Neurologia medico-chirurgica Advance Publication Date: October 27, 2021

Original Article doi: 10.2176/nmc.oa.2021-0182

Preoperative Apparent Diffusion Coefficient of Peritumoral Lesion Associate with Recurrence in Patients with Glioblastoma

Kenichiro Matsuda,[1] Yasuaki Kokubo,[1] Yonehiro Kanemura,[2] Masafumi Kanoto,[3] and Yukihiko Sonoda[1]

[1]*Department of Neurosurgery, Faculty of Medicine, Yamagata University, Yamagata, Yamagata, Japan*
[2]*Department of Biomedical Research and Innovation, Institute for Clinical Research, National Hospital Organization Osaka National Hospital, Osaka, Osaka, Japan*
[3]*Department of Radiology, Division of Diagnositc Radiology, Faculty of Medicine, Yamagata University, Yamagata, Yamagata, Japan*

Abstract

Additional resection beyond contrast enhanced lesion on MRI is recently considered to prolong survival in glioblastoma. Prediction of future recurrent site in the peritumoral lesion on preoperative MRI could be useful for surgical planning. The objective of this study was to determine if the preoperative ADC value was associated with the site of future recurrence in patients with glioblastoma. We retrospectively analyzed 21 patients with primary GBM. The ADC value on MRI were analyzed before and after operation and at recurrence. The region of interests (ROIs) were set to cover almost the FLAIR high-signal lesion surrounding contrast enhanced lesion. We determined whether the value of ADC on MRI was correlated with the spot of future recurrence. Among 1844 ROIs determined in the FLAIR high-signal lesion on preoperative MRI, new enhanced lesions occurred in 186 sites. The other 1258 sites showed no change or decrease in size on follow up MRI, and the other 400 sites were removed in first operation. The pre-operative ADC values of sites corresponding to future recurrence were significantly lower than that of non-recurrent sites ($p < 0.001$). We suggest that a low ADC values in FLAIR high-signal lesion is corresponding to recurrence, and useful for predicting recurrence of the lesion in cases of GBM. These results will be helpful for planning of surgery or radiation therapy and facilitate future prospective studies on GBM.

Keywords: glioblastoma, recurrence, ADC

Introduction

Glioblastoma (GBM) is the most common malignant brain tumor in adults. It is difficult to avoid recurrence in this disease with extremely poor prognosis.[1)] Despite therapeutic advances, the median survival period in such cases is approximately 14–18 months.[2–4)] Maximum safe resection followed by conventional radiotherapy (RT) (60 Gy in 30 fractions) combined with concurrent adjuvant temozolomide (TMZ) has now become the standard treatment for glioblastoma (GBM) patients.[2)] Several studies reported that age, sex, Karnofsky Performance Status (KPS), extent of resection, Ki67 labeling index, isocitrate dehydrogenase 1 (*IDH1*) mutation, O6-methylguanine methyltransferase (*MGMT*) gene promoter methylation, and alteration of 7p (*EGFR)*, and 10q *(PTEN*) were prognostic factors for survival.[5–9)]

Regarding to role of the surgery, overall survival of the patients underwent total resection of the enhanced lesion was still 18.8 months.[10)] Recently, to prolong the survival of the patients with GBM, more aggressive surgery using intraoperative magnetic resonance imaging (MRI), 5-aminolevulinic acid (5-ALA) has been proposed.[11,12)] Li et al. also reported that additional resection of FLAIR high-signal lesion around the enhanced mass was associated with

Received June 10, 2021; Accepted September 13, 2021

better prognosis than total resection of enhanced lesion alone.[13] However, since the resection of eloquent lesion surrounding tumor will result in severe morbidity, it could be often difficult to remove whole FLAIR high-signal lesion around the enhanced tumor bulk. Therefore, the important issue is to discriminate the invading tumor cells which is truly resected from edematous change in the FLAIR high-signal lesion. To overcome the limitations of conventional MRI, several efforts in the field of neuroimaging have been undertaken.

Previously, PET using radiolabeled amino acids has become a valuable diagnostic tool for various indications in patients with brain tumors. In particular, the high diagnostic value of amino acid PET compared to anatomical MRI for the differentiation of tumor progression from treatment-related changes has been reported in patients with glioma.[14,15]

Multimodal MRI characteristics including magnetic resonance spectroscopy (MRS) and perfusion MRI also provided the useful information to evaluate GBM invasiveness beyond contrast-enhanced lesion.[16] Similarly, apparent diffusion coefficients (ADC) calculated from diffusion-weighted MRI (DWI) have been used to predict the prognosis[17,18] and to predict the recurrence in GBM.[18–21] However, the ADC values in the surrounding lesion for preoperative planning are unclear.

In this study, to determine whether the preoperative ADC value was associated with the site of future recurrence, we analyzed the ADC value of FLAIR high-signal lesion on MRI in patients with GBM.

Materials and Methods

Patients and samples

This retrospective study was conducted with the approval of the Ethics Committees of the Yamagata University School of Medicine, and written informed consent was obtained from all subjects. We analyzed 21 patients with GBM in cerebral hemisphere treated in our institution between August 2012 and December 2017.

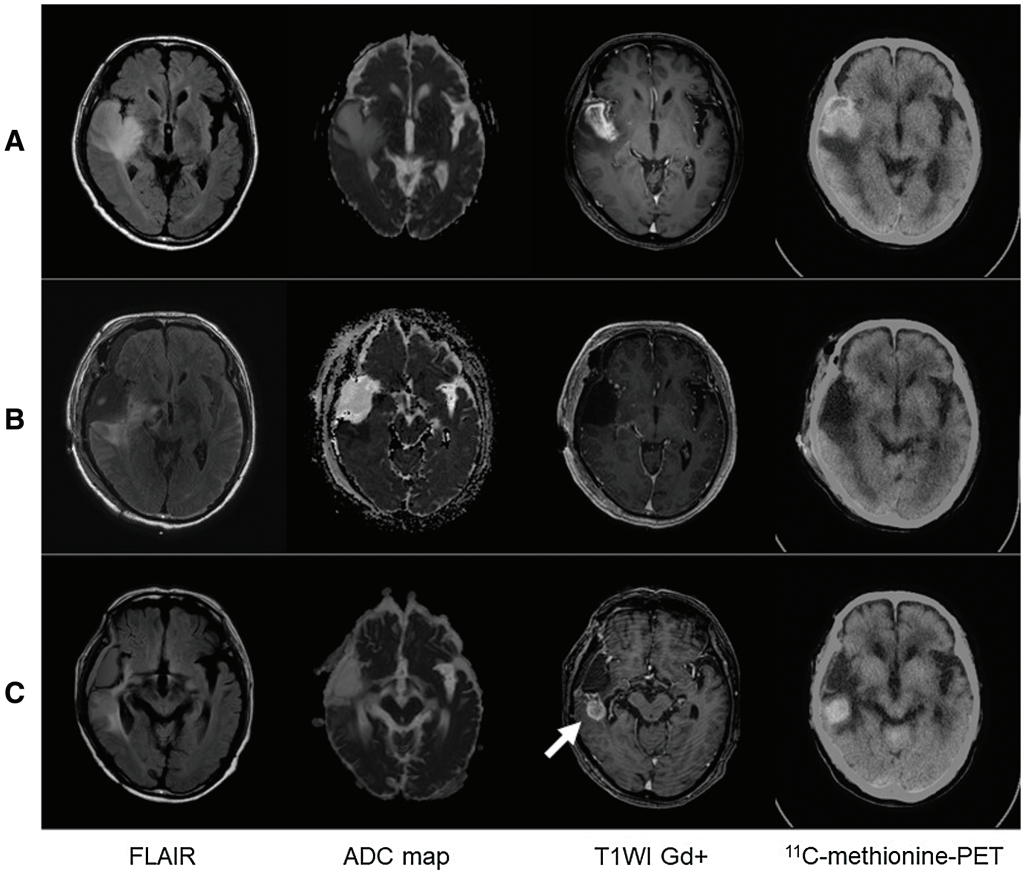

Fig. 1 Representative MRI scans and MET-PET of the patients treated at our institute. The scans were obtained before and after surgery and at the first recurrence. (A) Contrast-enhanced T1-weighted MRI revealed left temporal tumor with surrounding FLAIR high-signal lesion. (B) The enhanced tumor was totally removed. (C) New enhanced lesion appeared around resection cavity (arrow). The new recurrent tumor showed high uptake in ^{11}C-methionine PET. MRI: magnetic resonance imaging.

All patients met the following inclusion criteria: (1) a diagnosis of GBM multiforme, World Health Organization grade IV; (2) no history of lower-grade tumors; (3) genomic DNA being available; (4) information on events, such as recurrence or death during the follow-up period, being available or the patient not experiencing any such events for ≥12 months of follow-up; (5) treated with surgical removal of the tumor followed by adjuvant chemo-radiotherapy (RT) with temozolomide (TMZ) and total 60 Gy local irradiation; and (6) enough volume of the peri-tumoral FLAIR high-signal lesion on preoperative MRI.

Tumor specimens were obtained from a lesion that exhibited enhancement on gadolinium (Gd)-enhanced MRI studies and immediately stored at −80°C until DNA extraction. Evaluation with MRI had examined in preoperative period and within 48 hours after surgery. Follow-up MRI has been performed every 2 months during follow-up periods (Fig. 1).

Magnetic resonance imaging

All patients were examined within 7 days prior to surgery, within 48 hours after surgery, and at recurrence in follow-up study in a 3 tesla MRI scanner (Achieva 3.0T, Philips Medical Systems, Amsterdam, Netherlands). DWI was acquired with b-values 0 and 1000 s/mm^2 and used for generating ADC maps. Sequence details are 30 slices and slices of 5 mm thickness. For data evaluation, the Picture Archiving and Communication System (PACS) (Impax ee, Agfa Healthcare, Bonn, Germany) was used. In the examination on FLAIR, we had set repetition time; 9000 msec, echo time; 125 msec, and inversion time; 2500 msec. First, we had set up the several regions of interests (ROIs) of about 25 mm^2 in almost of the FLAIR high-signal region surrounding the tumor body at least 3 mm away from enhanced lesion in each tumor in the FLAIR images. We examined the ADC values of corresponding ROIs on FLAIR high-signal lesion (Fig. 2A and 2B). Then we categorized the fates of ROIs in three categories: recurrent, stable, and removed (Fig. 2C).

We determined that the recurrence had occurred by the appearance of the contrast-enhanced lesion in follow-up MRI. Additionally, patients who underwent re-operation were considered to have recurrence if there were any histological evidence of recurrent disease (7 cases). And patients who had been revealed that the suspicious lesion had high uptake in Met-PET (13 cases) and/or progressive clinical course or radiological findings in follow-up observation were also considered to have recurrence.

^{11}C-methionine-PET

The uptake on ^{11}C-methionine PET (Met-PET) studies were also measured on tumor, FLAIR high-signal lesion which has used in evaluation of ADC in preoperative MRI, and in some cases, evaluation

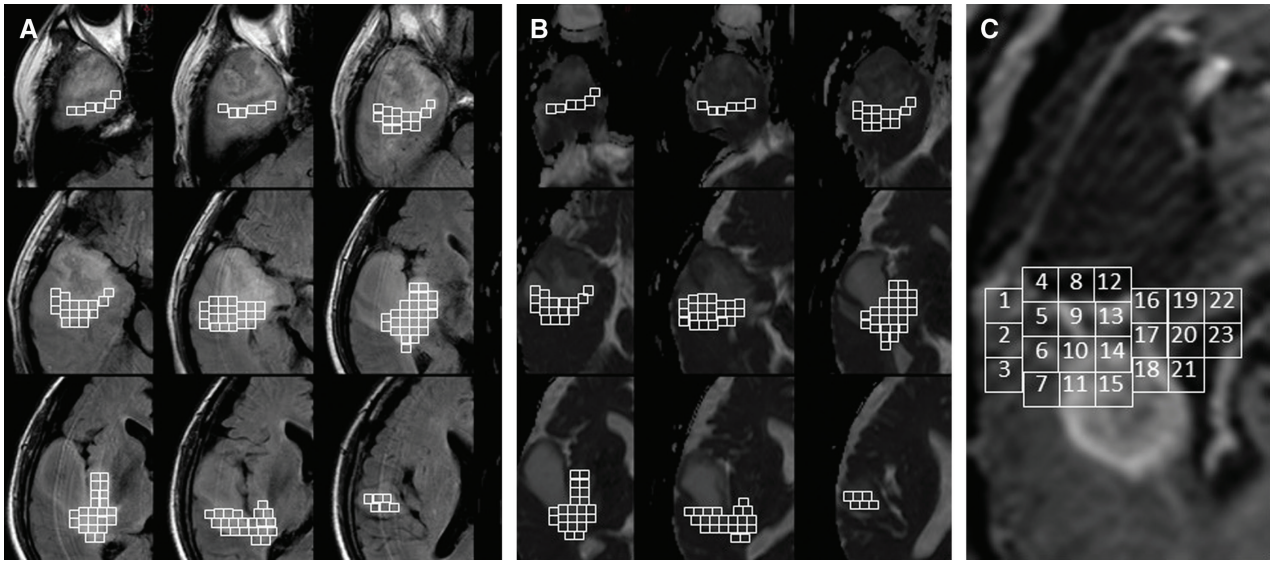

Fig. 2 Representative analysis of ADC values on FLAIR high-signal lesion. (A) In this case, a total of 144 ROIs were set in the FLAIR high-signal lesion around enhanced tumor in preoperative MRI. (B) The ADC value was calculated at the ROIs on ADC map corresponding to that of FLAIR images. (C) The fates of ROIs were determined on follow-up MRI with recurrence. There were three categories in plotted numbers: recurrent (9–11, 13–15, and 16–18), stable (1–3, 5–7, and 19–23), and removed (4, 8, and 12). ADC: apparent diffusion coefficient, MRI: magnetic resonance imaging, ROIs: regions of interest.

of recurrent lesion in follow-up studies. ^{11}C-methionine was intravenously administered to each patient. We started to perform Met-PET and brain computed tomography (CT) 20 minutes after intravenous injection in all cases by Biograph mCT (Siemens, Munich Germany). PET images were obtained with the following settings: image reconstruction method, ordered subsets-expectation maximization, point spread function, and time of flight (OSEM, PSF, and TOF); iteration, 4; subset, 21; matrix size, 200; filter, Gaussian filter; full width at half maximum, 3 mm; acquisition duration, 10 min; reconstructed slice thickness, 2 mm. Brain CT images were obtained with the following settings: X-ray tube voltage, 120 kV; acquisition thickness and slice count, 0.6 mm × 40 slices; reconstructed slice thickness, 2 mm. Afterward, we made a fusion image of the PET and CT images.

Molecular analysis

Genomic DNA was extracted with the QIAamp DNA mini kit (QIAGEN, Hilden, Germany), according to the manufacturer's protocol. Mutational status of *IDH1, TERT* promoter genes were analyzed using Sanger sequencing described previously.[22] In the *MGMT* promoter methylation analysis, we performed quantitative methylation-specific PCR (qMSP) following the bisulfite modification of tumor DNA.[22]

Statistical analysis

Statistical analyses were performed using SPSS (IBM Japan, Tokyo, Japan). The relationship between two variables was evaluated using the Mann–Whitney U test.

Results

Patient characteristics

A total of 21 cases including 12 males and 9 females with a median of age is 66 years (range: 44–85). Tumors infiltrated the frontal lobe in 7 cases, the temporal lobe in 10, the parietal lobe in 2, and the occipital lobe in 2. Gross total surgical resection was achieved in 21 (100%) patients. *MGMT* gene promotor methylation was detected in eight cases (38.1%). *TERT* promoter and *IDH1* gene mutation were found in 14 (66.7%) and one patient (4.8%), respectively. During follow-up period (15–60 months, median 28 months), 18 cases had recurrence (85.7%) (Table 1).

Table 1 Characteristics of patients

	Total (n = 21)
Sex, female, n (%)	9 (42.9)
Age, y, median (range)	66 (44–85)
Preoperative KPS ≥80, n (%)	17 (81.0)
Gross total resection, n (%)	21 (100)
Location	
Frontal	7 (33.3)
Temporal	10 (47.6)
Parietal	2 (9.5)
Occipital	2 (9.5)
Ki-67 labeling index, mean	5–70 (31.8)
MGMT promoter methylation, n (%)	8 (38.1)
TERT promoter mutation, n (%)	14 (66.7)
IDH1 mutation, n (%)	1 (4.8)
Median PFS, months (range)	8 (2–30)
Median OS, months (range)	21 (12–60)
Mean number of ROIs (range)	88 (4–230)

PFS: progression-free survival, OS: overall survival.

ADC values in preoperative MRI

We had set up the several ROIs in the FLAIR high-signal lesion with mean number of 88 (range: 4–230). In total, the ROIs of 1844 sites were determined to cover the FLAIR high-signal lesion around the enhanced tumor body in the preoperative MRI (Fig. 1). We determined fates of ROIs in three categories: recurrent, stable, and removed. Among 1844 sites, new enhanced lesions occurred in 186 sites (recurrent). However, the other 1258 sites showed no evidence of recurrence on follow-up MRI (stable), and the other 400 sites were removed in first operation (removed).

The preoperative ADC values on total ROIs were 548.7×10^{-6} mm^3 to 2579.3×10^{-6} mm^3 (mean: 1492.4×10^{-6} mm^3). The preoperative ADC values of the sites corresponding to future recurrence were 548.7×10^{-6} mm^3 to 1822.1×10^{-6} mm^3 (mean: 1148.6×10^{-6} mm^3). The preoperative ADC values with no future recurrence were 686.1×10^{-6} mm^3 to 2579.3×10^{-6} mm^3 (mean: 1543.2×10^{-6} mm^3). The preoperative ADC value of the sites corresponding to recurrence was significantly lower than that of non-recurrent sites (mean 1148.6 vs 1543.2, $p < 0.001$) (Table 2, Fig. 3A).

To eliminate the effect of TMZ, we divided the patients into two groups according to *MGMT* gene promotor methylation status. As a result, the preoperative ADC value of sites corresponding to future recurrence was also significantly lower than that of non-recurrent sites in *MGMT*-methylated group (mean 1043.2 vs 1526.2, $p < 0.001$) and *MGMT*-unmethylated group (mean 1234.7 vs 1551.6, $p < 0.001$) (Table 2, Fig. 3B and 3C).

Finally, we performed ROC analysis to investigate the boundary between the site with recurrence and non-recurrence in the future. The ROC curves

Table 2 Characteristics of ROIs on FLAIR high-signal lesion

	No.	mean ADC (range)	
ROIs			
Total	1844	1492.4 (548.7–2579.3)	
Recurrent	186	1148.6 (548.7–1822.1)	p <0.001
Stable	1258	1543.2 (686.1–2579.3)	
Removed	400	1423.3 (748.3–2101.0)	
MGMT promotor: Methylated			
Total	518	1442.3 (548.7–2579.3)	
Recurrent	90	1043.2 (548.7–1795.8)	p <0.001
Stable	428	1526.2 (686.1–2579.3)	
MGMT promotor: Unmethylated			
Total	937	1515.1 (691.4–2417.7)	
Recurrent	108	1234.7 (691.4–1822.1)	p <0.001
Stable	829	1551.6 (723.7–2417.7)	

ADC: apparent diffusion coefficient.

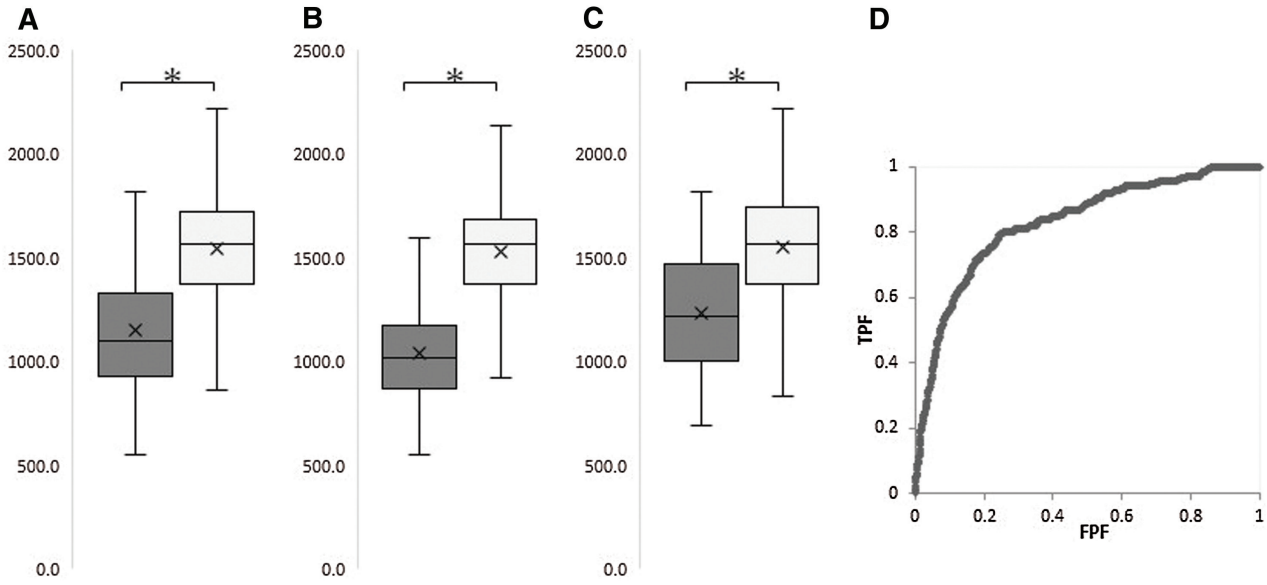

Fig. 3 Slab and bar graphs of the ADC values comparing recurrent and non-recurrent sites. The ADC value of ROIs with future recurrence (dark slab) revealed significantly lower than that without recurrence (pale slab) in preoperative MRI (A). ADC values were also significantly associated with the recurrence in both *MGMT* promotor methylated (B) and unmethylated (C) groups (*p <0.001). The ROC curve generated from total ADC values in recurrent and non-recurrent site are shown. The AUC was 0.830. The cutoff point of 1364.1 ($\times 10^{-6}$ mm^3) showed nearest point to the left corner of the plot (D). ADC: apparent diffusion coefficients, AUC: area under the curves, MRI: magnetic resonance imaging, ROIs: regions of interest.

generated from total ADC values in recurrent and non-recurrent site are shown in Fig. 3D. The area under the curves (AUC) was 0.830. The cutoff point of 1364.1 ($\times 10^{-6}$ mm^3) showed nearest point to the left corner of the plot, at which points the TPF (true-positive fraction) and FPF (false-positive fraction) are 0.790 and 0.241, respectively.

Discussion

The actual importance of surgery in GBM is still unclear; however, currently, the goal of surgery for neurosurgeon seems to be maximum resection without severe morbidity.[23,24] On the other hand, despite multimodal therapies including TMZ-based

chemo-RT, tumor-treating fields, the recurrence is not nearly avoided in GBM.[2,10,25] To prolong the survival, the role of surgery should be re-considered.

In this manner, supra-total resection should be considered as the next step. The area outside the contrast enhancement region on a T1-weighted MR image is usually infiltrated by tumor cells. FLAIR images are thought to represent these invasive cells, as well as cerebral edema, demyelination.[26] Recently, aggressive resection beyond contrast-enhanced lesion on MRI was proposed in some advanced institutes. However, since the rate of gross total resection which means resection of contrast-enhanced lesion was reported to be less than 50%, it could be more difficult to achieve complete removal of FLAIR high lesion.[10,23] Therefore, we determined whether the area showing lower value of ADC on preoperative MRI would be recurrent lesion in the future.

As a result, the ADC value in preoperative MRI is very useful for evaluating the possibility of recurrence, and it is suggested that the recurrence may occur significantly in the portion with lower ADC value in the FLAIR high-signal lesion around the enhanced tumor. *MGMT* promotor methylation status is said to be related to some extent at the site of recurrence.[27] Furthermore, we confirmed that the ADC value was useful to predict the recurrence site regardless to *MGMT* promoter methylation status.

On the other hand, the ADC value on postoperative MRI was not predictor for future recurrence site. Ischemic change or damaged brain by surgery could affect the ADC value on postoperative MRI.

The ROC analysis suggested that the ADC value of 1346.1 ($\times 10^{-6}$ mm^3) is useful for identifying recurrent and non-recurrent sites in future. For example, by creating the ADC map based on this ADC value in preoperative MRI, it might be able to utilize in planning in extent of resection or radiation therapy.[28]

This study had limitations, primarily because of its retrospective nature. Also, this study was limited to patients treated at a single institution. In image evaluation, because MRI and methionine PET have different resolutions, it may be impossible to measure SUVs that equivalent to the ROI settings by MRI.

Additionally, because of surgery and subsequent radio-chemotherapy, as well as brain atrophy and deformation at the time of recurrence, it is hardly possible to overlap the exact recurrent site in follow-up MRI with the equivalent site in preoperative MRI. However, we are convinced that predicting the areas with a high recurrence tendency before surgery will lead to improved surgical results and improved outcome.

Conclusion

We retrospectively investigated whether the ADC of preoperative MRI could predict the site of future recurrence in GBM. We suggest that a low ADC value is useful for predicting recurrence of the lesion in cases of GBM. It is considered to contribute to the improvement of the treatment results of GBM.

Acknowledgments

The authors thank Medical English Service (www.med-english.com) for the English language review.

Funding

This work was supported by JSPS KAKENHI Grant Number 17K10856.

Conflict of Interest Disclosure

All authors declare that they have no conflict of interest.

References

1) Louis DN, Ohgaki H, Wiestler OD, et al.: WHO Classification of Tumours of the Central Nervous System. Lyon, IARC, 2016
2) Stupp R, Mason WP, van den Bent MJ, et al.: Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. *N Engl J Med* 352: 987–996, 2005
3) Chinot OL, Wick W, Mason W, et al.: Bevacizumab plus radiotherapy-temozolomide for newly diagnosed glioblastoma. *N Engl J Med* 370: 709–722, 2014
4) Gilbert MR, Dignam JJ, Armstrong TS, et al.: A randomized trial of bevacizumab for newly diagnosed glioblastoma. *N Engl J Med* 370: 699–708, 2014
5) Weller M, Felsberg J, Hartmann C, et al.: Molecular predictors of progression-free and overall survival in patients with newly diagnosed glioblastoma: a prospective translational study of the German Glioma Network. *J Clin Oncol* 27: 5743–5750, 2009
6) Hegi ME, Diserens AC, Gorlia T, et al.: MGMT gene silencing and benefit from temozolomide in glioblastoma. *N Engl J Med* 352: 997–1003, 2005
7) Ohgaki H, Dessen P, Jourde B, et al.: Genetic pathways to glioblastoma: a population-based study. *Cancer Res* 64: 6892–6899, 2004
8) Smith JS, Tachibana I, Passe SM, et al.: PTEN mutation, EGFR amplification, and outcome in patients with anaplastic astrocytoma and glioblastoma multiforme. *J Natl Cancer Inst* 93: 1246–1256, 2001
9) Shibahara I, Sonoda Y, Saito R, et al.: The expression status of CD133 is associated with the pattern and timing of primary glioblastoma recurrence. *Neurooncol* 15: 1151–1159, 2013

10) Stupp R, Hegi ME, Mason WP, et al.: Effects of radiotherapy with concomitant and adjuvant temozolomide versus radiotherapy alone on survival in glioblastoma in a randomised phase III study: 5-year analysis of the EORTC-NCIC trial. *Lancet Oncol* 10: 459–466, 2009
11) Stummer W, Pichlmeier U, Meinel T, et al.: Fluorescence-guided surgery with 5-aminolevulinic acid for resection of malignant glioma: a randomised controlled multicentre phase III trial. *Lancet Oncol* 7: 392–401, 2006
12) Senft C, Bink A, Franz K, Vatter H, Gasser T, Seifert V: Intraoperative MRI guidance and extent of resection in glioma surgery: a randomised, controlled trial. *Lancet Oncol* 12: 997–1003, 2011
13) Li YM, Suki D, Hess K, Sawaya R: The influence of maximum safe resection of glioblastoma on survival in 1229 patients: Can we do better than gross-total resection? *J Neurosurg* 124: 977–988, 2016
14) Sonoda Y, Kumabe T, Takahashi T, Shirane R, Yoshimoto T: Clinical usefulness of 11C-MET PET and 201T1 SPECT for differentiation of recurrent glioma from radiation necrosis. *Neurol Med Chir (Tokyo)* 38: 342–347; discussion 347-348, 1998
15) Xu W, Gao L, Shao A, Zheng J, Zhang J: The performance of 11C-Methionine PET in the differential diagnosis of glioma recurrence. *Oncotarget* 8: 91030–91039, 2017
16) Li C, Wang S, Yan JL, et al.: Characterizing tumor invasiveness of glioblastoma using multiparametric magnetic resonance imaging. *J Neurosurg* 26: 1–8, 2019
17) Burth S, Kickingereder P, Eidel O, et al.: Clinical parameters outweigh diffusion- and perfusion-derived MRI parameters in predicting survival in newly diagnosed glioblastoma. *Neuro Oncol* 18: 1673–1679, 2016
18) Elson A, Paulson E, Bovi J, Siker M, Schultz C, Laviolette PS: Evaluation of pre-radiotherapy apparent diffusion coefficient (ADC): patterns of recurrence and survival outcomes analysis in patients treated for glioblastoma multiforme. *J Neurooncol* 123: 179–188, 2015
19) Chang PD, Chow DS, Yang PH, Filippi CG, Lingnelli A: Predicting glioblastoma recurrence by early changes in the apparent diffusion cefficient value and signal intensity on FLAIR images. *Am J Radiol* 208: 57–65, 2017
20) Chang W, Pope WB, Harris RJ, et al.: Diffusion MR characteristics following concurrent radiochemotherapy predicts progression-free and overall survival in newly diagnosed glioblastoma. *Tomography* 1: 37–43, 2015
21) Gupta A, Young RJ, Karimi S, et al.: Isolated diffusion restriction precedes the development of enhancing tumor in a subset of patients with glioblastoma. *AJNR Am J Neuroradiol* 32: 1301–1306, 2011
22) Sasaki T, Fukai J, Kodama Y, et al.: Characteristics and outcomes of elderly patients with diffuse gliomas: a multi-institutional cohort study by Kansai Molecular Diagnosis Network for CNS tumors. *J Neurooncol* 140: 329–339, 2018
23) Lacroix M, Abi-Said D, Fourney DR, et al.: A multivariate analysis of 416 patients with glioblastoma multiforme: prognosis, extent of resection, and survival. *J Neurosurg* 95: 190–198, 2001
24) Sanai N, Polley MY, McDermott MW, Parsa AT, Berger MS: An extent of resection threshold for newly diagnosed glioblastomas. *J Neurosurg* 115: 3–8, 2011
25) Stupp R, Taillibert S, Kanner A, et al.: Effect of tumor-treating fields plus maintenance temozolomide vs maintenance temozolomide alone on survival in patients with glioblastoma: a Randomized Clinical Trial. *JAMA* 318: 2306–2316, 2017
26) Kelly PJ, Daumas-Duport C, Kispert DB, Kall BA, Scheithauer BW, Illig JJ: Imaging-based stereotaxic serial biopsies in untreated intracranial glial neoplasms. *J Neurosurg* 66: 865–874, 1987
27) Jada ST, Diez-Valle Aldave G, et al.: Factors associated with a higher rate of distant failure after primary treatment for glioblastoma. *J Neuroncol* 116: 169–175, 2014
28) Duma CM, Kim BS, Chen PV, et al.: Upfront boost Gamma Knife leading-dege radiosurgery to FLAIR MRI-defined tumor migration pathways in 174 patients with glioblastoma multiforme: a 15-year assessment of a novel therapy. *J Neurosurg* 125: 40–49, 2016

Corresponding author: Kenichiro Matsuda, MD, PhD
Department of Neurosurgery, Faculty of Medicine, Yamagata University, 2-2-2 Iidanishi, Yamagata, Yamagata 990-9585, Japan.
e-mail: matsuk@med.id.yamagata-u.ac.jp