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Original Article

Association of ADC of hyperintense lesions on FLAIR images with TERT promoter mutation status in glioblastoma IDH wild type

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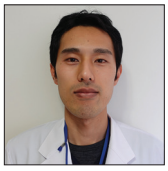

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ABSTRACT

Background: Although mutations in telomerase reverse transcriptase (*TERT*) promoter (*TERT*p) are the most common alterations in glioblastoma (GBM), predicting *TERT*p mutation status by preoperative imaging is difficult. We determined whether tumour-surrounding hyperintense lesions on fluid-attenuated inversion recovery (FLAIR) were superior to those of contrast-enhanced lesions (CELs) in assessing *TERT*p mutation status using magnetic resonance imaging (MRI).

Methods: This retrospective study included 114 consecutive patients with primary isocitrate dehydrogenase (*IDH*)-wild-type GBM. The apparent diffusion coefficient (ADC) and volume of CELs and FLAIR hyperintense lesions (FHLs) were determined, and the correlation between MRI features and *TERT*p mutation status was analyzed. In a subset of cases, FHLs were histopathologically analyzed to determine the correlation between tumor cell density and ADC.

Results: *TERT*p mutations were present in 77 (67.5%) patients. The minimum ADC of FHLs was significantly lower in the *TERT*p-mutant group than in the *TERT*p-wild-type group (mean, 958.9×10^{-3} and 1092.1×10^{-3} mm^2/s, respectively, $P < 0.01$). However, other MRI features, such as CEL and FHL volumes, minimum ADC of CELs, and FHL/CEL ratio, were not significantly different between the two groups. Histopathologic analysis indicated high tumor cell density in FHLs with low ADC.

Conclusion: The ADC of FHLs was significantly lower in *IDH*-wild-type GBM with *TERT*p mutations, suggesting that determining the ADC of FHLs on preoperative MRI might be helpful in predicting *TERT*p mutation status and surgical planning.

Keywords: Apparent diffusion coefficients (ADC), Fluid-attenuated inversion recovery hyperintense lesion, Glioblastoma, Telomerase reverse transcriptase (TERT)

INTRODUCTION

Glioblastoma (GBM) is the most common primary malignant tumor of the central nervous system in adults.[17] In patients with GBM, the primary aim of surgical resection is the complete

disappearance of contrast-enhanced lesions (CELs) on magnetic resonance imaging (MRI) to achieve gross total resection.[13,22] However, median survival remains approximately 24 months despite gross total resection in combination with concomitant chemoradiation therapy based on temozolomide (TMZ).[28,29]

Several genetic markers, such as methylguanine methyltransferase promoter unmethylation, phosphatase and tensin homolog gene mutations, and epidermal growth factor receptor gene amplification, are associated with poor survival in patients with GBM.[8,26] In addition, recent reports indicate that 70–80% of GBMs harbor either the C228T or C250T mutation in the promoter region of telomerase reverse transcriptase (*TERT*).[20,21] Although several studies reported the prognostic significance of *TERT* promoter (*TERT*p) mutations in patients with GBM, their clinical and pathologic impact remains unclear.[25,27]

Necrosis detected by MRI has been reported to indicate the presence of *TERT*p mutations.[33] However, predicting *TERT*p status by preoperative imaging studies alone remains difficult.

We recently reported that *TERT*p mutations were strongly associated with poor prognosis and multifocal/distant lesions in isocitrate dehydrogenase (*IDH*)-wild-type GBMs.[11] Another study demonstrated that GBM cells infiltrated the tissue surrounding CELs on T1-weighted MRI scans.[10] Fluid-attenuated inversion recovery (FLAIR) images are considered to represent such invasive cells as well as cerebral edema. However, discriminating tumor invasion from cerebral edema in FLAIR hyperintense lesions (FHLs) remains a challenge. We previously reported that the apparent diffusion coefficient (ADC) calculated using diffusion-weighted imaging was useful in evaluating tumor invasion in FHLs.[19] This finding raises the possibility that *IDH*-wild-type GBMs with *TERT*p mutations might be invasive and that MRI might aid in the detection of tumor cells infiltrating the tissue beyond CELs. However, to our knowledge, no study to date has examined the relationship between the *TERT*p mutation status and FHLs on MRI.

Therefore, we aimed to determine if the *TERT*p mutation status correlated with MRI features, with a focus on the ADC of FHLs.

MATERIALS AND METHODS

Patients and samples

This retrospective study was conducted with the approval of the Ethics Committee of the Yamagata University Faculty of Medicine (Ethical Approval Number: 2021-214, Ethical Approval Date: 2021/9/3), and written informed consent using the opt-out approach was obtained from all patients or their families. Among 115 consecutive patients treated with surgical removal of the tumor followed by adjuvant chemo-radiotherapy with irradiation and/or TMZ between January 2009 and October 2021, 114 patients who met the following inclusion criteria were included: (1) diagnosis of grade 4 *IDH*-wild-type GBM according to the 2021 World Health Organization classification;[17] (2) no history of former lower-grade tumors; (3) available genomic DNA; and (4) available neuroradiological examinations including contrast-enhanced MRI and FLAIR images on preoperative MRI.

In all patients, tumor specimens were obtained from lesions that exhibited enhancement on gadolinium-enhanced MRI scans and immediately stored at −80°C until DNA extraction.

MRI

All patients underwent preoperative MRI within seven days before surgery with a 1.5- or 3.0-T Achieva MRI scanner (Philips Medical Systems, Amsterdam, Netherlands). For data collection and evaluation, the Picture Archiving and Communication System (Impax ee, Agfa Healthcare, Bonn, Germany) was used. Diffusion-weighted imaging was conducted with b-values of 0 and 1000 s/mm^2 to generate ADC maps. Sequences were obtained using 30 slices with a slice thickness of 5 mm. In the FLAIR examination, the following settings were used: set repetition time, 9000 ms; echo time, 125 ms; inversion time, 2500 ms; and slice thickness, 6 mm. First, FLAIR images were used to set several regions of interest (ROIs) in almost all FHLs surrounding the CEL; the ROIs were placed at least 3 mm away from the CEL in each tumor in the FLAIR images, as we previously reported.[19] Next, ADCs of corresponding ROIs on FHLs are determined [Figure 1].

Tumor and FHL volumes were measured after image fusion using iPlan 3.0 (BrainLab AG). On gadolinium-enhanced and FLAIR images, CEL and FHL segmentations based on differences in signal intensity were created using the "smart brush" tool. Next, volumetric evaluations of CELs and FHLs were completed using multiple ROIs [Figure 1]. Additional neuroradiological features, such as necrosis, multifocal lesions, and lesions crossing midline, were also evaluated in MRI scans.

Molecular analysis

Genomic DNA was extracted using the QIAamp DNA mini kit (Qiagen), according to the manufacturer's instructions. Mutation status for *IDH1*, *IDH2,* and *TERT*p was analyzed using Sanger sequencing, as described previously.[23]

Statistical analysis

Statistical analyses were performed using SPSS ver. 26 (IBM Japan, Tokyo, Japan). Relationships between two variables

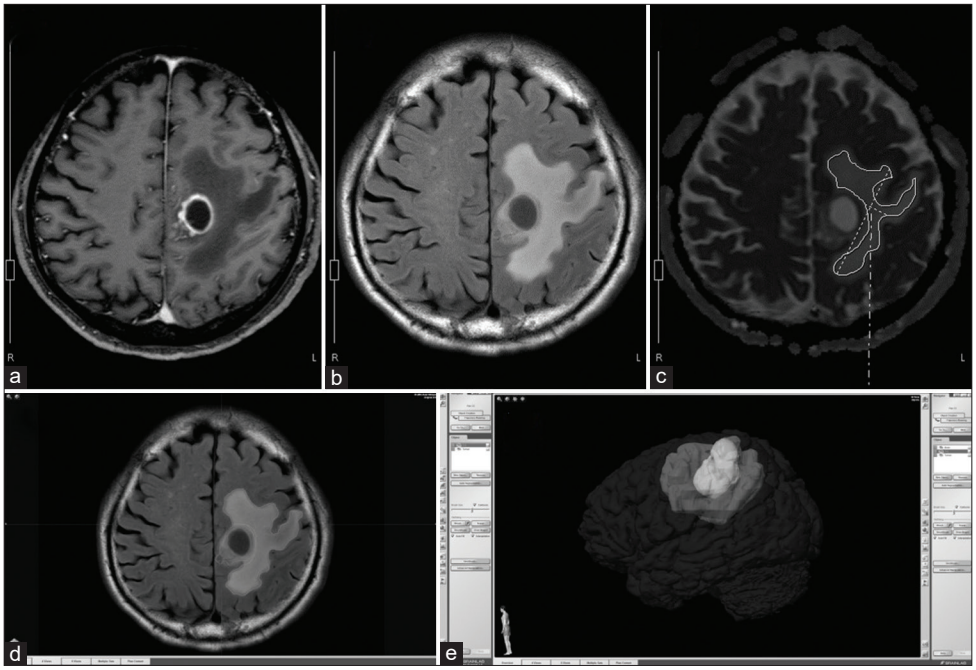

Figure 1: Image analysis of preoperative magnetic resonance imaging scans. Several regions of interest (ROIs) of hyperintense lesions on fluid-attenuated inversion recovery (FLAIR) high lesion (FHLs) at least 3 mm away from (a) the contrast-enhanced lesion (CEL) on (b) FLAIR. (c) Next, apparent diffusion coefficients (ADCs) of corresponding ROIs in FHLs were calculated on the ADC map. CEL and FHL volumes were measured after image fusion of contrast-enhanced T1-weighted and FLAIR images. (d) Segmentations of CEL and FHL were based on differences in signal intensity using the semiautomatic "smartbrush" tool. (e) Finally, 3D volumetric evaluations of CELs and FHLs were performed. FHL: FLAIR high lesion.

were evaluated using the Mann–Whitney *U*-test. Pearson's correlation coefficient analysis was used to evaluate the association between ADC and tumor cell density.

Histopathological analysis of FHLs

For the comparison of tumor cell density and ADC of biopsied FHLs, navigation-guided multiple tumor sampling of FHLs was performed in the last ten consecutive patients with GBM who had available tissue samples. Tumor cell counts were determined in three high-powered fields of view (400×) in each sample, as previously described.[12] All cells left after the exclusion of normal cells, such as vascular cells and hematogenic cells, were counted.

RESULTS

Patient characteristics

Among 115 cases with the histological features of GBM, one patient with *IDH1* mutation was excluded from the study. Therefore, a total of 114 patients with *IDH*-wild type GBM, including 56 male and 58 female patients, with a median age of 68 years (range 39–86 years), were included in the present study. The tumors were located in the frontal, temporal, parietal, and occipital lobes in 40, 36, 26, and 4 patients, respectively, and in the insula, basal ganglia, and corpus callosum in 5, 2, and 1 patient, respectively. Gross total surgical resection was performed in 69 (60.5%) patients. *TERT*p mutations were found in 77 of the 114 (67.5%) patients; of these, 89 patients were previously reported.[11] There were no significant differences in age, sex, preoperative Karnofsky performance scale core, tumor localization, and removal rate between the patients with and without *TERT*p mutations [Table 1].

ADC volume and value of CELs and FHLs

As shown in Figure 1, the ROIs were set around the CELs and FHLs and minimum ADCs of ROIs in both lesions were calculated. Total CEL and FHL volumes were also measured using volumetric analysis [Figure 1]. The results are summarized in Table 2. Briefly, the mean CEL and FHL volumes were 40.2 and 57 cm^3, respectively; these values were not significantly different between the *TERT*p-wild type and *TERT*p-mutant groups (CEL, 41.6 vs 39.5 cm^3, respectively, $P = 0.48$; FHL, 53.5 vs. 58.8 cm^3, $P = 0.50$, respectively). Similarly, the FHL/CEL ratio was larger in the

Table 1: Characteristics of the patients.

	Total (*n*=114)	*TERTp* wild type (*n*=37)	*TERTp* mutant (*n*=77)	*P*
Sex, female, *n* (%)	58 (50.9)	25 (67.6)	33 (42.9)	0.21
Age, y, median (range)	68 (39–86)	67 (41–82)	66 (39–86)	0.30
Preoperative KPS ≥80, *n* (%)	67 (58.8)	19 (51.3)	48 (62.3)	0.21
Tumor location				
Frontal	40 (35.1)	19 (51.3)	21 (27.3)	0.71
Temporal	36 (31.6)	8 (21.6)	28 (36.7)	0.41
Parietal	26 (22.8)	7 (18.9)	19 (24.7)	0.73
Occipital	4 (3.5)	1 (2.7)	3 (3.9)	0.91
Others	8 (7.0)	2 (5.4)	6 (7.8)	0.86
Gross total resection, *n* (%)	69 (60.5)	21 (56.8)	48 (62.3)	0.26

KPS: Karnofsky Performance Scale, *TERTp*: Telomerase reverse transcriptase promoter

Table 2: Summary of MRI features.

	Total (*n*=114)	*TERTp* wild type (*n*=37)	*TERTp* mutant (*n*=77)	*P*
CEL				
Volume (cm^3)	40.2 (1.1–125.4)	41.6 (1.1–108.7)	39.5 (1.2–125.4)	0.48
Minimum ADC ($\times 10^{-3}$ mm^2/s)	682.4 (320.5–1231.5)	661.8 (320.5–1224.0)	691.5 (339.9–1231.5)	0.55
FHL				
Volume (cm^3)	57 (0.8–165.9)	53.5 (3.4–165.9)	58.8 (0.8–148.0)	0.50
Minimum ADC ($\times 10^{-3}$ mm^2/s)	999.1 (473.0–1630.7)	1092.1 (679.4–1447.6)	958.9 (473.0–1630.7)	**<0.01**
Volume ratio; FHL/CEL	1.40 (0.01–24.45)	1.11 (0.09–24.45)	1.82 (0.01–22.26)	0.39
Necrotic cyst (%)	29 (25.4)	8 (21.6)	21 (27.3)	0.47
Multifocal lesions (%)	18 (15.8)	2 (5.4)	16 (20.8)	**0.03**
Cross mid-line (%)	19 (16.7)	7 (18.9)	12 (15.6)	0.70

Data are presented as the mean value and range of lowest and largest values. Boldface type indicates statistical significance. CEL: Contrast-enhanced lesion, FHL: FLAIR high lesion, MRI: Magnetic resonance imaging, ADC: Apparent diffusion coefficient, *TERTp*: Telomerase reverse transcriptase promoter

*TERT*p-mutant group than in the *TERT*p-wild-type group, although the difference was not statistically significant (mean, 1.82 vs. 1.11, $P = 0.39$).

The minimum ADC of CELs was not significantly different between the *TERT*p-wild type and *TERT*p-mutant groups (mean, 661.8×10^{-3} and 691.5×10^{-3} mm^2/s, respectively; $P = 0.55$) [Figure 2a]. However, the minimum ADC of FHLs was significantly lower in the *TERT*p-mutant group than in the *TERT*p-wild-type group (mean, 958.9×10^{-3} and 1092.1×10^{-3} mm^2/s, respectively; $P < 0.01$) [Figure 2b]. Furthermore, the frequency of multifocal lesions was significantly higher in the *TERT*p-mutant group than in the *TERT*p-wild-type group ($P = 0.03$), as we previously reported,[11] whereas the other MRI features were not significantly different between the two groups [Table 2].

Correlation between the tumor cell density and ADC of FHLs

As shown in Figure 3, sparse tumor cells were found in FHLs with high ADCs (1534.9×10^{-3} mm^2/s) [Figure 3a], whereas tumor cell density was higher in FHLs with low ADC (1272.5×10^{-3} mm^2/s) [Figure 3b]. There was a trend toward a negative correlation between ADC and tumor cell density; however, a statistically significant correlation could not be observed due to the small number of tumor samples [Figure 3c].

DISCUSSION

*TERT*p mutations are the most common genetic abnormality in GBM. The previous studies suggested that *TERT*p mutations were involved in multiple lesions, remote recurrence, and poor prognosis in GBM.[11,20,21,25,27] Furthermore, *TERT*p mutations were shown to be associated with invasiveness and metastasis in other carcinomas, such as urothelial cancer, thyroid cancer, melanoma, non-small-cell lung cancer, and squamous cell carcinoma.[2,18,31,32,34]

ADC, a well-known parameter associated with tumor cell density and infiltration, has been used to predict prognosis and evaluate recurrent lesions in patients with GBM.[1,2,4-7,14] In addition, we recently reported that FHLs with lower ADC were associated with future relapse sites,[19] suggesting the presence of infiltrating tumor cells around CELs in FHLs with low ADC.

In the present study, we could not detect differences in the MRI features of CELs and FHLs between the *TERT*p-wild

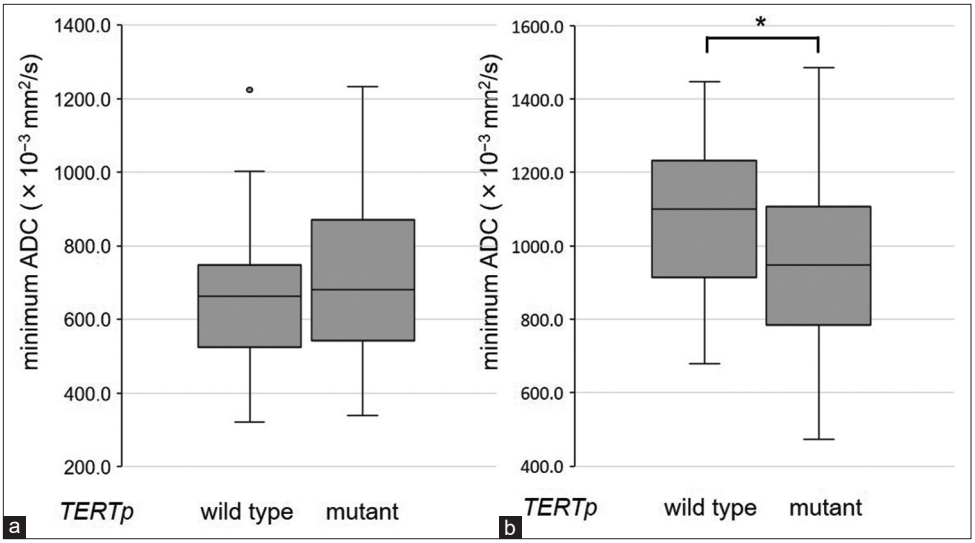

Figure 2: Bar graphs show the comparison of minimum apparent diffusion coefficients values of (a) contrast-enhanced lesions and (b) FLAIR hyperintense lesions between the groups without or with telomerase reverse transcriptase promoter mutations. Relationships between the two groups were evaluated using the Mann–Whitney *U*-test (**P* < 0.05).

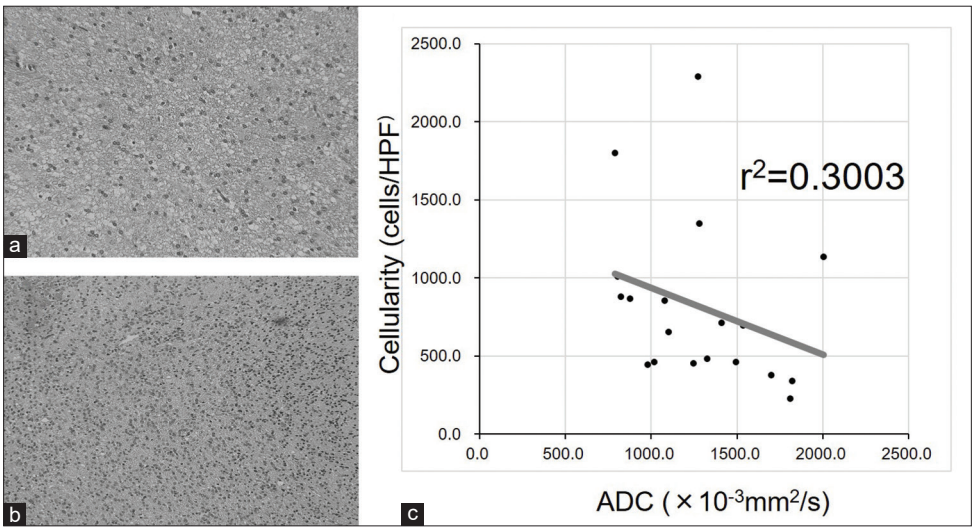

Figure 3: Histological features of FLAIR hyperintense lesions. (a) Note sparse tumor cells in a tissue sample collected from a lesion with high apparent diffusion coefficient (ADC) (1534.9 × 10^{-3} mm^2/s). (b) Note high tumor cell density in a tissue sample collected from a lesion with low ADC (1272.5 × 10^{-3} mm^2/s). (c) There was a trend toward a negative correlation between ADC and tumor cell density, although a statistically significant correlation could not be observed due to the small number of tumor samples.

type and *TERT*p-mutant groups. These results confirm previous studies suggesting that predicting *TERT*p mutation status by preoperative MRI alone was difficult.[9,24,33]

In the present study, we also confirmed the findings of a previous study, which reported that the ADC of CELs did not differ between *TERT*p wild type and *TERT*p-mutant GBMs.[9] However, we found that the minimum ADC of FHLs was significantly lower in the *TERT*p-mutant group than in the *TERT*p-wild-type group, suggesting that GBMs with *TERT*p mutations were more aggressive and that the number of tumor cells infiltrating the FHL was high. In the present study, we histologically confirmed aggressive tumor invasion in areas with low ADC in FHLs. However, the problem is that it is unknown why FHLs exhibit lower ADC in the cases of TERTp mutation status. One possible reason for this is that

GBM with TERTp mutation status has been reported to have a high Ki-67 labeling index, which may result in rapid cell division and, as a result, high cell density.[16]

Several recent studies reported the clinical utility of the additional removal of FHLs beyond gross total resection.[3,15,30] However, complete removal of FHLs without inducing morbidity is difficult.[15,30] In such cases, resection of areas with low ADC in FHLs might be considered as a new resection approach in GBM surgery. Particularly, GBMs with *TERT*p mutations harboring low-ADC lesions in FHLs might be good candidates for this approach.

This study has several limitations. First, this was a single-center study, including the analysis of retrospectively collected datasets. Second, there were relatively small cases in which tumor cell density was determined with histological evaluation.

CONCLUSION

ADC of FHLs was significantly lower in GBMs with *TERT*p mutations than in those with wild-type *TERT*p. These results suggest that the ADC of FHLs on preoperative MRI might be helpful in predicting the *TERT*p mutation status and surgical planning.

Ethical approval

The research/study approved by the Institutional Review Board at the Ethical Review Committee of Yamagata University Faculty of Medicine, number 2021–214, dated 2021/9/3.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent.

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Conflicts of interest

There are no conflicts of interest.

Use of artificial intelligence (AI)-assisted technology for manuscript preparation

The authors confirm that there was no use of artificial intelligence (AI)-assisted technology for assisting in the writing or editing of the manuscript and no images were manipulated using AI.

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