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Importance of Age and Noncontrast-Enhancing Tumor as Biomarkers for Isocitrate Dehydrogenase–Mutant Glioblastoma: A Multicenter Study

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Purpose: This study aimed to investigate the most useful clinical and magnetic resonance imaging (MRI) parameters for differentiating isocitrate dehydrogenase (IDH)-mutant and -wildtype glioblastomas in the 2016 World Health Organization Classification of Tumors of the Central Nervous System.

Methods: This multicenter study included 327 patients with IDH-mutant or IDH-wildtype glioblastoma in the 2016 World Health Organization classification who preoperatively underwent MRI. Isocitrate dehydrogenase mutation status was determined by immunohistochemistry, high-resolution melting analysis, and/or IDH1/2 sequencing. Three radiologists independently reviewed the tumor location, tumor contrast enhancement, noncontrast-enhancing tumor (nCET), and peritumoral edema. Two radiologists independently measured the maximum tumor size and mean and minimum apparent diffusion coefficients of the tumor. Univariate and multivariate logistic regression analyses with an odds ratio (OR) were performed.

Results: The tumors were IDH-wildtype glioblastoma in 306 cases and IDH-mutant glioblastoma in 21. Interobserver agreement for both qualitative and quantitative evaluations was moderate to excellent. The univariate analyses revealed a significant difference in age, seizure, tumor contrast enhancement, and nCET ($P < 0.05$). The multivariate analysis revealed significant difference in age for all 3 readers (reader 1, odds ratio [OR] = 0.960, $P = 0.012$; reader 2, OR = 0.966, $P = 0.048$; reader 3, OR = 0.964, $P = 0.026$) and nCET for 2 readers (reader 1, OR = 3.082, $P = 0.080$; reader 2, OR = 4.500, $P = 0.003$; reader 3, OR = 3.078, $P = 0.022$).

Conclusions: Age and nCET are the most useful parameters among the clinical and MRI parameters for differentiating IDH-mutant and IDH-wildtype glioblastomas.

Key Words: IDH mutation, glioblastoma, MRI

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Glioblastoma is the most frequent malignant brain tumor in adults, accounting for approximately 15% of all intracranial neoplasms and 45% to 50% of all primary malignant brain tumors.[1] In the 2016 World Health Organization (WHO) classification,[2] glioblastomas are divided into the following 3 types: (*a*) isocitrate dehydrogenase (IDH) wildtype, which most frequently corresponds with the clinically defined primary or de novo glioblastoma; (*b*) IDH mutant, which corresponds to so-called secondary glioblastoma with a history of lower-grade diffuse glioma; and (*c*) not otherwise specified, for which full IDH evaluation cannot be performed. Isocitrate dehydrogenase–mutant glioblastoma was reclassified as IDH-mutant astrocytoma grade 4 in the current 2021 WHO classification edition because of the large increase in knowledge of the molecular basis of these tumors.[1]

Isocitrate dehydrogenase–mutant gliomas are associated with longer overall survival compared with IDH-wildtype gliomas.[3] Patients with IDH-mutant and IDH-wildtype glioblastoma had a median overall survival of 31 and 15 months, respectively, after surgical treatment followed by concomitant chemoradiotherapy.[3] In addition, patients with IDH-wildtype anaplastic astrocytomas exhibited worse prognoses than those with IDH-mutant glioblastomas.[4] Thus, distinguishing the presence of IDH mutation in gliomas is important to provide accurate classification and determine prognosis.[3,4]

Tissue sampling by stereotactic, open, or endoscopic procedures is needed to perform immunohistochemistry and genomic sequencing for detecting the definite IDH mutation status of gliomas.[5] However, biopsies may provide inaccurate diagnoses from small and/or heterogeneous lesions.[5] Therefore, predicting the IDH mutation status of gliomas using noninvasive methods would be useful.

Consequently, several researchers have studied various clinical and magnetic resonance imaging (MRI) parameters of patients with glioblastoma to identify IDH mutation status.[6–18] The parameters included age, tumor location, tumor size, tumor contrast enhancement, noncontrast-enhancing tumor (nCET), apparent diffusion coefficient (ADC) value, perfusion MR indices, etc.[6–18] However, to our knowledge, no previous multicenter studies have evaluated both clinical and MRI parameters to determine the most useful ones for predicting IDH mutation status of glioblastomas. Therefore, this multicenter study aimed to investigate the most useful clinical and MRI parameters for identifying the IDH mutation status of glioblastomas.

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MATERIALS AND METHODS

As a funding source, this retrospective multicenter case-control study was supported by Bayer Yakuhin (Osaka, Japan), which had no role in the study concept, design, data analysis and interpretation, or reporting of results. The study was approved by the ethics committee of each participating institution, and informed consent for the use of database images and patient clinical parameters was waived. Moreover, our study was officially registered in the Clinical Trials Registry of University Hospital Medical Information Network (no. 000029521).

Study Participants

We retrospectively collected clinical and MRI data of 347 patients with glioblastoma in the 2016 WHO classification who preoperatively underwent 1.5- or 3-T MRI studies from 22 facilities from April 2013 to March 2017. The inclusion criteria were as follows: (*a*) patients older than 20 years; (*b*) newly diagnosed glioblastoma on histopathology; (*c*) diagnosis of IDH-wildtype or IDH-mutant glioblastoma according to the 2016 WHO classification by immunohistochemistry for IDH1 R132H mutation, high-resolution melting analysis[19] and/or IDH1/2 sequencing; (*d*) patients with clinical information, including age, sex, height, weight, symptoms, and MRI data; and (*e*) patients who preoperatively underwent conventional 1.5- or 3-T MRI studies, including diffusion-weighted imaging (DWI). The analysis details of IDH mutation status are given in the online Appendix (http://links.lww.com/RCT/A164).

The exclusion criteria were as follows: (*a*) patients taking drugs (eg, steroids) that affect imaging findings; (*b*) patients diagnosed with giant cell glioblastoma, gliosarcoma, and epithelioid glioblastoma; (*c*) patients with inadequate MR image quality for evaluation; (*d*) patients with recurrent lesions after treatment; (*e*) patients who were determined inappropriate as subjects by the principal investigator.

After assessing 347 patients with glioblastoma for the inclusion and exclusion criteria, 20 patients were excluded because of insufficient IDH mutation status information (n = 14), ages younger than 20 years (n = 3), MRI examinations outside the study period (April 2013 to March 2017) (n = 3), and lacking contrast-enhanced T1-weighted imaging (CE-T1WI) (n = 2). Finally, this study included 327 patients with glioblastoma (194 males, 133 females; age range: 24–89 years; mean age: 65 years), of whom 306 (93.6%) harbored IDH-wildtype glioblastoma and 21 (6.4%) patients had IDH-mutant glioblastoma (IDH1-mutant glioblastoma, n = 18; IDH2-mutant glioblastoma, n = 3).

Magnetic Resonance Imaging

Magnetic resonance data were acquired by either a 1.5-T or a 3-T MR imaging unit, manufactured by GE Medical Systems (Milwaukee, Wis), Siemens Healthcare (Erlangen, Germany), Philips Medical Systems (Best, the Netherlands), Hitachi Medical Corporation (Tokyo, Japan), or Toshiba Medical Systems (Otawara, Japan) at 22 participating sites. Conventional MRI data were obtained with the T1WI sequences, 2-dimensional T1-weighted spin-echo sequence or 3-dimensional T1-weighted gradient-echo sequence, the T2-weighted spin-echo imaging (T2WI) sequence, and the fluid-attenuated inversion-recovery (FLAIR) sequence. In addition, acquired CE-T1WIs shortly after intravenous injection of a standard dose (0.1 mmol/kg body weight) of a gadolinium-based contrast agent, including gadobutrol (Gadovist; Bayer Yakuhin), gadopentetate dimeglumine (Magnevist; Bayer Yakuhin), gadoteridol (ProHance; Eisai, Tokyo, Japan), gadodiamide (Omniscan; GE Healthcare Pharma, Tokyo, Japan), or gadoterate meglumine (Magnescope; Guerbet Japan, Tokyo, Japan), were matched to precontrast T1WIs obtained with similar sequence parameters.

Diffusion-weighted imaging was performed using a single-shot spin-echo echo-planar sequence. Diffusion-sensitizing gradients were sequentially applied in the *x*, *y*, and *z* directions with *b* factors of 0 and 800 to 2000 s/mm^2.

Qualitative Evaluation

Image sets of T1WI, T2WI, FLAIR, and CE-T1WI were randomly presented on a picture archiving and communication system workstation to 3 readers (M.A., K.K., and Y.W., with 10, 21, and 23 years of experience in neuroradiology, respectively) who were blinded to the clinical and pathologic information and IDH mutation status. They independently evaluated the tumor location (frontal lobe or nonfrontal lobe), tumor contrast enhancement (presence or absence), nCET (presence or absence), and peritumoral edema (no/little or moderate/severe). The presence of tumor contrast enhancement was defined as a significantly higher signal on the CE-T1W images in all or portions of the tumor compared with

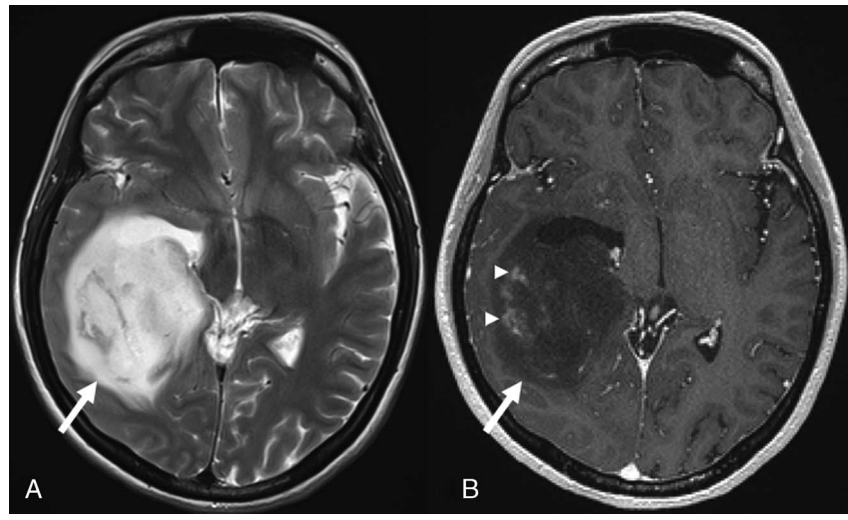

FIGURE 1. A 33-year-old woman with IDH-mutant glioblastoma. A, T2-weighted image shows a hyperintense mass lesion (arrow) of the right medial temporal lobe. B, Contrast-enhanced T1-weighted image shows a hypointense mass lesion (arrow) with subtle contrast enhancement (arrowheads). A large portion of the mass lesion is not enhanced, indicating nCET.

precontrast T1W images, according to definitions of imaging findings from the previous study.[6] Otherwise, is the absence of tumor contrast enhancement. Noncontrast-enhancing tumor was defined as regions of T2W hyperintensity (less than the intensity of cerebrospinal fluid, with corresponding T1W hypointensity) that are associated with mass effect and architectural distortion, including gray-white interface blurring, and which showed no obvious enhancement (Fig. 1).[6,8] No peritumoral edema meant that T2WI did not show any hyperintense areas beyond the tumor margin. Little peritumoral edema was defined as edema extending at ≤1 cm from the tumor margin based on T2WI; otherwise, edema was graded as moderate to severe.[6]

Quantitative Evaluation

Two observers (M.T. and M.A., with 5 and 10 years of neuroradiology experience, respectively) independently measured the maximum tumor size and intratumoral ADC values in tumor enhancement areas on CE-T1WIs using a picture archiving and communication system, whereas they performed in an area presumed as a solid mass on conventional MRIs if the lesion did not have tumor contrast enhancement. Four or more circular regions of interest (ROIs, area: ≥10 mm^2) were placed on ADC maps within the area that corresponded to the solid tumor area for ADC measurements, and the mean ADC value was obtained for each ROI.[7] Regions with relatively low ADC were targeted, whereas blood vessels, necrosis, and hemorrhages were strictly avoided for ROI placement. The lowest and the average mean ADC values within all ROIs were determined as the minimum and mean ADCs, respectively.[7]

Statistical Analysis

All statistical analyses were performed with International Business Machines Corporation Statistical Package for the Social Sciences (SPSS) version 23 (https://en.wikipedia.org/wiki/SPSS; IBM Corp, Armonk, NY) and R (version 3.4.1) statistical software (https://www.r-project.org/; R foundation for Statistical Computing, Vienna, Austria). The Mann-Whitney *U* test (age, height, and weight) and Fisher exact test (sex, MRI field strength, and symptoms) were used to assess the clinical parameter differences between IDH-mutant and IDH-wildtype glioblastomas. The interobserver agreement of the 3 observers was analyzed with the Fleiss κ coefficient for qualitative assessments (κ = 0.00–0.20 = poor, κ = 0.21–0.40 = fair, κ = 0.41–0.60 = moderate, κ = 0.61–0.80 = good, κ = 0.81–1.0 = excellent agreement). The quantitative assessments of the 2 observers assessed the interobserver agreement using the intraclass correlation coefficient (ICC) (κ = 0.00–0.20 = poor, κ = 0.21–0.40 = fair, κ = 0.41–0.60 = moderate, κ = 0.61–0.80 = good, κ = 0.81–1.0 = excellent agreement).

The sensitivity, specificity, accuracy, and the area under the receiver operating characteristic curve (AUC) of parameters were calculated to demonstrate the diagnostic performance of the parameters. Univariate and multivariate logistic regression analyses with odds ratio (OR) and 95% confidence interval (CI) were used to determine the significant parameters between IDH-mutant and IDH-wildtype glioblastomas. *P* values less than 0.05 were considered statistically significant.

RESULTS

Clinical Parameters

The clinical parameter evaluations revealed a significant difference in age ($P = 0.012$) and seizure ($P = 0.041$) between patients with IDH-mutant and IDH-wildtype glioblastomas but no significant differences for sex, height, weight, MRI field strength, focal neurologic deficit, psychiatric symptoms, symptoms of intracranial hypertension, and other symptoms (Table 1). The univariate logistic regression analysis revealed that age (OR = 0.955, 95% CI = 0.925–0.985; $P = 0.004$), and seizure (OR = 3.252, 95% CI = 1.106–9.568; $P = 0.032$) were significantly associated with IDH mutation status of glioblastomas. Odds ratio for age were defined as the ORs for having IDH mutations when 1 year older.

TABLE 1. Clinical Parameters of Patients With Glioblastoma

Clinical Parameters	IDH Wildtype	IDH Mutant	*P*
Number	306 (93.6%)	21 (6.4%)	
Age, y	65.7 ± 12.1	57.4 ± 14.0	0.012*
Sex			0.359 †
Male	184 (60.1%)	10 (47.6%)	
Female	122 (39.9%)	11 (52.4%)	
Height, cm	160.6 ± 9.4	158.9 ± 9.9	0.513 *
Weight, kg	56.0 ± 10.7	53.7 ± 9.2	0.277 *
MRI field strength			0.277 †
1.5 T	66 (21.6%)	7 (33.3%)	
3.0 T	235 (76.8%)	14 (66.7%)	
Seizure			0.041 †
Presence	27 (8.8%)	5 (23.8%)	
Absence	279 (91.2%)	16 (76.2%)	
Focal neurologic deficit			0.823 †
Presence	159 (52.0%)	10 (47.6%)	
Absence	147 (48.0%)	11 (52.4%)	
Psychiatric symptoms			0.389 †
Presence	61 (20.0%)	2 (9.5%)	
Absence	245 (80.0%)	19 (90.5%)	
Symptoms of intracranial hypertension			1.000 †
Presence	42 (13.7%)	3 (14.3%)	
Absence	264 (86.3%)	18 (85.7%)	
Other symptoms			0.612 †
Presence	82 (26.8%)	7 (33.3%)	
Absence	224 (73.2%)	14 (66.7%)	

*The difference between the 2 groups was evaluated using the Mann-Whitney *U* test.

†The difference between the 2 groups was evaluated using Fisher exact test.

Qualitative MRI Parameters

Interobserver agreement of the 3 observers for the qualitative MRI parameter evaluations was excellent for tumor location (κ = 0.911), good for tumor contrast enhancement (κ = 0.748), moderate for nCET (κ = 0.473), and excellent for peritumoral edema (κ = 0.825). The qualitative evaluation results of the 3 readers are shown in Table 2. The univariate logistic regression analysis of the qualitative MRI parameters revealed significant difference in nCET for all 3 readers (reader 1, OR = 3.726, $P = 0.038$; reader 2, OR = 6.160, $P = 0.001$; reader 3, OR = 3.774, $P = 0.005$) and in tumor contrast enhancement for reader 2 (OR = 0.031, $P = 0.005$) although without significant differences for tumor location and peritumoral edema (Table 2). The sensitivity, specificity, accuracy, and AUC of each qualitative MRI parameter for predicting IDH mutation status are shown in Table 3.

Quantitative MRI Parameters

The interobserver agreement of the 2 observers for the quantitative MRI parameter evaluations was excellent for maximum tumor diameter (ICC = 0.954), moderate for mean ADC value

TABLE 2. Qualitative Evaluation Results and Univariate Logistic Regression Analysis for MRI Parameters

	Reader 1		Reader 2		Reader 3	
MRI Parameters	**IDH Wildtype**	**IDH Mutant**	**IDH Wildtype**	**IDH Mutant**	**IDH Wildtype**	**IDH Mutant**
Location of tumor						
Frontal lobe	106 (34.6%)	10 (47.6%)	111 (36.3%)	11 (52.4%)	104 (34.0%)	11 (52.4%)
Nonfrontal lobe	200 (65.4%)	11 (52.4%)	195 (63.7%)	10 (47.6%)	202 (66.0%)	10 (47.6%)
OR*	1.732 (0.713–4.210)		1.932 (0.796–4.694)		2.137 (0.879–5.195)	
P	0.225		0.146		0.094	
Contrast enhancement of tumor						
Presence	304 (99.3%)	20 (95.2%)	305 (99.7%)	19 (90.5%)	305 (99.7%)	20 (95.2%)
Absence	2 (0.7%)	1 (4.8%)	1 (0.3%)	2 (9.5%)	1 (0.3%)	1 (4.8%)
OR*	0.131 (0.011–1.504)		0.031 (0.003–0.359)		0.066 (0.004–1.008)	
P	0.103		0.005		0.057	
nCET						
Presence	190 (62.1%)	18 (85.7%)	75 (24.5%)	14 (66.7%)	106 (34.6%)	14 (66.7%)
Absence	116 (37.9%)	3 (14.3%)	231 (75.5%)	7 (33.3%)	200 (65.4%)	7 (33.3%)
OR*	3.726 (1.074–12.924)		6.160 (2.297–15.832)		3.774 (1.478–9.635)	
P	0.038		0.001		0.005	
Peritumoral edema						
No	11 (3.6%)	2 (9.5%)	7 (2.3%)	1 (4.8%)	7 (2.3%)	1 (4.8%)
Little	100 (32.7%)	9 (42.9%)	85 (27.8%)	8 (38.1%)	86 (28.1%)	8 (38.1%)
Moderate/severe	195 (63.7%)	10 (47.6%)	214 (69.9%)	12 (57.1%)	213 (69.6%)	12 (57.1%)
OR*	0.512 (0.211–1.244)		0.573 (0.233–1.407)		0.582 (0.237–1.429)	
P	0.140		0.225		0.238	

*Data in parentheses are 95% CIs.

(ICC = 0.532), and moderate for minimum ADC value (ICC = 0.598). The quantitative evaluation results of the 2 readers are detailed in Table 4. No significant difference was observed in the univariate analysis for the 3 MRI parameters (Table 5). The cutoff value, sensitivity, specificity, accuracy, and AUC of the 2 parameters to detect IDH mutation status are summarized in Table 6.

TABLE 3. Sensitivity, Specificity, Accuracy, and AUC of Each Qualitative MRI Parameter for Predicting IDH Mutation in Glioblastomas

MRI Parameters	**Reader 1**	**Reader 2**	**Reader 3**
Location of tumor			
Sensitivity	47.6%	52.4%	52.4%
Specificity	65.6%	63.7%	66.0%
Accuracy	64.4%	63.0%	65.1%
AUC	0.566 (0.453–0.679)	0.581 (0.468–0.693)	0.592 (0.479–0.705)
Contrast enhancement of tumor			
Sensitivity	4.8%	9.5%	4.8%
Specificity	99.4%	99.7%	99.7%
Accuracy	93.3%	93.9%	93.6%
AUC	0.521 (0.474–0.567)	0.546 (0.482–0.61)	0.522 (0.475–0.569)
nCET			
Sensitivity	85.7%	66.7%	66.7%
Specificity	38.3%	75.5%	65.4%
Accuracy	41.3%	74.9%	65.4%
AUC	0.62 (0.539–0.701)	0.711 (0.605–0.817)	0.66 (0.553–0.767)
Peritumoral edema			
Sensitivity	52.4%	42.9%	42.9%
Specificity	64.0%	69.9%	69.6%
Accuracy	63.2%	68.2%	67.9%
AUC	0.582 (0.469–0.694)	0.564 (0.453–0.675)	0.562 (0.451–0.674)

Data in parentheses are 95% CIs.

TABLE 4. Quantitative Evaluation Results of 2 Readers for MRI Parameters

	Reader 1		Reader 2	
MRI Parameters	**IDH Wildtype**	**IDH Mutant**	**IDH Wildtype**	**IDH Mutant**
Maximum tumor size, mm	49.52 ± 16.24	46.61 ± 17.02	48.93 ± 15.84	48.11 ± 19.58
Mean ADC, $\times 10^{-3}$ mm^2/s	0.986 ± 0.234	1.044 ± 0.308	1.078 ± 0.302	1.147 ± 0.287
Minimum ADC, $\times 10^{-3}$ mm^2/s	0.918 ± 0.201	0.941 ± 0.353	0.921 ± 0.258	0.936 ± 0.234

Data are shown as mean ± SD.

Multivariate Analysis of Clinical and MRI Parameters

Age, seizure, tumor contrast enhancement, and nCET were used as independent variables in multivariate logistic regression analysis using patient background and qualitative evaluation to predict IDH mutation. The multivariate analysis revealed a significant difference in age for all 3 readers (reader 1, OR = 0.960, $P = 0.012$; reader 2, OR = 0.966, $P = 0.048$; reader 3, OR = 0.964, $P = 0.026$) and nCET for 2 readers (reader 1, OR = 3.082, $P = 0.080$; reader 2, OR = 4.500, $P = 0.003$; reader 3, OR = 3.078, $P = 0.022$; Table 7). No significant differences were found for seizure and tumor contrast enhancement.

The diagnostic performance for the combined evaluation of age and nCET was relatively good (AUC = 0.691–0.730) with a sensitivity and specificity of 61.9% to 85.7% and 54.9% to 81.7%, respectively (Table 8).

DISCUSSION

Our retrospective multicenter case-control study compared clinical and MRI parameters to predict the IDH mutation status of glioblastoma. The univariate analyses revealed significant differences in age, seizure, tumor contrast enhancement, and nCET between IDH-mutant and IDH-wildtype glioblastomas. However, the multivariate analyses of the 3 readers revealed that only age and nCET were significant independent parameters for predicting IDH mutation of glioblastoma. Moreover, receiver operating characteristic analysis combining the 2 parameters showed a relatively good diagnostic performance (AUC = 0.691–0.730).

Several investigators pointed out that the patient's age was one of the important clinical indicators for estimating IDH mutation status of glioblastoma.[15–18] The population-based studies by Ohgaki et al[15,16] revealed that the mean age of patients with secondary glioblastoma is 45 years, which is significantly younger than that of patients with primary glioblastoma (62 years). Similarly, Nobusawa et al[17] reported that IDH-mutant glioblastomas developed in significantly younger patients (mean: 48 years) than IDH-wildtype glioblastomas (mean: 61 years). Several hospital-based studies also demonstrated that patients with IDH-mutant glioblastomas were significantly younger than those with IDH-wildtype glioblastomas.[3,18] Our study revealed a significantly younger mean age of patients with IDH-mutant glioblastomas (57.4 years) than that of patients with IDH-wildtype glioblastomas (65.7 years) although the mean age was relatively higher in ours than the previous studies due to unknown reasons but may be due to the differences in study design and race/ethnicity.

The processes manipulating the relationship between age and the IDH mutation status of glioblastomas are not properly understood. Lötsch et al[20] reported the absence of telomerase activity and human telomerase reverse transcriptase (TERT) expression in all younger (≤60 years) patients with IDH-mutant glioblastomas. They revealed the association between telomerase activity and human TERT expression and the relationship between IDH mutation status and age.[20]

Several MRI parameters have been evaluated for predicting the IDH mutation status of glioblastomas.[6–14] Among them, nCET was one of the useful MRI parameters to assess the IDH mutation status of glioblastoma.[8–12,14] Carrillo et al[8] revealed that nCET could be used to determine IDH1 mutational status with 97.5% accuracy. Hong et al[10] revealed that IDH-mutant glioblastomas showed a larger volume on T2WI and a higher volume ratio between T2WI and CE-T1WI than the IDH-wildtype glioblastomas ($P < 0.05$). Lasocki et al[9] revealed higher rates of nCET in IDH1-mutant glioblastomas than IDH1-wildtype glioblastomas, but without a statistical significance ($P = 0.073$). In addition, this study revealed nCET in 57% of IDH-wildtype glioblastomas. In our study, the evaluation results of the 3 readers revealed that the nCET was more common in IDH-mutant glioblastomas (66.7%–85.7%) than in IDH-wildtype glioblastomas (24.5%–62.1%). An additive definition of nCET would be necessary to improve the interobserver reliability because the interobserver agreement of the 3 observers for nCET in our study was moderate ($\kappa = 0.473$). Lasocki et al[11] proposed that a mass-like morphology of nCET could potentially provide better specificity for predicting IDH mutation than the presence of nCET alone. Recently, Patel et al[12] reported that fluid attenuation in nCET derived in part from the "T2-FLAIR mismatch sign" represented a novel marker associated with IDH-mutant glioblastoma with a high interobserver agreement. Therefore, further studies are needed to confirm the usefulness of the novel MRI metrics.

TABLE 5. Univariate Logistic Regression Analysis of Quantitative MRI Parameters

	Reader 1		Reader 2	
MRI Parameters	**OR**	***P***	**OR**	***P***
Maximum tumor size, mm	0.989 (0.962–1.016)	0.429	0.997 (0.970–1.025)	0.821
Mean ADC, $\times 10^{-3}$ mm^2/s	2.271 (0.480–10.75)	0.301	1.892 (0.528–6.777)	0.327
Minimum ADC, $\times 10^{-3}$ mm^2/s	1.604 (0.204–12.593)	0.653	1.246 (0.231–6.720)	0.798

Data in parentheses are 95% CIs.

TABLE 6. Cutoff Value, Sensitivity, Specificity, Accuracy, and AUC of Each Quantitative MRI Parameter to Estimate IDH Mutation Status

MRI Parameters	Reader 1	Reader 2
Maximum tumor size		
Cutoff value	≤45.1	≤41.0
Sensitivity	61.9%	42.9%
Specificity	62.1%	71.7%
Accuracy	62.1%	69.8%
AUC	0.578 (0.451–0.704)	0.54 (0.398–0.682)
Mean ADC		
Cutoff value	≥1.014	≥0.976
Sensitivity	55.0%	85.0%
Specificity	70.3%	40.7%
Accuracy	69.3%	43.5%
AUC	0.548 (0.383–0.712)	0.61 (0.486–0.734)
Minimum ADC		
Cutoff value	≥1.014	≥0.866
Sensitivity	45.0%	75.0%
Specificity	74.7%	45.9%
Accuracy	72.8%	47.7%
AUC	0.533 (0.364–0.701)	0.539 (0.412–0.665)

Data in parentheses are 95% CIs.

The brain tumor classification of our study was based on the 2016 WHO classification. According to the current 2021 WHO classification, IDH-wildtype glioblastoma is a diffuse, astrocytic glioma that is IDH wildtype and H3 wildtype and has one or more of the following histological or genetic features: microvascular proliferation, necrosis, TERT promoter mutation, estimated glomerular filtration rate gene amplification, and +7/−10 chromosome copy-number changes.[1] Our study confirmed the histopathology and IDH mutation status but did not assess H3 mutations and other genetic markers. Although IDH-wildtype glioblastoma in our case is not directly applicable to IDH-wildtype glioblastoma in the 2021 WHO classification, many cases in our study may be amenable to the new classification because of the advanced age of our patients with IDH-wildtype glioblastoma (mean age: 65.7 years). In addition, all our cases with IDH-mutant glioblastoma had consistent histopathology (necrosis and/or microvascular proliferation) with glioblastoma, although we did not evaluate the homozygous deletion of CDKN2A and/or CDKN2B for IDH-mutant astrocytoma grade 4 in the 2021 WHO classification.[1,21] Isocitrate dehydrogenase–mutant glioblastoma in our case may be applicable for IDH-mutant astrocytoma grade 4 in the 2021 WHO classification because of consistent histopathology with glioblastoma. At present, IDH-mutant astrocytoma grade 4 and IDH-wildtype glioblastoma may not differ in treatment, but the emergence of molecularly targeted drugs suitable for each may change the treatment methods in the future.

TABLE 7. Multivariate Analysis of Clinical and MRI Parameters

Parameters	Reader 1	Reader 2	Reader 3
Age			
OR	0.960 (0.930–0.991)	0.966 (0.934–1.000)	0.964 (0.933–0.996)
P	0.012	0.048	0.026
nCET			
OR	3.082 (0.873–10.875)	4.500 (1.671–12.117)	3.078 (1.172–8.082)
P	0.080	0.003	0.022

Data in parentheses are 95% CIs.

TABLE 8. Diagnostic Performance for the Combined Evaluation of Age and nCET in Differentiating IDH-Mutant Glioblastoma From IDH-Wildtype Glioblastoma

	Reader 1	Reader 2	Reader 3
AUC	0.715 (0.5922–0.8378)	0.730 (0.5882–0.8721)	0.691 (0.5474–0.8353)
Sensitivity	85.7%	66.7%	61.9%
Specificity	54.9%	81.7%	79.7%

Data in parentheses are 95% CIs.

Our study has several limitations. First, the number of patients with IDH-mutant glioblastoma was small because IDH mutations are rare in patients with glioblastoma.[1] This small sample size might have induced sampling bias and consequently interfered with our results. Second, this study included 2 types of MRI field strength and various MRI sequence parameters of because the data had to be collected from many institutions. The measurement of the ADC values might have been some variations because of the differences in MRI field strength and parameters. Third, we did not include perfusion MRI in the study analysis because of a large difference in the method and parameters depending on the facility.

CONCLUSIONS

Age and nCET are the most useful parameters, among the clinical and MRI parameters, for estimating IDH mutation status of glioblastomas. The combined use of these 2 parameters may provide a noninvasive index to help distinguish between IDH-mutant and IDH-wildtype glioblastomas.

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