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Radiological features combined with *IDH1* status for predicting the survival outcome of glioblastoma patients

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Background. Radiological characteristics may reflect the biological features of brain tumors and may be associated with genetic alterations that occur in tumorigenesis. This study aimed to investigate the relationship between radiological features and *IDH1* status as well as their predictive value for survival of glioblastoma patients.

Methods. The clinical information and MR images of 280 patients with histologically confirmed glioblastoma were retrospectively reviewed. The radiological characteristics of tumors were examined on MR images, and the *IDH1* status was determined using DNA sequencing for all cases. The Kaplan-Meier method and Cox regression model were used to identify prognostic factors for progression-free and overall survival.

Results. The *IDH1* mutation was associated with longer progression-free survival ($P = .022$; hazard ratio, 0.602) and overall survival ($P = .018$; hazard ratio, 0.554). In patients with the *IDH1* mutation, tumor contrast enhancement and peritumoral edema indicated worse progression-free survival ($P = .015$ and $P = .024$, respectively) and worse overall survival ($P = .024$ and $P = .032$, respectively). For tumors with contrast enhancement, multifocal contrast enhancement of the tumor lesion was associated with poor progression-free survival ($P = .002$) and poor overall survival ($P = .010$) in patients with wild-type *IDH1* tumors.

Conclusions. Combining the radiological features and *IDH1* status of a tumor allows more accurate prediction of survival outcomes in glioblastoma patients. The complementary roles of genetic changes and radiological features of tumors should be considered in future studies.

Keywords: glioblastoma, *IDH1*, radiology, survival outcome.

Glioblastoma is the most common and aggressive type of malignant brain tumor in adults.[1] Its clinical outcome varies substantially, with some patients succumbing to progressive disease within weeks while others survive for decades. The standard treatment is maximal surgical resection with radiation therapy and chemotherapy.[2,3] Although various treatment strategies have been used, glioblastoma patients typically still have a poor prognosis with median progression-free survival (PFS) and overall survival (OS) of 6.9 months and 14.7 months, respectively.[4] Clinical characteristics, including patient age, KPS, and the extent of resection have been previously investigated as prognostic factors for glioblastoma.[5–8]

IDH1 is a previously characterized biomarker in glioblastoma and is mutated in 70%–80% of secondary tumors and <10% of primary tumors.[9–11] These mutations are considered important molecular events in gliomagenesis. As an independent prognostic indicator, *IDH1* mutations are associated with a favorable outcome and longer survival in glioblastoma patients.[12–15] Furthermore, tumors with an *IDH1* mutation have markedly different clinical presentations, overall natural history, and concurrent molecular genetic alterations compared with their *IDH1* wild-type counterparts.[16]

In addition to genetic signatures, radiological features of glioblastoma have also been identified as prognostic factors.

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It has been shown that tumor contrast enhancement,[17,18] multifocality,[19] tumor location,[20,21] edema,[17,19] and cysts[22,23] are potentially associated with survival outcome in glioblastoma patients. Specifically, tumor-induced edema could be used to predict the survival outcomes of glioblastoma patients on the basis of *MGMT* promoter methylation but not the *IDH1* status,[15] which implies that there may be a relationship between genetic changes and radiological features. However, the relationship between *IDH1* expression and certain MR imaging-derived features of glioblastoma have rarely been investigated. Therefore, we aimed to identify the association between the *IDH1* tumor status and radiological features and to determine whether combining these factors could better predict the outcome for glioblastoma patients.

Materials and Methods

Patients

In total, 280 adult patients who were diagnosed with glioblastoma and who underwent surgical treatment at our institution between April 2007 and May 2010 were systematically reviewed. Cases were included if they met the following criteria: (i) aged ≥18 years; (ii) presurgical MR scans available (including T1-weighted, T2-weighted, and postcontrast T1-weighted); (iii) pathologically confirmed glioblastoma based on the WHO histological grading system; (iv) no previous diagnosis of any type of brain tumor; and (v) no previous adjuvant treatment. The histopathological diagnosis was evaluated and confirmed by 2 independent senior neuropathologists who were blinded to patients' clinical and radiological information. Gross total resection (GTR) was defined as no visible contrast enhancement on postoperative MR images within 48 hours after surgery for contrast-enhanced tumors or the disappearance of all abnormal hyperintense changes on preoperative MR images for tumors not demonstrating contrast enhancement. In this study, resections that were not GTR were considered residual tumors (<GTR). The adjuvant treatment was radiation therapy alone or concomitant temozolomide administration with fractionated radiotherapy followed by up to 6 cycles of adjuvant temozolomide.[4] The overall follow-up duration of the study was 74 months during the period between May 2007 and July 2013. This study was approved by our institutional review board, and written consent was obtained from all enrolled patients.

Image Acquisition

MR imaging was performed using a Siemens Trio 3T scanner (Siemens Healthcare). It typically included axial T1-weighted (repetition time [TR], 450 ms; echo time [TE], 15 ms; section thickness, 5 mm), T2-weighted fast spin-echo (TR, 6000 ms, TE, 140 ms; section thickness, 5 mm), and gadopentetate dimeglumine (DTPA-Gd Injection; (Beilu Pharma; 0.1 mmol/kg)-enhanced axial T1-weighted images (TR, 450 ms; TE, 15 ms; section thickness, 5 mm), with a 24 cm field of view and a matrix size of 256 × 256. Postcontrast images were acquired immediately after injection of the contrast agent. The interval between contrast injection and the start of contrast-enhanced T1-weighted image acquisition was always 75–85 seconds. Postoperative MR scans for determining the extent of resection were performed within 72 hours of this procedure, and the radiological parameters were maintained in accordance with the preoperative scans.

Identification of Imaging Features

Tumor contrast enhancement was assessed by 2 experienced neuroradiologists blinded to the patients' clinical information. A third senior neuroradiologist re-examined the images and determined which should be used if the types of enhancement identified by the first 2 neuroradiologists were inconsistent. Briefly, a small (or no) region of edema (−) was defined as edema extending ≤1 cm from the margin of the tumor based on T2-weighted images; otherwise edema was graded as moderate to severe (+).[15] Contrast enhancement was defined as a newly identified, unequivocal increase in signal intensity on a T1-weighted contrast image compared with a noncontrast T1-weighted image. Nonenhancement was defined as no apparent hyperintensity in the tumor-involved area on a postcontrast T1-weighted image. A multifocal-enhancing tumor was defined as more than one area of tumor enhancement located separately from each of the other enhanced areas on a postcontrast T1-weighted image.[15] Patterns of tumor enhancement were identified based on the morphological feature of the largest enhanced tumor area on contrast-enhanced MR images, and ring-like enhancement was defined as cystic necrosis with peripheral enhancement, while any other pattern was defined as non-ring-like.

Detection of IDH1 *Mutations and* MGMT *Promoter Methylation*

IDH1 mutations were identified using DNA pyrosequencing, which we have described previously.[24,25] Briefly, a QIAamp DNA Mini Kit (Qiagen) was used to isolate genomic DNA from frozen tumor tissue samples. The genomic region spanning the wild-type R132 of *IDH1* was analyzed by amplifying a 75-base pair (bp) fragment with the following primers: 5′-GCTTGTGAGTGGATGGGTAAAAC-3′ and 5′-biotin-TTGCCAAC ATGACTTACTTGATC-3′. Duplicate PCR analyses were performed in 40 μL reaction volumes containing 1 μL each of 10 μM forward and reverse primers, 4 μL of 10× buffer, 3.2 μL of 2.5 mM dNTPs, 2.5 U HotStar *Taq* (Takara), and 2 μL of 10 μM DNA. The PCR conditions were as follows: 95°C for 3 minutes; 50 cycles of 95°C for 15 seconds, 56°C for 20 seconds, and 72°C for 30 seconds; and 72°C for 5 minutes (ABI PCR System 9700; Applied Biosystems). Single-stranded DNA was purified from the PCR products and pyrosequenced with a PyroMark Q96 ID System (Qiagen) using a 5′-TGGATGGGTAAAACCT-3′ primer and an EpiTect Bisulfite Kit (Qiagen). The methylation status of the *MGMT* promoter was determined by methylation-specific PCR after sodium bisulfite DNA modification, as described previously.[25]

Statistical Analysis

We used the chi-square test for categorical variables to compare each clinical and imaging feature between patients with *IDH1*-mutant and wild-type tumors. The agreement between

judgments of the enhancement patterns was assessed by the 2 radiologists and was evaluated using the kappa consistency test. Kappa values ≥0.81, 0.61–0.80, and ≤0.60 were considered to reflect excellent, good, and poor agreement, respectively. Additionally, log-rank analyses of Kaplan–Meier survival curves were performed to compare the PFS and OS of the cohort. Factors that were significant ($P < .05$) in univariate analysis were entered into multivariate survival analysis based on the Cox proportional hazard ratio (HR) model. In addition, patients were further divided into subgroups according to their *IDH1* status and radiological features in order to identify the prognostic values of these factors.

Results

Patient Characteristics

The clinical information and radiological data of 280 glioblastoma patients were systematically reviewed; the results are summarized in Table 1. The *IDH1* mutation was detected in 45 tumors (16.1%). Age at diagnosis, contrast enhancement, and enhancing foci were significantly different between patients with mutant and wild-type *IDH1* tumors ($P < .001$, chi-square test). A total of 145 patients (51.8%) underwent GTR, and 135 (48.2%) patients had residual tumors. Of the 280 patients in the study, 234 (83.6%) received the standard adjuvant therapy, 19 patients (6.8%) received only radiation treatment after surgery, and the other 27 patients (9.6%) did not receive any adjuvant therapy because of financial reasons. The chi-square test and Fisher exact test were performed in order to identify the clinical factors that contributed to patients not receiving adjuvant therapy in the mutant *IDH1* group (Supplementary Table S1).

Association Between the IDH1 *Status and Radiological Features*

Among the 280 patients, those with *IDH1*-mutant tumors were less likely to have contrast enhancement on MR images than patients with wild-type IDH1 tumors(73.3% vs 94.9%; $P < .001$; chi-square test) (see Supplementary Fig. S1). Of the 256 glioblastomas tumors with contrast enhancement (91.4%), multi-enhancing foci were more likely to be present in tumors with an *IDH1* mutation compared with wild-type *IDH1* tumors (42.4% vs 19.3%; $P = .003$). In addition, the pattern of tumor contrast enhancement was assessed in glioblastoma with enhancement. Tumor enhancement in a ring-like pattern was present in 165 patients (64.5%). The kappa value for the agreement of enhancement pattern judgments between the 2 evaluators was 0.98 ($P = .08$, kappa consistency test). Distribution of the tumor contrast enhancement patterns was not significantly different between patients with mutant and wild-type *IDH1* tumors ($P = .621$, chi-square test).

Table 1. IDH*1* mutation status of glioblastoma patients ($n = 280$)

Characteristics	*IDH1* Status			*P* Value[a]
	Total ($n = 280$)	Mutant ($n = 45$)	Wild-type ($n = 235$)	
Age				
≥50/<50 years	139/141	6/39	133/102	<.001
Sex				
Male/female	159/121	23/22	136/99	.402
KPS				
≥80/<80	122/158	25/20	97/138	.077
Contrast enhancement				
Yes/no	256/24	33/12	223/12	<.001
Enhancing foci[b]				
Single/multiple foci	199/57	19/14	180/43	.003
Pattern of enhancement[b]				
Ring-like/non-ring-like	165/91	20/13	145/78	.621
Peritumoral edema				
≤1 cm/>1 cm	67/213	13/32	54/181	.395
MGMT promoter methylation				
Yes/no	62/218	6/39	56/179	.120
Extent of resection				
GTR/<GTR	145/135	28/17	117/118	.126
Adjuvant therapy				
Standard therapy[c]/radiation therapy/no therapy	234/19/27	38/2/5	196/17/22	.757

Abbeviation: GTR, gross-total resection.
[a]Result obtained with the chi-square test.
[b]Radiological features for tumors with contrast enhancement ($n = 256$).
[c]Standard therapy includes concomitant temozolomide administration with fractionated radiotherapy followed by up to 6 cycles of adjuvant temozolomide.

Thirteen of 45 patients with an *IDH1*-mutant tumor (28.9%) and 54 of 235 patients (23.0%) with an *IDH1* wild-type tumor did not show peritumoral edema. No significant difference in the incidence of edema was found between patients with mutant and wild-type *IDH1* tumors ($P = .395$, chi-square test).

Prognostic Factors

Tumor occurrence was observed in 228 patients during the follow-up period, and the median PFS of patients enrolled in this study was 9.8 months (range, 2.3–73.1 mo). At the time of analysis, 66 patients (whose follow-up data were available) were still alive, with a median OS of 14.4 months (range, 1.0–86.8 mo). Univariate survival analysis in the entire cohort of patients showed that age at diagnosis (≥50 y vs <50 y, $P = .008$), preoperative KPS (≥80 vs <80, $P = .019$), contrast enhancement ($P = .042$), extent of resection (GTR vs <GTR, $P = .029$), *IDH1* status ($P = .022$), and the administration of standard adjuvant therapy ($P = .001$) were significant prognostic factors for PFS. These were also predictive factors for OS (Supplementary Table S2).

Multivariate analysis revealed that age ≥50 years ($P = .040$; HR, 2.014), preoperative KPS <80 ($P = .032$; HR, 1.536), <GTR ($P = .023$; HR, 1.610), wild-type *IDH1* ($P = .029$; HR, 1.372), and standard adjuvant therapy ($P = .024$; HR, 0.106) were significant prognostic factors for PFS. In addition, age ≥50 years ($P = .046$; HR, 1.725), preoperative KPS <80 ($P = .030$; HR, 1.668), <GTR ($P = .035$; HR, 1.506), and wild-type *IDH1* ($P = .026$; HR, 1.851) predicted worse OS for glioblastoma patients, while the use of standard adjuvant therapy ($P = .021$; HR, 0.080) indicated a favorable OS (Supplementary Table S3). Univariate and step-wise multivariate analyses were performed for the mutant *IDH1* tumor subgroup (Table 2) and for the wild-type *IDH1* tumor subgroup (Table 3) in order to investigate specific prognostic factors according to the *IDH1* status.

Prognostic Role of Radiological Characteristics

Among patients with *IDH1*-mutant tumors, those with nonenhanced lesions had a significantly longer median PFS and OS compared with those having contrast-enhanced lesions (for PFS, 11.4 vs 9.6 mo; $P = .015$; for OS, 18.5 vs 16.4 mo; $P = .024$) (Fig. 1). However, in patients with wild-type *IDH1* tumors, contrast enhancement had no prognostic value for either PFS or OS ($P = .098$ and $P = .073$, respectively).

Notably, in 256 patients with contrast-enhanced tumors, the multifocality of enhancement combined with the *IDH1* status improved the stratification of survival outcome (Fig. 2). In patients with a wild-type *IDH1* tumor, a single enhancing focus was associated with a longer PFS ($P = .002$) and a longer OS ($P = .010$) than those with multifocal enhancement. However, among patients with a mutant *IDH1* tumor, the number of enhancing foci had no prognostic value for either PFS or OS ($P = .711$ and $P = .977$, respectively).

Kaplan–Meier analysis revealed that patients with mutant *IDH1* tumors, but no apparent edema, lived significantly longer than all other patients ($P = .003$ for PFS, and $P = .004$ for OS) (Fig. 3). Specifically, in the mutant *IDH1* group, the absence of peritumoral edema predicted longer PFS ($P = .024$) and longer OS ($P = .032$). However, peritumoral edema had no prognostic

Table 2. Univariate and multivariate analysis of survival outcomes for glioblastoma patients with an *IDH1*-mutant tumor ($n = 45$)

	PFS						OS					
	Univariate			Multivariate			Univariate			Multivariate		
Characteristic	*P* Value[b]	HR	95% CI	*P* Value[c]	HR	95% CI	*P* Value[b]	HR	95% CI	*P* Value[c]	HR	95% CI
Age ≥ 50 y	.460	1.582	0.176–2.078				.507	1.392	0.215–2.365			
Sex (male)	.219	1.472	0.743–2.933				.761	1.007	0.470–2.042			
Preoperative KPS <80	.926	1.073	0.431–3.552				.691	1.463	0.173–2.983			
Contrast enhancement	.015	1.112	1.051–2.649	.306	1.403	0.742–6.126	.024	1.282	1.103–3.265	.519	1.268	.579–5.721
Multifocal[a]	.711	0.821	0.318–2.131				.977	0.984	0.383–2.671			
Ring-like[a]	.745	1.138	0.522–2.489				.461	1.322	0.278–1.861			
Edema (>1 cm)	.024	1.811	1.742–4.451	.036	2.874	1.592–13.825	.032	1.177	1.046–3.621	.021	4.631	1.907–13.429
<GTR	.016	2.123	1.273–5.520	.028	3.966	1.465–12.587	.037	2.179	1.156–4.281	.033	2.164	1.203–9.315
MGMT promoter methylation	.029	0.312	0.032–0.753	.528	0.596	0.120–2.967	.041	0.357	0.043–0.829	.295	0.729	0.204–4.219
Standard adjuvant therapy	.013	0.056	0.009–0.451	.014	0.165	0.025–0.948	.017	0.236	0.071–0.726	.028	0.358	0.050–0.971

Abbreviations: CI, confidence interval; GTR, gross total resection; HR, hazard ratio; OS, overall survival; PFS, progression-free survival; y, year.
[a]In patients with tumor contrast enhancement ($n = 33$).
[b]Log-rank analysis of Kaplan-Meier survival curves.
[c]Cox proportional hazard regression analyses.

Table 3. Univariate and multivariate analysis of survival outcomes for glioblastoma patients with an *IDH1* wild-type tumor ($n = 235$)

	PFS						OS					
	Univariate			Multivariate			Univariate			Multivariate		
Characteristic	*P* Value[b]	HR	95% CI	*P* Value[c]	HR	95% CI	*P* Value[b]	HR	95% CI	*P* Value[c]	HR	95% CI
Age ≥ 50 y	.025	1.480	1.045–2.179	.034	6.531	1.392–33.896	.006	1.602	1.125–2.328	.039	2.708	1.771–27.342
Sex (male)	.142	1.288	0.921–1.779				.258	1.247	0.865–1.719			
Preoperative KPS <80	.868	1.058	0.532–2.115				.459	0.767	0.646–2.615			
Contrast enhancement	.098	2.643	0.837–8.335				.073	3.621	0.889–14.633			
Multifocal[a]	.002	2.136	1.317–3.462	.469	2.555	0.411–7.998	.010	1.908	1.168–3.115	.583	2.310	0.512–6.624
Ring-like[a]	.261	0.337	0.047–2.440				.022	0.093	0.012–0.710	.087	0.139	0.074–1.010
Edema (>1 cm)	.242	1.309	0.833–2.057				.191	1.372	0.855–2.193			
<GTR	.005	1.802	1.191–2.726	.352	2.387	0.232–5.519	.011	1.773	1.141–2.726	.176	2.881	0.397–5.264
MGMT promoter methylation	.481	0.785	0.400–1.539				.868	0.926	0.469–1.894			
Standard adjuvant therapy	.005	0.239	0.095–0.593	.027	0.038	0.016–0.828	.001	0.203	0.073–0.491	.035	0.064	0.031–0.902

Abbreviations: CI, confidence interval; GTR, gross total resection; HR, hazard ratio; OS, overall survival; PFS, progression-free survival; y, year.
[a]In patients with tumor contrast enhancement ($n = 223$).
[b]Log-rank analysis of Kaplan–Meier survival curves.
[c]Cox proportional hazard regression analyses.

value in patients with *IDH1* wild-type tumors with respect to PFS ($P = .242$) and OS ($P = .191$) (Fig. 3).

Discussion

In the present study, we combined clinical, radiological, and genetic characteristics to predict the prognosis of glioblastoma patients. Radiological features, including tumor contrast enhancement, multi-enhancing foci, and peritumoral edema, were found to be associated with the survival outcomes of glioblastoma patients stratified according to the *IDH1* status.

As an outward manifestation of tumor-related genetic changes, radiological features may provide important information about the biological characteristics of glioblastoma. Tumor contrast enhancement is a key radiological feature of malignant gliomas. Previous studies found that the overexpression of genes including *VEGF* and *NPTX2* was associated with edema, hypoxia, and angiogenesis in completely enhancing tumors[26] and the upregulation of *HIF1A*, *PGF*, and *VEGF* was associated with angiogenesis within contrast-enhancement regions.[27,28] Additionally, certain gene expression profiles (associated with microvascular expression, hypoxia, cellular mitosis, and overall cellularity) could be found in tumor regions with high blood volume and low apparent diffusion coefficient, which are related to angiogenesis and tumor aggressiveness.[29] *IDH1* mutations in glioblastoma and astrocytic neoplasms were also found to be associated with radiological characteristics including contrast enhancement, cysts, satellite lesions, frontal-lobe location, sharp tumor margins, and homogeneous signal intensity.[15,30] In this study, we also found that *IDH1*-mutant glioblastomas were less likely to show contrast enhancement on MR images compared with their *IDH1* wild-type counterparts. In addition, multifocal enhancement was more likely to be present on postcontrast T1-weighted images in *IDH1*-mutant tumors compared with wild-type *IDH1* tumors. However, the frequency of edema did not vary with respect to the tumor *IDH1* status.

In the current study, the *IDH1* mutation was found in 16.1% of glioblastomas, consistent with the previously reported incidence (16.1%) among Chinese patients,[25] and the standardized pyrosequencing protocol for *IDH1* detection used in the current study was the same as that used in our previous studies.[24,25,31,32] Thus, the higher incidence of *IDH1* mutation may reflect ethnic differences as well as a different referral pattern at our institution. The *IDH1* mutation has been shown to enable stratification of glioblastoma patients with respect to prognosis.[14,16,33,34] Consistent with these findings, we also found that patients harboring *IDH1*-mutant tumors had significantly better survival than those with wild-type *IDH1* tumors. The relationship between *IDH1* mutations and other clinical factors in predicting prognosis should be considered further. Firstly, tumor *IDH1* mutations were more frequent in younger patients,[33] and age is widely regarded as a significant prognostic factor.[35–37] Thus, it is likely that the age at diagnosis could be combined with the *IDH1* status to determine survival outcomes. Secondly, *IDH1* mutations occur frequently in low-grade gliomas but only rarely in primary glioblastomas.[9,37,38] As recurrent glioblastomas were not included in this study, histopathology along with the *IDH1* status may be useful for

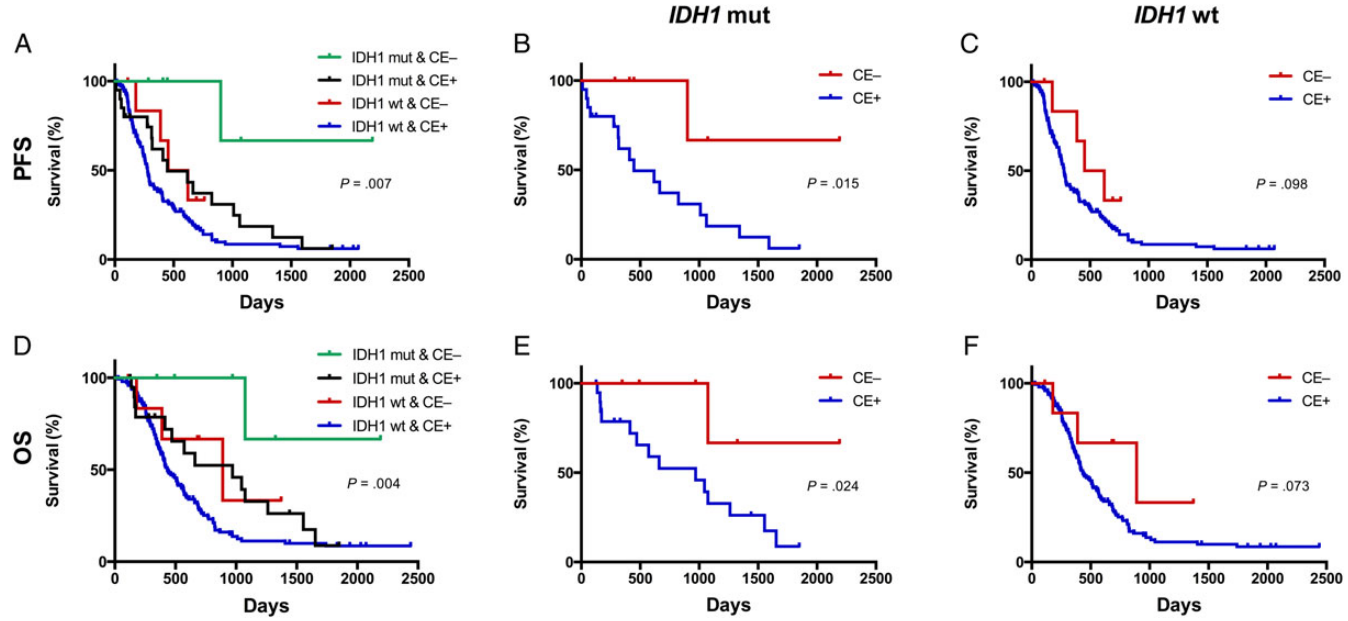

Fig. 1. Kaplan–Meier analyses of survival among glioblastoma patients with respect to the tumor *IDH1* status and contrast enhancement (CE). Mutant *IDH1* tumors with no CE predicted better survival (progression-free survival [PFS], $P = .007$; overall survival [OS], $P = .004$, log-rank) (A and D). Furthermore, contrast enhancement was predictive of PFS ($P = .015$, log-rank) and OS ($P = .024$, log-rank) for tumors with mutant *IDH1* (B and E), but not for wild-type (wt) *IDH1* tumors (PFS, $P = .098$; OS, $P = .073$, log-rank) (C and F).

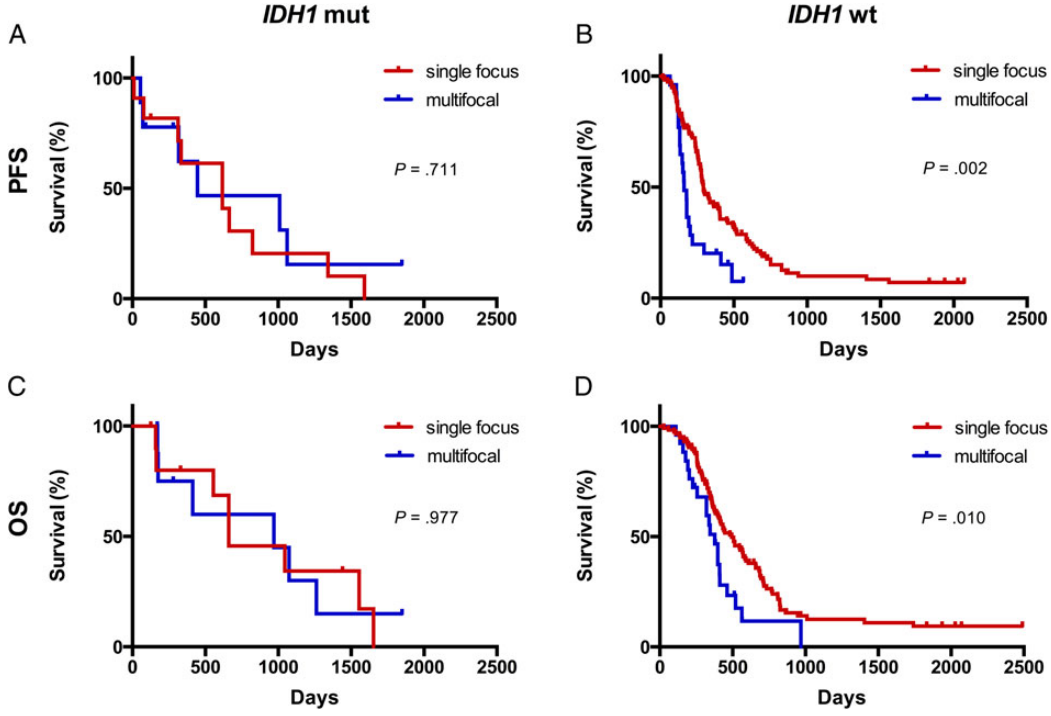

Fig. 2. Kaplan–Meier survival curves showing the prognostic value of multifocal enhancement. In patients with wild-type (wt) *IDH1* tumors, lesions with multifocal enhancement were associated with shorter survival ($P = .002$ for progression-free survival [PFS]; $P = .010$ for overall survival [OS], log-rank) (B and D). However, multifocal enhancement was not a significant prognostic factor for patients with mutant (mut) *IDH1* tumors ($P = .711$ for PFS; $P = .977$ for OS, log-rank) (A and C).

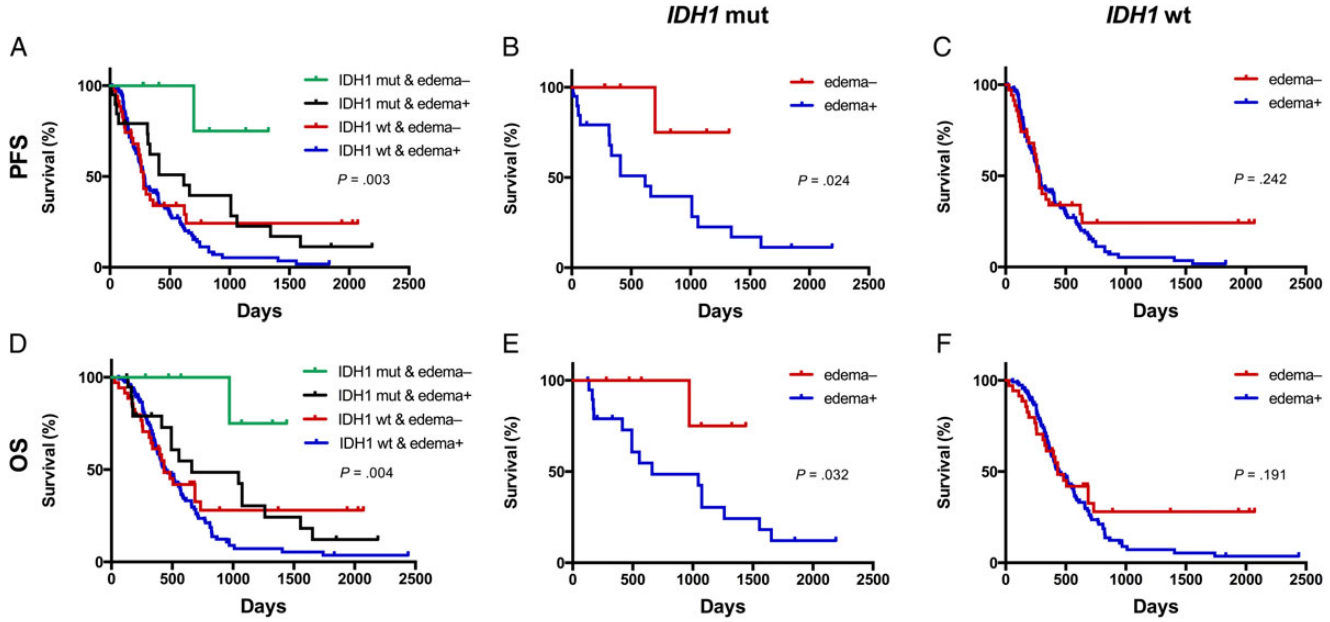

Fig. 3. Kaplan–Meier plots for all 288 patients showing progression-free survival (PFS) and overall survival (OS) according to the combined *IDH1* and tumor edema status. Mutant (mut) *IDH1* tumors with no edema predicted better survival (PFS, $P = .003$; OS, $P = .004$, log-rank) (A and D). In patients with mutated *IDH1*, the absence of edema was also a significant prognostic factor for PFS ($P = .024$, log-rank) and OS ($P = .032$, log-rank) (B and E). However, the edema was not associated with survival in patients with wild-type (wt) *IDH1* tumors (PFS, $P = .242$; OS, $P = .191$, log-rank) (C and F).

determining survival outcomes. In addition, mutations in the *IDH1* gene have been shown to be an early genetic event in tumorigenesis and to drive other genetic changes in tumor cells.[33] Tumors carrying an *IDH1* mutation may consequently have specific genetic changes that lead to varied biological features.

We found that radiological characteristics combined with the *IDH1* status better predicted the survival of glioblastoma patients. Notably, patients with tumors harboring *IDH1* mutations who did not show enhancement on MR images survived significantly longer than other patients. This suggests that the combination of contrast enhancement and an *IDH1* mutation may reflect a higher malignant potential of tumors. Interestingly, the multifocality of enhancement was identified as a prognostic indicator only in patients with wild-type, but not mutant, *IDH1* tumors. Multifocality was suggested to predict a poor outcome for patients with high-grade gliomas.[19] However, the multifocality of tumor enhancement has rarely been investigated in glioblastoma, especially combined with genetic changes in the tumor. During tumorigenesis, the *IDH1* mutation may drive other genetic alterations that determine the biological features and radiological characteristics of tumors, which could be associated with the survival outcome of patients.[33,39–41] The association between the *IDH1* status and radiological characteristics in predicting the survival of glioblastoma patients remains to be investigated.

Tumor-induced edema is an inflammatory reaction that has also been found to be associated with a poor outcome.[19,42] For example, edema was identified as a prognostic factor in patients with tumors carrying *MGMT* promoter hypermethylation.[15] Interestingly, in this study, we found that tumor-related edema was associated with survival outcome in patients with mutant *IDH1* tumors but not wild-type *IDH1* tumors. Glioblastomas have been classified into four molecular subtypes (ie, proneural, neural, classical, and mesenchymal),[39] and *IDH1* mutations occur more frequently in the first of these, which is associated with a better prognosis in glioblastoma patients.[39,41,43] It was hypothesized that tumors with little or no edema may be more likely to be categorized into the proneural subset.[15] Therefore, the prognostic value of tumor-related edema may be attributed to the accompanying mutations that these tumors carry.

Previous studies showed that glioma patients with a methylated *MGMT* promoter generally survived longer,[12,44,45] although another study failed to find any prognostic role for *MGMT* promoter methylation.[46] A strong association was also found between *MGMT* promoter methylation, the *IDH1* status, and age, whereby the prognostic significance of *MGMT* promoter methylation was lost in glioblastoma patients aged >50 years old.[47] Moreover, *MGMT* promoter methylation is prognostic for patients with *IDH1*-mutant gliomas, while *MGMT* promoter methylation in patients with *IDH1* wild-type tumors is associated with a better response to alkylating chemotherapy but does not predict survival.[48]

Several limitations of this study should be considered. First, the patients were enrolled from a single institution, and the data were analyzed retrospectively. Second, although the study was carefully controlled, a slight discrepancy in the interval duration between contrast injection and image acquisition could still exist between individuals. Third, the cohort may have included patients with secondary glioblastoma, which could account for the higher incidence of *IDH1* mutations in the

present study. In addition, the molecular subtype could not be determined in most glioblastomas because of the limited number of cases evaluated for other genetic alterations (eg, loss of *ATRX* and 1p19q codeletion). The prognostic role of radiological features associated with *IDH1* mutations needs to be validated in future, prospectively designed investigations.

We found that radiological biomarkers, including contrast enhancement, multifocal enhancement, and tumor-related edema, were predictive factors in survival and could be combined with the tumor *IDH1* status to provide a more accurate prediction of survival in glioblastoma patients. Further study is needed to elucidate the molecular basis of this association.

Supplementary Material

Supplementary material is available at *Neuro-Oncology Journal* online (http://neuro-oncology.oxfordjournals.org/).

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Conflict of interest statement. None declared.

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