.0004–1.70]	.087
ADC, 25th percentile	.0097 [.00007–1.36]	.066
ADC, median	.022 [.0004–1.14]	.058
ADC, mean	.45 [.087–2.34]	.34

*$P < .05$

In post hoc subgroup analyses including patients who similarly underwent partial rather than gross total resection and those who received chemotherapy and radiation postoperatively, these associations remained significant ($P \leq .05$).

Prognostic Utility of Tumor Cellularity and Other Clinical Variables

Tumor ADC values showed a nonsignificant trend toward decreased risk of progression and death (Table 3).

Having a KPS of over 80 was associated with lower risk of tumor progression (HR = .39; $P = .025$). Age ($P = .09$ and .10), grade ($P = .23$ and .14), initial gross total resection ($P = .42$ and $\geq .99$), sex ($P = .49$ and .85), preoperative tumor volume ($P = .59$ and .21), treatment by radiation before progression ($P = .06$ and .28), and treatment by chemotherapy before progression ($P = .33$ and .51) were not associated with progression or survival. All five patients who died during follow-up received radiation and chemotherapy following initial resection.

Discussion

SVZ involvement has been shown to predict poor outcomes in GBMs,[1-3] and some studies have reported that irradiating the ipsilateral SVZ may improve progression-free and overall survival.[22-24] This study sought to determine whether SVZ involvement likewise conferred poor prognosis in LGGs, as well as how SVZ involvement was related to tumor genetics and cellularity.

The first major finding of our study was that SVZ involvement is common in LGGs, but in contrast to what has been previously reported in GBMs, it was overall not a stronger predictor of poor outcomes in our LGG cohort. Similarly, the distance between the tumor border and the SVZ was not found to be prognostic, which aligns with a previous paper that found no difference in the distance to the SVZ between IDH-mutated and IDH-wild-type LGGs.[25] Only occipital SVZ involvement was prognostic for tumor progression and survival. Seventy percent of the tumors in our cohort demonstrated SVZ involvement, a proportion similar to prior studies that included grade II[7] and grade III gliomas.[9] As in these prior papers,[7,9] regional SVZ involvement varied in prevalence, with occipital SVZ involvement being uncommon, only seen in two patients (4%) of our cohort. Nevertheless, only occipital SVZ involvement was associated with tumor progression and survival, consistent with the results from the prior study of grade III gliomas.[9] Recent experimental evidence suggests that gliomas may be drawn to the SVZ through CXCL12/CXCR4 signaling pathways,[26] where they can recruit aggressive stem cells.[27] Various growth factors in the SVZ environment, including epidermal growth

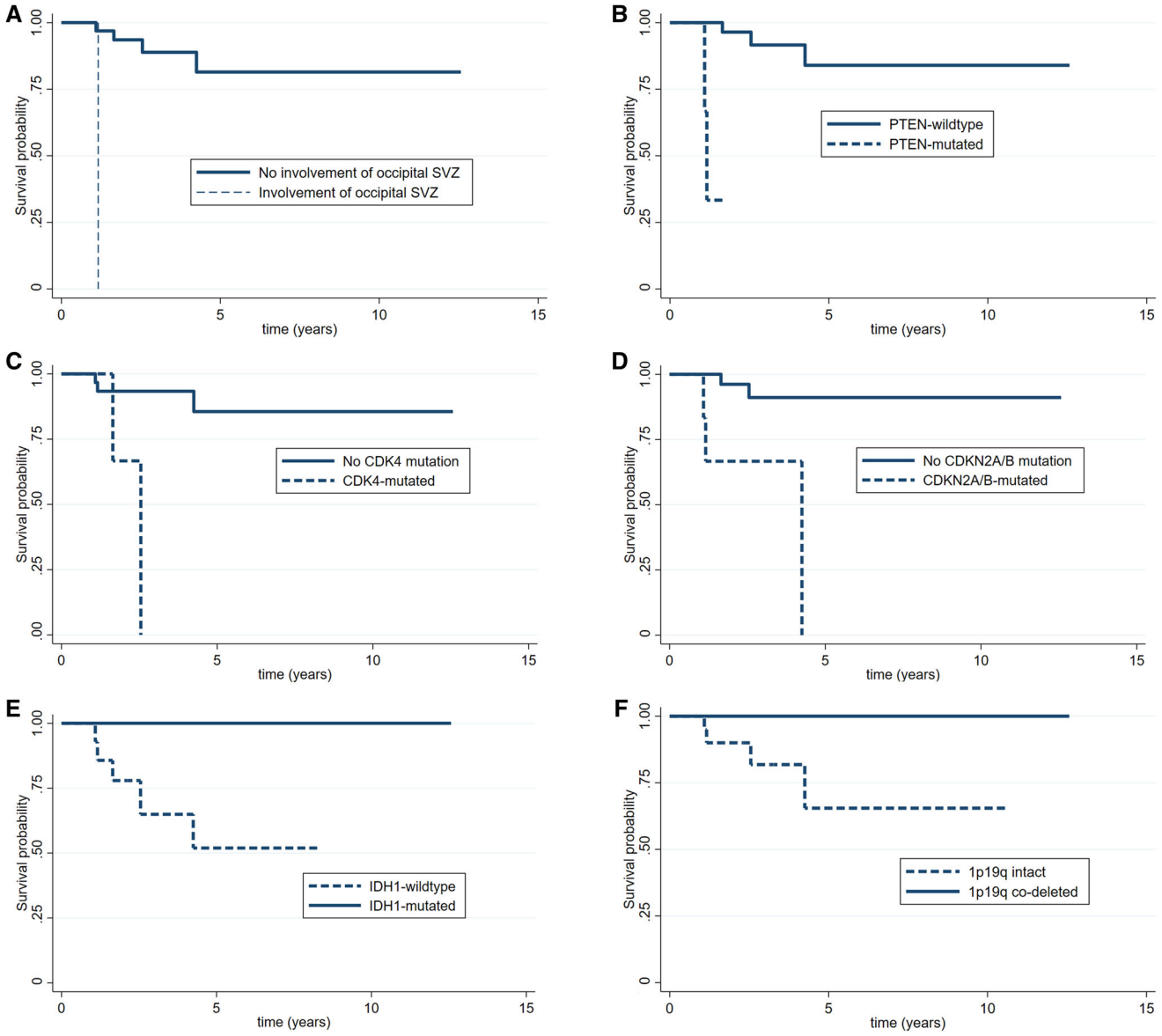

Fig 3. Kaplan-Meier curves for overall survival, stratified by occipital subventricular zone involvement (hazard ratio = 31, $P = .015$) (A), PTEN mutation (hazard ratio = 33, $P = .005$) (B), CDK4 mutation (hazard ratio = 11, $P = .017$) (C), CDKN2A/B mutation (hazard ratio = 13, $P = .006$) (D), IDH1 mutation (E), and 1p19q codeletion (F). None of the patients who had 1p19q-codeleted and/or IDH1-mutated tumors died during the time of follow-up, with hazard ratios approaching 0.

factor, brain-derived neurotrophic factor, and vascular endothelial growth factor C, have also been reported to promote glioma stem cell proliferation.[28] It is possible that gliomas that are exposed to the SVZ environment likewise acquire proliferative and aggressive features, leading to a poorer prognosis. However, the reason for occipital SVZ involvement to be particularly detrimental remains to be elucidated, as only one study thus far has investigated cellular differences in the regional organization of the SVZ.[29]

Our second major finding was that overall SVZ involvement was neither associated with tumor genetics nor cellularity. This finding mirrors the results of a prior study in GBMs that reported that SVZ involvement, though associated with decreased survival in GBMs, did not have a distinct molecular signature.[30] This prior study assessed tumor mutations, DNA methylation, gene expression, and protein expression, which suggests that SVZ involvement and molecular alterations may be independent prognostic factors. Among LGGs, SVZ involvement by oligodendrogliomas was previously reported to be associated with a mutation in the Capicua transcriptional repressor gene.[31] We did not find this association in our cohort, because two oligodendrogliomas had this mutation; one had SVZ involvement and the other did not. Post hoc, in our cohort, we did find an association between having a CDKN2A/B mutation and occipital SVZ involvement. Furthermore, we found an association between occipital SVZ involvement and ADC values on the lower spectrum of the histogram. This raises the possibility that CDKN2A/B mutation may lead to biological characteristics in tumors that predict a poor prognosis, such as hypercellularity and occipital SVZ involvement; these molecular mechanisms warrant further investigation.

Third, we found several genetic alterations that were associated with LGG outcomes. This result corroborates recent robust evidence demonstrating the importance of tumor genetics

in glioma prognostication,[10,12,32,33] particularly IDH mutations in predicting improved overall survival.[33-36] Among LGGs, median survival has been reported to range from 1.5 years for IDH-wild-type tumors[33] to up to 15 years for tumors with an IDH mutation and 1p/19q codeletion (ie, oligodendrogliomas by current WHO diagnostic criteria).[37] Twenty-six (58%) of the LGGs in our cohort had an IDH mutation (24 IDH1 and two IDH2), similar in prevalence to a prior study,[11] and these tumors, 10 of which also had a 1p19q-codeletion, were indeed associated with the lowest risk of death; all of these patients survived to the end of this study. We also found that an IDH mutation was associated with a slower rate of progression, compatible with prior literature demonstrating that IDH-mutated gliomas respond better to chemotherapy[38] and have a slower rate of malignant transformation.[39]

Besides IDH, we found that mutations in PTEN ($n = 6$; 13% of our cohort), CDK4 ($n = 4$; 9%), and CDKN2A/B ($n = 8$; 18%) were also associated with survival in our cohort. PTEN is a tumor suppressor gene that normally acts as a negative regulator of the cell survival kinase pathway PI3K and is inactivated by a mutation in 20% of GBMs.[40] Resulting overactivation of PI3K pathway drives tumor progression,[40] resulting in higher grade malignancy and reduced survival,[41] as well as SVZ precursor cells that were more migratory and resistant to apoptosis.[42] Compatible with our results, meta-analyses of mixed glioma cohorts have shown that PTEN mutations are associated with worse survival,[43,44] and that LGGs with a PTEN mutation can be considered "molecularly high grade."[45]

Cyclin-dependent kinase CDK4 regulates the cell cycle through phosphorylation of Rb and activation of genes resulting in cell cycle progression from G1 to S phase.[46] The CDK4/6-Rb-E2F axis is dysregulated in about 80% of GBMs.[47] CDKN2A and CDKN2B are cyclin-dependent kinase inhibitors, which form complexes with CDK4 or CDK6 to regulate cell growth and cell cycle G1 progression.[48] CDKN2A/B deletion has been reported in 40-70% of GBMs,[48,49] and CKDN2A deletion is associated with poorer survival in LGGs,[50] even among IDH-mutant gliomas.[51] As shown in our cohort, mutations in CDK4 and CDKN2A/B were associated with worse survival, suggesting that these mutations likewise make LGGs molecularly high grade.

We found that molecular alterations in EGFR ($n = 10$, 22% of our cohort) were associated with more rapid tumor progression but not overall survival. EGFR is a growth factor receptor gene, and mutations in EGFR have been reported in 20% of GBMs[40] and up to 15% of LGGs.[52] Similarly, we detected EGFR alterations in 22% of our cohort. Our finding that EGFR alterations were associated with more rapid tumor progression is consistent with prior studies that have reported poorer prognosis in cohorts that included mixed grade[53] and grade II gliomas.[54] Our findings are also consistent with a prior study that found no association between EGFR molecular alterations and overall survival[55]

We found that lower ADC values, commonly used as a noninvasive measure of tumor cellularity,[13-15] showed a nonsignificant trend toward more rapid tumor progression and death. This somewhat contradicts prior papers that have shown that ADC values are prognostic in cohorts with similar duration of progression-free and overall survival.[14,15] Sample size and technical scanner differences may play a role.

Finally, besides KPS, clinical variables were not significant predictors of outcome. The majority of the cohort ($n = 41$; 91%) received both radiation therapy and chemotherapy during follow-up after the initial resection, and all five deaths occurred in patients who received both radiation therapy and chemotherapy. Because all of these patients were managed per standard-of-care, we could not detect a significant difference in outcome related to treatment, unlike in a clinical trial, in which groups receiving radiation or chemotherapy are balanced to evaluate treatment response. Furthermore, it is possible that adjuvant radiation and chemotherapy may only benefit younger patients[56] or only be evident during much longer follow-up periods.[57] Similarly, we found that gross total resection did not confer a better prognosis relative to partial resection, as other papers have reported[58-61]; one prior paper also reported that gross total resection may only be prognosis in IDH-mutated gliomas.[62] Age, sex, and tumor grade were also not prognostic in our cohort, consistent with prior analyses in LGG cohorts[60,61,63] and that tumor genetics are stronger predictors than histological grade.[10,11]

The main limitations of our study were the retrospective single-center design and sample size. In particular, occipital SVZ involvement was only present in two patients. The cohort was also heterogeneous in terms of tumor management (Table 1), although neither chemotherapy nor radiation therapy were found to be significantly prognostic in regression models and subgroup analyses of patients with similar treatment regimens did not change the results. In addition, we did not include other potentially prognostic imaging modalities in our analysis, such as MR spectroscopy or MR perfusion, because they are not routinely included in our preoperative imaging for surgical guidance. Nevertheless, we provide further evidence supporting the role of tumor genetics in determining prognosis in LGGs and the potential role of occipital SVZ involvement as an additional independent risk factor. Our results warrant further validation in larger multicenter cohorts with longer periods of follow-up.

In conclusion, we found that mutations in PTEN, CDK4, CDKN2A/B, and EGFR were strong predictors of LGG outcomes, in addition to IDH1. Although these mutations were not associated with overall SVZ involvement, CDKN2A/B was associated with occipital SVZ involvement. Occipital SVZ involvement, though uncommon, was prognostic of both tumor progression and survival. ADC values, as a measure of tumor cellularity, were neither prognostic nor associated with SVZ involvement.

References

1. Jafri NF, Clarke JL, Weinberg V, et al. Relationship of glioblastoma multiforme to the subventricular zone is associated with survival. Neuro Oncol 2013;15:91-6.
2. Adeberg S, König L, Bostel T, et al. Glioblastoma recurrence patterns after radiation therapy with regard to the subventricular zone. Int J Radiat Oncol Biol Phys 2014;90:886-93.
3. Lim DA, Cha S, Mayo MC, et al. Relationship of glioblastoma multiforme to neural stem cell regions predicts invasive and multifocal tumor phenotype. Neuro Oncol 2007;9:424-9.
4. Gong X, Schwartz PH, Linskey ME, et al. Neural stem/progenitors and glioma stem-like cells have differential sensitivity to chemotherapy. Neurology 2011;76:1126-34.
5. Bao S, Wu Q, McLendon RE, et al. Glioma stem cells promote radioresistance by preferential activation of the DNA damage response. Nature 2006;444:756-60.

6. Lee JH, Lee JE, Kahng JY, et al. Human glioblastoma arises from subventricular zone cells with low-level driver mutations. Nature 2018;560:243-7.
7. Liu S, Wang Y, Fan X, et al. Anatomical involvement of the subventricular zone predicts poor survival outcome in low-grade astrocytomas. PLoS One 2016;11:e0154539.
8. Wen B, Fu F, Hu L, et al. Subventricular zone predicts high velocity of tumor expansion and poor clinical outcome in patients with low grade astrocytoma. Clin Neurol Neurosurg 2018;168:12-7.
9. Liu S, Wang Y, Fan X, et al. Association of MRI-classified subventricular regions with survival outcomes in patients with anaplastic glioma. Clin Radiol 2017;72:426.e1-e6.
10. 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;372:2499-508.
11. Cancer Genome Atlas Research Network, Brat DJ, Verhaak RG, et al. Comprehensive, integrative genomic analysis of diffuse lower-grade gliomas. N Engl J Med 2015;372:2481-98.
12. Yan H, Parsons DW, Jin G, et al. IDH1 and IDH2 mutations in gliomas. N Engl J Med 2009;360:765-73.
13. Cuccarini V, Erbetta A, Farinotti M, et al. Advanced MRI may complement histological diagnosis of lower grade gliomas and help in predicting survival. J Neurooncol 2016;126:279-88.
14. Villanueva-Meyer JE, Wood MD, Choi BS, et al. MRI features and IDH mutational status of grade II diffuse gliomas: impact on diagnosis and prognosis. AJR Am J Roentgenol 2018;210:621-8.
15. Wu CC, Jain R, Radmanesh A, et al. Predicting genotype and survival in glioma using standard clinical MR imaging apparent diffusion coefficient images: a pilot study from the Cancer Genome Atlas. AJNR Am J Neuroradiol 2018;39:1814-20.
16. Gevaert O, Mitchell LA, Achrol AS, et al. Glioblastoma multiforme: exploratory radiogenomic analysis by using quantitative image features. Radiology 2014;273:168-74.
17. Diehn M, Nardini C, Wang DS, et al. Identification of noninvasive imaging surrogates for brain tumor gene-expression modules. Proc Natl Acad Sci USA 2008;105:5213-8.
18. Jungk C, Mock A, Exner J, et al. Spatial transcriptome analysis reveals notch pathway-associated prognostic markers in IDH1 wildtype glioblastoma involving the sub ventricular zone. BMC Med 2016;14:170.
19. Jamshidi N, Diehn M, Bredel M, et al. Illuminating radiogenomic characteristics of glioblastoma multiform through integration of MR imaging, messenger RNA expression, and DNA copy number variation. Radiology 2014;270:1-2.
20. Frampton GM, Fichtenholtz A, Otto GA, et al. Development and validation of a clinical cancer genomic profiling test based on massively parallel DNA sequencing. Nat Biotechnol 2013;31:1023-31.
21. Lamborn KR, Chang SM, Prados MD. Prognostic factors for survival of patients with glioblastoma: recursive partitioning analysis. Neuro Oncol 2004;6:227-35.
22. Chen L, Guerrero-Cazares H, Ye X, et al. Increased subventricular zone radiation dose correlates with survival in glioblastoma patients after gross total resection. Int J Radiat Oncol Biol Phys 2013;86:616-22.
23. Lee P, Eppinga W, Lagerwaard F, et al. Evaluation of high ipsilateral subventricular zone radiation therapy dose in glioblastoma: a pooled analysis. Int J Radiat Oncol Biol Phys 2013;86:609-15.
24. Gupta T, Nair V, Paul SN, et al. Can irradiation of potential cancer stem-cell niche in the subventricular zone influence survival in patients with newly diagnosed glioblastoma? J Neurooncol 2012;109:195-203.
25. Skjulsvik AJ, Bo HK, Jakola AS, et al. Is the anatomical distribution of low-grade gliomas linked to regions of gliogenesis? J Neurooncol 2020;147:147-57.
26. Goffart N, Kroonen J, Di Valentin E, et al. Adult mouse subventricular zones stimulate glioblastoma stem cells specific invasion through CXCL12/CXCR4 signaling. Neuro Oncol 2015;17:81-94.
27. Kroonen J, Nassen J, Boulanger YG, et al. Human glioblastoma-initiating cells invade specifically the subventricular zones and olfactory bulbs of mice after striatal injection. Int J Cancer 2011;129:574-85.
28. Kusne Y, Sanai N. The SVZ and its relationship to stem cell based neuro-oncogenesis. Adv Exp Med Biol 2015;853:23-32.
29. Quinones-Hinojosa A, Sanai N, Gonzalez-Perez O, et al. The Human brain subventricular zone: stem cells in this niche and its organization. Neurosurg Clin N Am 2007;18:15-20.
30. Mistry AM, Wooten DJ, Davis LT, et al. Ventricular-subventricular zone contact by glioblastoma is not associated with molecular signatures in bulk tumor data. Sci Rep 2019;9:1842.
31. Liu Z, Liu H, Liu Z, et al. Oligodendroglial tumours: subventricular zone involvement and seizure history are associated with CIC mutation status. BMC Neurol 2019;19:134.
32. Kim YH, Nobusawa S, Mittelbronn M, et al. Molecular classification of low-grade diffuse gliomas. Am J Pathol 2010;177:2708-14.
33. 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;27:4150-4.
34. Sabha N, Knobbe CB, Maganti M, et al. Analysis of IDH mutation, 1p/19q deletion, and PTEN loss delineates prognosis in clinical low-grade diffuse gliomas. Neuro Oncol 2014;16:914-23.
35. Gittleman H, Sloan AE, Barnholtz-Sloan JS. An independently validated survival nomogram for lower-grade glioma. Neuro Oncol 2020;22:665-74.
36. Leu S, von Felten S, Frank S, et al. IDH/MGMT-driven molecular classification of low-grade glioma is a strong predictor for long-term survival. Neuro Oncol 2013;15:469-79.
37. Cairncross G, Wang M, Shaw E, et al. Phase III trial of chemoradiotherapy for anaplastic oligodendroglioma: long-term results of RTOG 9402. J Clin Oncol 2013;31:337-43.
38. Houillier C, Wang X, Kaloshi G, et al. IDH1 or IDH2 mutations predict longer survival and response to temozolomide in low-grade gliomas. Neurology 2010;75:1560-6.
39. Metellus P, Coulibaly B, Colin C, et al. Absence of IDH mutation identifies a novel radiologic and molecular subtype of WHO grade II gliomas with dismal prognosis. Acta Neuropathol 2010;120:719-29.
40. Lee SC. Diffuse gliomas for nonneuropathologists: the new integrated molecular diagnostics. Arch Pathol Lab Med 2018;142:804-14.
41. Kwon CH, Zhao D, Chen J, et al. Pten haploinsufficiency accelerates formation of high-grade astrocytomas. Cancer Res 2008;68:3286-94.
42. Li L, Liu F, Salmonsen RA, et al. PTEN in neural precursor cells: regulation of migration, apoptosis, and proliferation. Mol Cell Neurosci 2002;20:21-9.
43. Han F, Hu R, Yang H, et al. PTEN gene mutations correlate with poor prognosis in glioma patients: a meta-analysis. Onco Targets Ther 2016;9:3485-92.
44. Yang Y, Shao N, Luo G, et al. Mutations of PTEN gene in gliomas correlate to tumor differentiation and short-term survival rate. Anticancer Res 2010;30:981-5.
45. Rasheed BK, Stenzel TT, McLendon RE, et al. PTEN gene mutations are seen in high-grade but not in low-grade gliomas. Cancer Res 1997;57:4187-90.
46. Weinberg RA. The retinoblastoma protein and cell cycle control. Cell 1995;81:323-30.
47. Olmez I, Brenneman B, Xiao A, et al. Combined CDK4/6 and mTOR inhibition is synergistic against glioblastoma against multiple mechanisms. Clin Cancer Res 2017;23:6958-68.
48. Wrensch M, Jenkins RB, Chang JS, et al. Variants in the CDKN2B and RTEL1 regions are associated with high grade glioma susceptibility. Nat Genet 2009;41:905-8.
49. Purkait S, Jha P, Sharma MC, et al. CDKN2A deletion in pediatric versus adult glioblastomas and predictive value of p16 immunohistochemistry. Neuropathology 2013;33:405-12.
50. Reis GF, Pekmezci M, Hansen HM, et al. CDKN2A loss is associated with shortened overall survival in lower-grade (World Health Organization Grades II-III) astrocytomas. J Neuropathol Exp Neurol 2015;74:442-52.

51. Appay R, Dehais C, Maurage C, et al. CDKN2A homozygous deletion is a strong adverse prognosis factor in diffuse malignant IDH-mutant gliomas. Neuro Oncol 2019;21:1519-28.
52. Saadeh FS, Mahfouz R, Assi HI. EGFR as a clinical marker in glioblastomas and other gliomas. Int J Biol Markers 2018;33:22-32.
53. Li J, Liang R, Song C, et al. Prognostic significance of epidermal growth factor receptor expression in glioma patients. Onco Targets Ther 2018;11:731-42.
54. Varela M, Ranuncolo SM, Morand A, et al. EGF-R and PDGF-R, but not bcl-2, overexpression predict overall survival in patients with low-grade astrocytomas. J Surg Oncol 2004;86:34-40.
55. Viana-Pereira M, Lopes JM, Little S, et al. Analysis of EGFR overexpression, EGFR gene amplification and the EGFRvIII mutation in Portuguese high-grade gliomas. Anticancer Res 2008;28:913-20.
56. Nicolato A, Gerosa MA, Fina P, et al. Prognostic factors in low-grade supratentorial astrocytomas: a uni-multivariate statistical analysis in 76 surgically treated adult patients. Surg Neurol 1995;44:208-21.
57. Buckner JC, Shaw EG, Pugh SL, et al. Radiation plus procarbazine, CCNU, and vincristine in low-grade glioma. N Engl J Med 2016;374:1344-55.
58. Pignatti F, van den Bent M, Curran D, et al. Prognostic factors for survival in adult patients with cerebral low-grade glioma. J Clin Oncol 2002;20:2076-84.
59. Lote K, Egeland T, Hager B, et al. Survival, prognostic factors, and therapeutic efficacy in low-grade glioma: a retrospective study in 379 patients. J Clin Oncol 1997;15:3129-40.
60. Shibamoto Y, Kitakabu Y, Takahashi M, et al. Supratentorial low-grade astrocytoma. Correlation of computed tomography findings with effect of radiation therapy and prognostic variables. Cancer 1993;72:190-5.
61. Gorlia T, Wu W, Wang M, et al. 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;15:1568-79.
62. Patel SH, Bansal AG, Young EB, et al. Extent of surgical resection in lower-grade gliomas: differential impact based on molecular subtype. AJNR Am J Neuroradiol 2019;40:1149-55.
63. Claus EB, Walsh KM, Wiencke JK, et al. Survival and low-grade glioma: the emergence of genetic information. Neurosurg Focus 2015;38:E6.