pISSN 2384-1095
eISSN 2384-1109

iMRI 2022;26:10-19

https://doi.org/10.13104/imri.2022.26.1.10

iMRI
Investigative Magnetic Resonance Imaging

Added Value of Contrast Leakage Information over the CBV Value of DSC Perfusion MRI to Differentiate between Pseudoprogression and True Progression after Concurrent Chemoradiotherapy in Glioblastoma Patients

Elena Pak[1], Seung Hong Choi[1,2], Chul-Kee Park[3], Tae Min Kim[4], Sung-Hye Park[5], Jae-Kyung Won[5], Joo Ho Lee[6], Soon-Tae Lee[7], Inpyeong Hwang[1], Roh-Eul Yoo[1], Koung Mi Kang[1], Tae Jin Yun[1]

[1]Department of Radiology, Seoul National University Hospital, Seoul, Korea
[2]Center for Nanoparticle Research, Institute for Basic Science, and School of Chemical and Biological Engineering, Seoul National University, Seoul, Korea
[3]Department of Neurosurgery and Biomedical Research Institute, Seoul National University Hospital, Seoul, Korea
[4]Department of Internal Medicine and Cancer Research Institute, Seoul National University Hospital, Seoul, Korea
[5]Department of Pathology, Seoul National University Hospital, Seoul, Korea
[6]Department of Radiation Oncology and Cancer Research Institute, Seoul National University Hospital, Seoul, Korea
[7]Department of Neurology, Seoul National University Hospital, Seoul, Korea

Original Article

Received: October 4, 2021
Revised: December 9, 2021
Accepted: , 2022

Correspondence to:
Seung Hong Choi, M.D., Ph.D.
Department of Radiology, Seoul National University Hospital, 101 Daehak-ro, Jongno-gu, Seoul 03080, Korea.
Tel. +82-2-3668-7832
Fax. +82-2-743-6385
E-mail: verocay1@snu.ac.kr

Purpose: To evaluate whether the added value of contrast leakage information from dynamic susceptibility contrast magnetic resonance imaging (DSC MRI) is a better prognostic imaging biomarker than the cerebral blood volume (CBV) value in distinguishing true progression from pseudoprogression in glioblastoma patients.

Materials and Methods: Forty-nine glioblastoma patients who had undergone MRI after concurrent chemoradiotherapy with temozolomide were enrolled in this retrospective study. Twenty features were extracted from the normalized relative CBV (nCBV) and extraction fraction (EF) map of the contrast-enhancing region in each patient. After univariable analysis, we used multivariable stepwise logistic regression analysis to identify significant predictors for differentiating between pseudoprogression and true progression. Receiver operating characteristic (ROC) analysis was employed to determine the best cutoff values for the nCBV and EF features. Finally, leave-one-out cross-validation was used to validate the best predictor in differentiating between true progression and pseudoprogression.

Results: Multivariable stepwise logistic regression analysis showed that MGMT (O^6-methylguanine-DNA methyltransferase) and EF max were independent differentiating variables (P = 0.004 and P = 0.02, respectively). ROC analysis yielded the best cutoff value of 95.75 for the EF max value for differentiating the two groups (sensitivity, 61%; specificity, 84.6%; AUC, 0.681 ± 0.08; 95% CI, 0.524-0.837; P = 0.03). In the leave-one-out cross-validation of the EF max value, the cross-validated values for predicting true progression and pseudoprogression accuracies were 69.4% and 71.4%,

respectively.

Conclusion: We demonstrated that contrast leakage information parameter from DSC MRI showed significance in differentiating true progression from pseudoprogression in glioblastoma patients.

Keywords: Dynamic susceptibility contrast MRI; Extraction fraction; Pseudoprogression; Glioblastoma; True progression

INTRODUCTION

High-grade gliomas (HGGs) are tumors diagnosed as grade III (anaplastic astrocytoma or anaplastic oligodendroglioma) or grade IV (glioblastoma) (1). Glioblastoma leads to a high premature mortality rate in adults younger than 60 years and children younger than 15 years.

Currently, the standard of care for newly diagnosed glioblastoma is surgical resection followed by concurrent radiotherapy and chemotherapy with temozolomide (TMZ), and then maintenance TNZ for at least six months. Ionizing radiation induces free radical formation, which leads to double-stranded DNA damage and multiple modes of clonogenic cell death. Tumors endothelial cells are particularly vulnerable to radiation-induced damage, and the subsequent endothelial cell death can increase vascular permeability (2, 3). After the completion of concurrent chemoradiotherapy (CCRT) with TMZ, glioblastoma patients can show progressive contrast enhancement, followed by subsequent improvement or stabilization without further treatment, a phenomenon termed as "pseudoprogression" (4); when TMZ is added to radiation treatment, the incidence of pseudoprogression appears to be greater, activating its metabolite (methyltriazeno-imidazole-carboxamide) to methylate DNA within the cell and leading to apoptosis (2). The incidence of pseudoprogression varies between 12% and 64%, and this phenomenon usually happens in the first three months after CCRT with TMZ, sometimes persisting for up to six months after treatment (5). Thus, differentiating true progression from pseudoprogression is often difficult (6).

Glioblastomas are described by marked angiogenesis, which is marked for colonization and tumor growth in the brain (7). Dynamic susceptibility contrast (DSC) magnetic resonance imaging (MRI), as a surrogate marker for angiogenesis, can be used to assess glioma treatment response and differentiate pseudoprogression from tumor recurrence (8). The extraction fraction (EF) from DSC MRI is defined as the ratio of the permeability to perfusion (fractional tissue perfusion) and was proposed by Bjørnerud et al. (9, 10). In this method, both permeability and perfusion metrics are obtained by fitting appropriate kinetic models to the tissue residue function derived by deconvolution with an automatically received arterial input function (AIF) (11, 12).

Several studies have tried to distinguish true progression from pseudoprogression in patients with glioblastoma using advanced MR imaging techniques such as perfusion-weighted imaging (PWI) (13, 14). To the best of our knowledge, there is no report on the value of contrast leakage information from DSC MRI that differentiates between pseudoprogression and true progression in glioblastoma patients. Thus, our study aimed to assess whether the added value of contrast leakage information from DSC MRI is a superior prognostic imaging biomarker than the cerebral blood volume (CBV) value in distinguishing true progression from pseudoprogression in glioblastoma patients.

MATERIALS AND METHODS

Study Population

This retrospective study was approved by our institutional review board, and the requirement of informed consent was waived. We identified 404 newly diagnosed glioblastoma patients in the database of our institution who had undergone stereotactic biopsy or surgical resection at Seoul National University Hospital (SNUH) between October 2010 and July 2019. The inclusion criteria were as follows: 1) a histopathological diagnosis of glioblastoma based on the World Health Organization criteria before standard treatment; 2) baseline MRI with contrast enhancement within 24-48 hours after biopsy or surgery before subsequent CCRT with TMZ using 3T MRI scanners (Trio, Skyra or Verio, Siemens, Erlangen, Germany); 3) CCRT with TMZ after surgery or biopsy; 4) 1st follow-up 3T MRI with DSC MRI within two months (mean duration: 28.4 days; range: 5-47 days) after the end of CCRT with TMZ. The exclusion criteria were as follows: 1) no newly appeared

enhancing lesion on the 1st follow-up MR images (n = 222); 2) a newly appeared enhancing lesion that did not satisfy the criteria for measurable lesions according to the Response Assessment in Neuro-Oncology (RANO) criteria (15) on the 1st follow-up MR images after CCRT (n = 31); 3) other treatment regimens except the standard treatment (n = 32); 4) poor quality of the DSC MRI or contrast-enhanced (CE) T1 weighted image (WI) (n = 70). Forty-nine patients were classified into true disease progression (n = 21) and pseudoprogression (n = 28) groups according to the RANO criteria after CCRT during the standard treatment period. Among the 21 patients with true progression, six had undergone reoperation, and glioblastoma recurrence was confirmed.

Imaging Protocol

For each patient, after the completion of CCRT with TMZ, the brain MRI protocol included a 3T MR system using a 32-channel head coil. T1-weighted magnetization prepared rapid acquisition gradient echo (MPRAGE) sequences (repetition time [TR], 558 ms; echo time [TE], 1.9 ms; flip angle [FA], 9°; matrix, 256 × 232; field of view [FOV], 220 × 250; section thickness, 1 mm; and number of excitations [NEX], 1), transverse T2 fluid-attenuated inversion recovery (FLAIR) sequences (TR, 9000 ms; TE, 97; ms; inversion time, 2500 ms; FA, 130°; matrix, 384 × 348; FOV, 199 × 220; section thickness, 5 mm; and NEX, 1), and transverse T2WI with turbo spin echo (TSE) sequences (TR, 5160 ms; TE, 91 ms; FA, 124-130°; matrix, 640 × 510-580; FOV, 175-199 × 220; section thickness, 5 mm; NEX, 1), and structural imaging were performed.

Immediately following the acquisition of DSC-PWI, a single-shot gradient-echo echo-planar imaging sequence was performed during the intravenous injection of the contrast agent. DSC-PWI was performed using the following parameters: TR/TE, 1500/30-40 ms; FA, 35-90°; FOV, 240 × 240 mm; 15-20 sections; matrix, 128 × 128; section thickness, 5 mm; intersection gap, 1 mm; and voxel resolution of 1.86 × 1.86 × 5 mm. For each section, 60 images were obtained at intervals equal to the repetition time. After four to five-time points, a bolus of gadobutrol at a dose of 0.1 mmol/kg of body weight and a rate of 4 mL/sec was injected using an MR-compatible power injector (Spectris; Medrad, Pittsburgh, PA, USA). After injecting the bolus of the contrast material, a 30-mL bolus of saline was administered at the same injection rate.

Image Processing and Analysis

The MR data, including CE T1WI and DSC MRI, were transferred from the picture archiving and communication systems (PACS) workstation to a personal computer and processed using a software package (Nordic ICE v4.1.2; Nordic Neuro Lab, Bergen, Norway). The DSC perfusion MRI protocols were acquired using dedicated protocols in SNUH.

The arterial input function (AIF) was detected automatically using the software. This was preferred over the manual method which has several limitations in determining AIF :1) the calculation results are subjective, therefore there is no consistency between different operators and between different time points with the same operator; 2) time-consuming (16). Some of the papers were written using automatic AIF detection (17, 18). The automatic AIF detection based on a cluster analysis was robust and fast and it showed very low variability (19).

First, normalized relative CBV (nCBV) maps were acquired without contrast leakage correction based on DSC MRI using established tracer kinetic models applied to the first-pass data (20-23).

The contrast leakage information parameter (EF) from DSC MRI was obtained using a contrast agent extravasation-correction method based on fitting the tissue residue function, including both apparent tissue extravasation and a perfusion component, to the two-compartment uptake kinetic model (10, 12, 21, 23, 24). Next, we reconstructed CE T1WI from the sagittal to the axial plane and resampled the size of the CE T1WI image using one of the maps (nCBV or EF) as a reference.

We carefully excluded the vessels when drawing a region of interest (ROI). The ROIs for the contrast leakage lesions were chosen on CE T1WI, and were drawn semiautomatically using threshold segmentation, seed growing, and manually (25), by a radiologist (E.P.) supervised by one expert radiologist (S.H.C.) with 18 years of neuro-oncology imaging experience. ROI segmentation procedures were performed using the software tool NordicICE (v4.1.2). We used ROI analysis by the software to calculate EF and nCBV from all the pixels in the ROI (10). Twelve features were obtained from the nCBV and EF map of the contrast-enhancing region per person.

Statistical Analysis

All statistical analyses were performed using SPSS for Windows 25.0 and R version 3.6.1 (R-core Team, Vienna, Austria). $P < 0.05$ was considered statistically significant. Each patient's clinical characteristics, including sex, age,

Karnofsky performance score (KPS), date of CCRT ending, radiation dose, and genetic information including IDH1/2 mutation and O^6-methylguanine-DNA methyltransferase (MGMT) promoter methylation, were recorded. The data for each parameter were assessed for normality using the Kolmogorov-Smirnov test. Fisher's exact or chi-square test was performed for categorical data. Unpaired Student's t-test was employed to compare the data between the disease progression and pseudoprogression groups. Next, we used multivariable stepwise logistic regression analysis to determine the significant predictors for distinguishing pseudoprogression from true progression (26). Variables with $P < 0.05$ according to univariate analysis were used as input variables for multivariable stepwise logistic regression analysis, with the iterative entry of variables based on the test results ($P < 0.05$). Additionally, receiver operating characteristic (ROC) analysis was employed to determine the best cutoff values for the nCBV and EF features that proved to be significant predictors for differentiating true progression from pseudoprogression. Finally, leave-one-out cross-validation was used to validate the best predictor for differentiating between true progression and pseudoprogression.

Tissue diagnosis and genetic analysis are given in the Supplementary Material.

RESULTS

We enrolled 49 glioblastoma patients according to the inclusion and exclusion criteria (Fig. 1); 23 patients were classified in the true progression group and 26 patients in the pseudoprogression group. The MGMT promoter methylation status in the pseudoprogression group was greater than that in the true progression group (17 of 26 vs. 5 of 23, respectively; $P < 0.01$). The other clinical characteristics, including the radiation dose, age, sex, KPS, surgery method, and IDH 1/2 mutation status, were not significantly different between the two patient groups (all $Ps > 0.05$). The patient characteristics are detailed in Table 1.

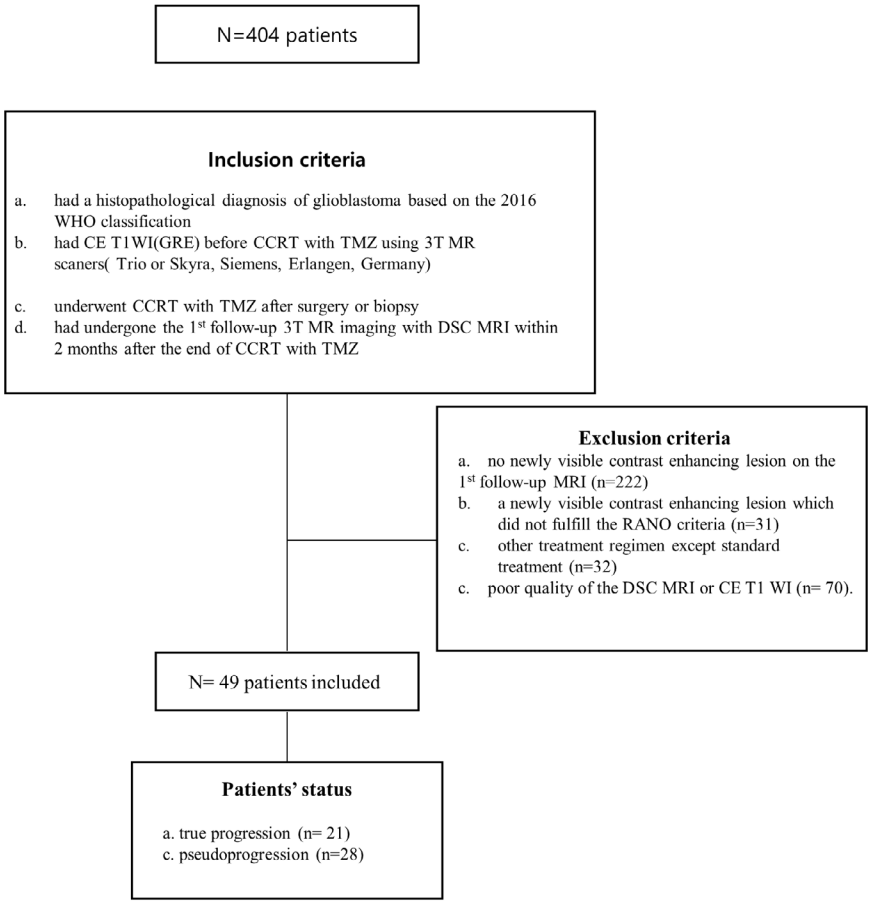

Fig. 1. Flowchart of the study population selection. CE T1WI(GRE) = contrast-enhanced T1 weighted image (gradient-echo); CCRT = concomitant chemoradiotherapy; DSC = dynamic susceptibility contrast; FLAIR = fluid-attenuated inversion recovery; TMZ = temozolomide; WHO = World Health Organization

Univariable and Multivariable Analysis and Validation of the Best Pharmacokinetic Predictor for Differentiating True Progression from Pseudoprogression

After univariable analysis, multivariable analysis which included MGMT, EF max, and nCBV 5th percentile values, showed significant differences between the true progression and pseudoprogression groups (Table 2). Multivariable stepwise logistic regression analysis showed that MGMT and EF max were independently differentiating variables (P = 0.004 and P = 0.02, respectively) (26).

ROC analysis yielded the best cutoff value of 95.75 for the EF max value for differentiating between the two groups of patients (sensitivity, 61%; specificity, 84.6%; the area under the ROC curve [AUC], 0.681 ± 0.08; 95% confidence interval [CI], 0.524-0.837; P = 0.03; Fig. 2). Representative cases are shown in Figures 3 and 4.

In the leave-one-out cross-validation of the EF max value, the cross-validated values for predicting true progression and pseudoprogression accuracies were 69.4% and 71.4%,

Table 2. Comparison of the Parametric Values of the True Progression and Pseudoprogression Groups

Parameters	True Progression (n = 23)	Pseudoprogression (n = 26)	P Value
Mean_EF	12.9 ± 10.9	9.8 ± 10.0	0.15
Median_EF	9.4 ± 8.6	7.2 ± 7.6	0.18
5 percentile_EF	1.4 ± 1.4	1.0 ± 1.4	0.23
95 percentile_EF	35.1 ± 29.6	27.2 ± 29.0	0.17
Min_EF	0.1 ± 0.1	0.1 ± 0.1	0.35
Max_EF	105.6 ± 64.7	63.8 ± 50.9	< 0.01
Mean_CBV	3.3 ± 1.4	3.9 ± 2.3	0.14
Median_CBV	2.7 ± 1.2	3.3 ± 2.3	0.1
5 percentile_CBV	0.6 ± 0.5	1.0 ± 1.0	0.05
95 percentile_CBV	8.2 ± 4.3	8.6 ± 4.2	0.36
Min_CBV	0.1 ± 0.1	0.3 ± 0.7	0.09
Max_CBV	15.1 ± 13.2	14.2 ± 8.1	0.4

Calculated using unpaired Student's t-test.

Table 1. Clinical Characteristic of the Study Population

Characteristic	Total (n = 49)	True progressiongroup (n = 23)	Pseudoprogressiongroup (n = 26)	P value
Mean age (y)	53 ± 12.8	51.4 ± 12.2	54.5 ± 13.4	0.2*
Sex				0.55†
Male	24	11	13	
Female	25	12	13	
Karnofsky Performance Scale score				0.11†
<70	12	8	4	
≥70	37	15	22	
Surgery				0.61‡
Biopsy	7	3	3	
Subtotal resection	7	2	5	
Gross total resection	35	17	18	
Mean radiation dose (Gy)	56.8 ± 7.3	56.2 ± 8.0	57.3 ± 6.8	0.29*
Methylated MGMT promoter				< 0.01†
Positive	22	5	17	
Negative	27	18	9	
IDH1/2 mutation				0.15†
Positive	3	0	3	
Negative	45	22	23	

IDH = isocitrate dehydrogenase; GTR = gross total resection; KPS = Karnofsky performance score; MGMT = O^6-methylguanine-DNA methyltransferase; STR = subtotal resection
Unless otherwise specified, the data represent the number of patients.
The data are expressed as means ± standard deviation.
*Calculated using unpaired Student's t-test.
†Calculated using Fisher's exact test.
‡Calculated using the chi-squared test.

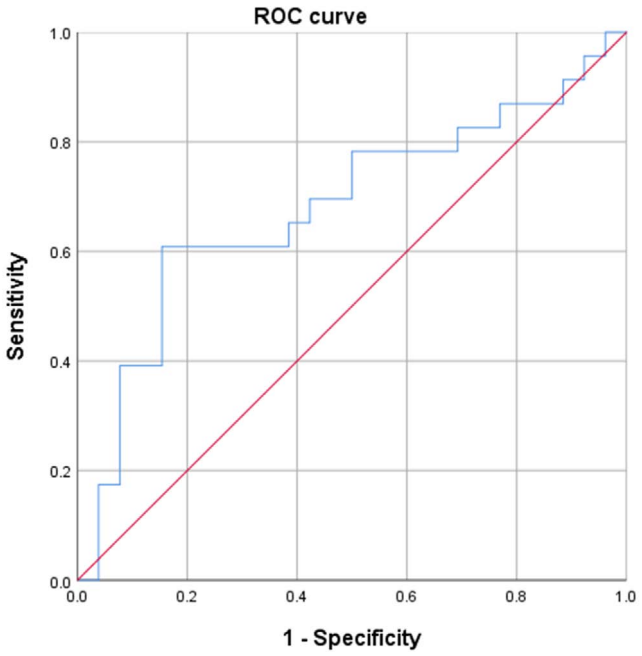

Fig. 2. ROC curve of the EF max value to differentiate between true tumor progression and pseudoprogression (AUC = 0.681). AUC = the area under the ROC curve; EF = extraction fraction

respectively.

DISCUSSION

In the present study, added value contrast leakage information from DSC MRI was analyzed to differentiate between true progression and pseudoprogression in glioblastoma patients after CCRT with TMZ. The significant finding of this study was that estimation of the contrast agent EF can help to differentiate between true progression and pseudoprogression. In particular, we found that the EF max value was higher in the true progression group than in the pseudoprogression group. The best cutoff of the EF max value from the ROC analysis was 95.75. Additionally, multivariable stepwise logistic regression analysis showed that the EF max value and MGMT promoter methylation status had higher diagnostic performance in differentiating the two groups of patients compared with nCBV.

Differentiating true progression from pseudoprogression in glioblastoma patients after CCRT with TMZ is an important clinical problem. In some reports, advanced MRI showed high levels of diagnostic accuracy in differentiating pseudoprogression from true progression, but these studies are generally retrospective, small and heterogeneous (27, 28). The underlying mechanism of pseudoprogression and true progression is the destruction of the blood-brain barrier (BBB), which causes an increase in the nonspecific contrast-enhancing lesion on MRI (29). Vascular permeability in pseudoprogression is likely secondary to proinflammatory mediators, direct endothelial damage, cellular hypoxia, and exaggerated radiation-induced reactive changes (30). Therefore, pseudoprogression is highly likely to be misdiagnosed, leading to inadequate treatment (29).

PWI is a method that reflects information on cerebral physiology at the capillary level (31). DSC MRI is a PWI technique in which the first pass of a bolus of gadolinium-based contrast agent through brain tissue is tracked using a series of T2- or T2*-weighted MR images (32). This technique is useful in discriminating between recurrent tumors and radiation-induced necrosis (33). DSC MRI provides map noninvasive measurements of relative CBV (rCBV), defined in brain tumors as the ratio between CBV within the tumor and CBV in the white matter of the contralateral hemisphere (31). The CBV parameter reflects angiogenesis; thus, it is elevated in tumors with a high rate of pathologic neoangiogenesis (31, 34). Several reports have demonstrated that CBV is significant in differentiating HGG recurrence from the posttreatment radiation effect (6, 35). In the present study, the 5th percentile of nCBV showed significance in differentiating between the two groups of patients (P = 0.05), but multivariable logistic regression demonstrated no relationship with an outcome of interest. Patients with treatment-induced necrosis showed lower CBV than those with recurrent tumor patients (36). Recurrent tumors are likely to show high VEGF expression, leading to high vascularization compared with radiation necrosis (37).

We used a contrast agent extravasation-correction method based on analysis of the tissue residue function (9) in this study. Initially, this method corrected only T1-dominant leakage and then was modified to correct T2*dominant leakage (9, 11). T2*-dominant leakage results in a positive tail, and T1-dominant leakage results in a negative tail in the residue function (9). The evaluation of perfusion theoretically is independent of leakage, change in the contribution of two relaxation effects postextravasation would directly affect the magnitude of the resulting EF value (9, 10). Thus, EF parameters from DSC-MRI cannot replace parameters from the DCE-MRI even if both were obtained using a contrast agent extravasation-correction method. Nevertheless, the EF may be a more sensitive parameter that is influenced by the T2* effect to contrast

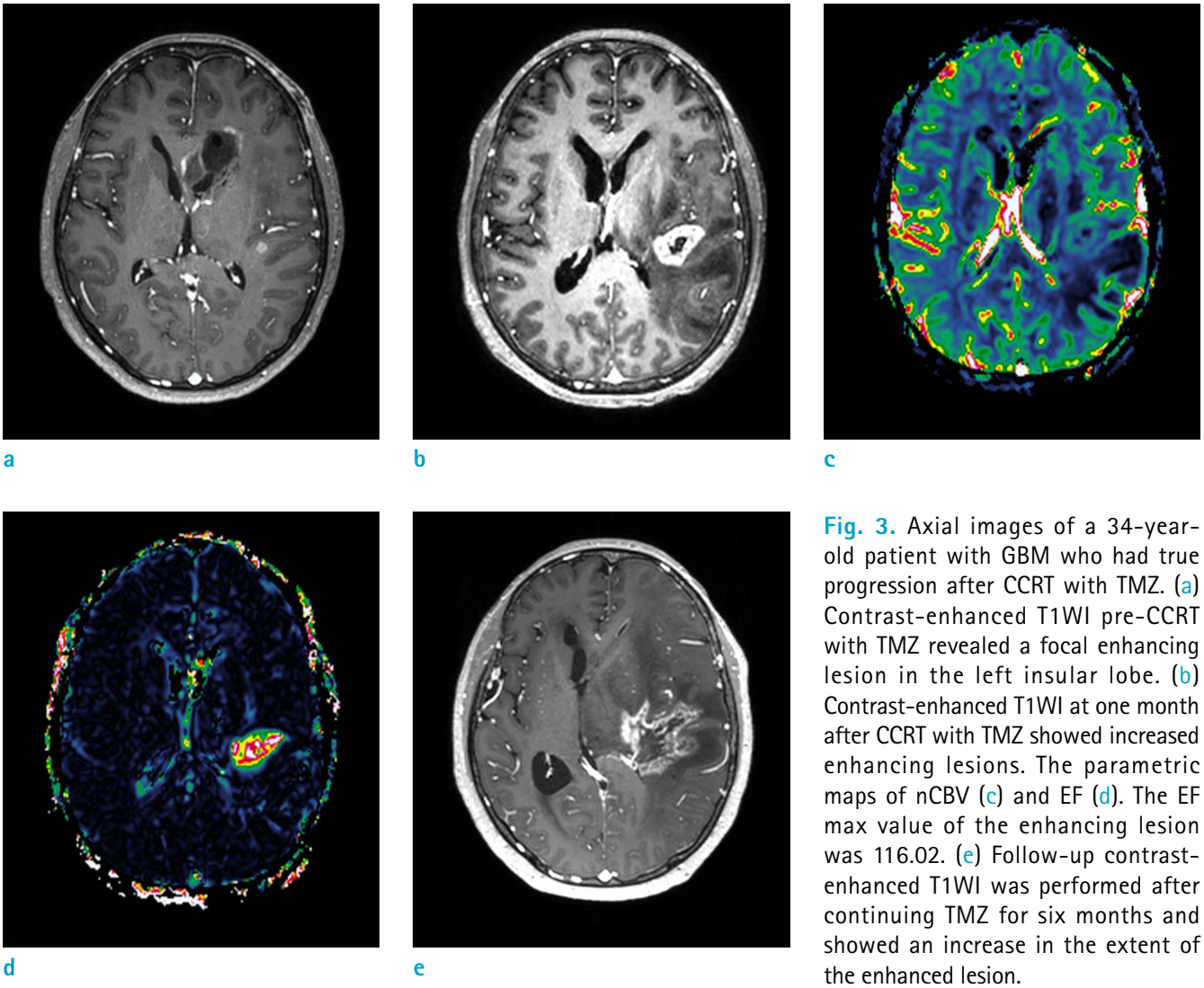

Fig. 3. Axial images of a 34-year-old patient with GBM who had true progression after CCRT with TMZ. (a) Contrast-enhanced T1WI pre-CCRT with TMZ revealed a focal enhancing lesion in the left insular lobe. (b) Contrast-enhanced T1WI at one month after CCRT with TMZ showed increased enhancing lesions. The parametric maps of nCBV (c) and EF (d). The EF max value of the enhancing lesion was 116.02. (e) Follow-up contrast-enhanced T1WI was performed after continuing TMZ for six months and showed an increase in the extent of the enhanced lesion.

leakage (10). Studies have demonstrated the opportunity for contrast leakage information parameters to predict prognosis after standard treatment in glioblastoma patients (10) and differentiate primary central nervous system lymphoma from glioblastoma (11).

Among the various genetic markers related to gliomas, the MGMT gene promoter is related to glioblastoma prognosis (38). MGMT encodes a protein that inhibits DNA repair by the treatment effect by removing alkyl groups from guanine, a target site for alkylating chemotherapy agents such as TMZ. Epigenetic silencing of the MGMT protein by promoter methylation may suppress the repair mechanism, consequently increasing the CCRT and TMZ cytotoxicity (39). Brandes et al. (40) showed that pseudoprogression was dependent on the methylated MGMT promoter. Similarly, in our study, 17 (77.3%) patients with a methylated MGMT promoter showed pseudoprogression ($P < 0.01$).

This study has several potential limitations. First, it was a retrospective study, which could have resulted in some sample selection bias and small sample size. Second, there lacked histological confirmation of pseudoprogression and true progression. Third, we semiautomatically drew ROIs using image-analysis software, which might have resulted in observer bias. However, we tried to draw the ROIs carefully, and all ROIs were checked by an expert (neuroradiologist). Fourth, in our study, DSC perfusion MRI protocols were used, which were acquired using dedicated protocols at our institute. Therefore, changing the imaging parameters may lead to different results.

In conclusion, our findings demonstrated that one dose of contrast agent can achieve combined perfusion- and permeability-related metrics from DSC MRI, which can

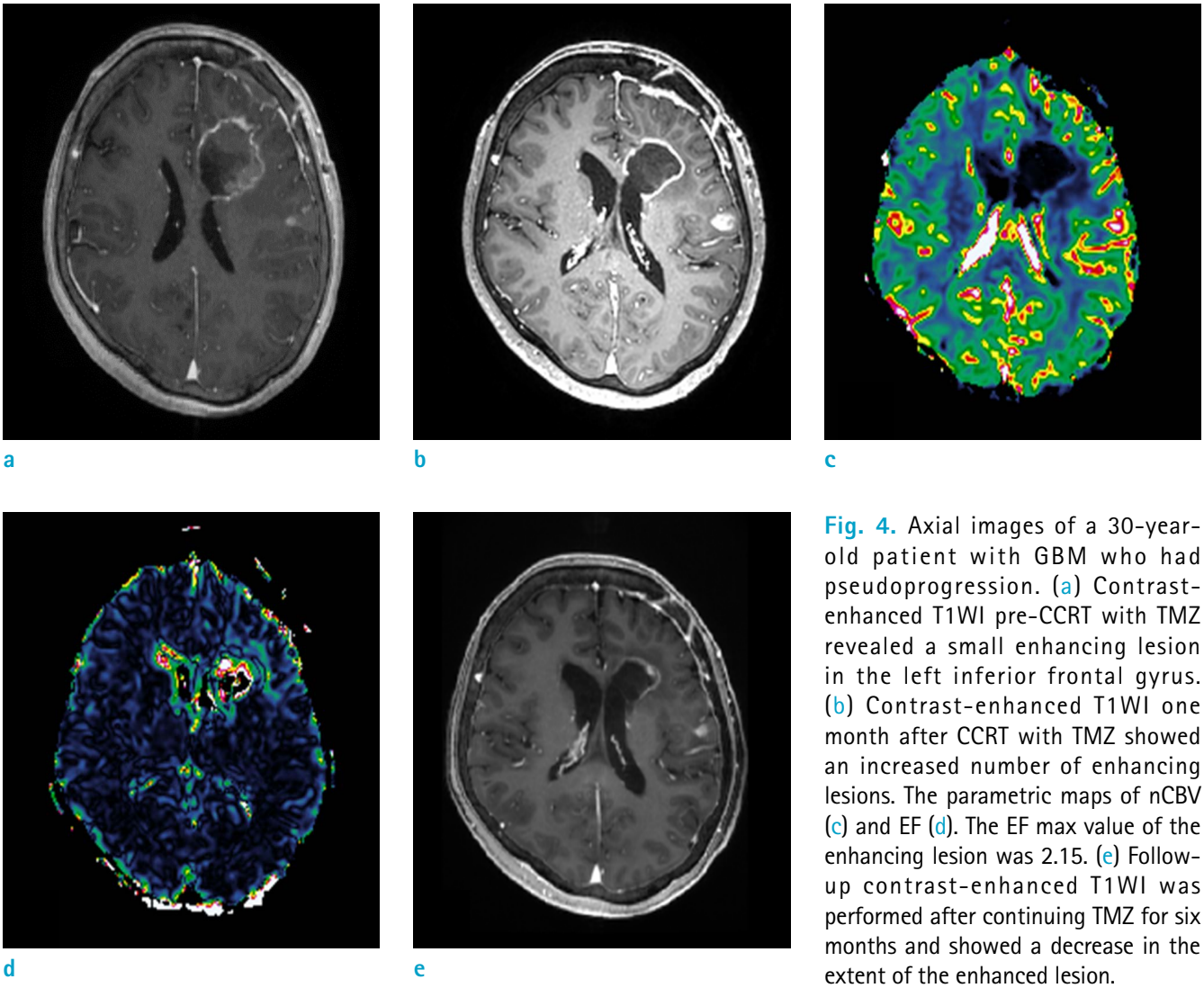

Fig. 4. Axial images of a 30-year-old patient with GBM who had pseudoprogression. (a) Contrast-enhanced T1WI pre-CCRT with TMZ revealed a small enhancing lesion in the left inferior frontal gyrus. (b) Contrast-enhanced T1WI one month after CCRT with TMZ showed an increased number of enhancing lesions. The parametric maps of nCBV (c) and EF (d). The EF max value of the enhancing lesion was 2.15. (e) Follow-up contrast-enhanced T1WI was performed after continuing TMZ for six months and showed a decrease in the extent of the enhanced lesion.

be easily used in clinical practice. Application of the EF max value can help differentiate true progression from pseudoprogression and therefore enable adequate treatment in glioblastoma patients after CCRT with TMZ.

Acknowledgments

This study was supported by a grant from the Korea Healthcare technology R&D Projects, Ministry for Health, Welfare & Family Affairs (HI16C1111), by the Brain Research Program through the National Research Foundation of Korea (NRF) funded by the Ministry of Science, ICT & Future Planning (NRF-2016M3C7A1914002), by Basic Science Research Program through the National Research Foundation of Korea (NRF) funded by the Ministry of Science, ICT & Future Planning (NRF-2020R1A2C2008949 and NRF-2020R1A4A1018714), by Creative-Pioneering Researchers Program through Seoul National University (SNU), and by the Institute for Basic Science (IBS-R006-A1).

Supplementary Material

The Supplement is available with this article at https://doi.org/10.13104/imri.2022.26.1.10

REFERENCES

1. de Groot JF. High-grade gliomas. Continuum (Minneap Minn) 2015;21:332-344
2. Ellingson BM, Chung C, Pope WB, Boxerman JL, Kaufmann TJ. Pseudoprogression, radionecrosis, inflammation or true tumor progression? challenges associated with glioblastoma response assessment in an evolving therapeutic landscape.

J Neurooncol 2017;134:495-504
3. Fajardo LF, Berthrong M, Anderson RE. Radiation pathology. New York: Oxford University Press, 2001
4. Hygino da Cruz LC Jr, Rodriguez I, Domingues RC, Gasparetto EL, Sorensen AG. Pseudoprogression and pseudoresponse: imaging challenges in the assessment of posttreatment glioma. AJNR Am J Neuroradiol 2011;32:1978-1985
5. Linhares P, Carvalho B, Figueiredo R, Reis RM, Vaz R. Early pseudoprogression following chemoradiotherapy in glioblastoma patients: the value of RANO evaluation. J Oncol 2013;2013:690585
6. Barajas RF Jr, Chang JS, Segal MR, et al. Differentiation of recurrent glioblastoma multiforme from radiation necrosis after external beam radiation therapy with dynamic susceptibility-weighted contrast-enhanced perfusion MR imaging. Radiology 2009;253:486-496
7. Würdinger T, Tannous BA. Glioma angiogenesis: towards novel RNA therapeutics. Cell Adh Migr 2009;3:230-235
8. Abbasi AW, Westerlaan HE, Holtman GA, Aden KM, van Laar PJ, van der Hoorn A. Incidence of tumour progression and pseudoprogression in high-grade gliomas: a systematic review and meta-analysis. Clin Neuroradiol 2018;28:401-411
9. Bjørnerud A, Sorensen AG, Mouridsen K, Emblem KE. T1- and T2*-dominant extravasation correction in DSC-MRI: part I--theoretical considerations and implications for assessment of tumor hemodynamic properties. J Cereb Blood Flow Metab 2011;31:2041-2053
10. Kim SH, Cho KH, Choi SH, et al. Prognostic predictions for patients with glioblastoma after standard treatment: application of contrast leakage information from DSC-MRI within nonenhancing FLAIR high-signal-intensity lesions. AJNR Am J Neuroradiol 2019;40:2052-2058
11. Lee B, Park JE, Bjørnerud A, Kim JH, Lee JY, Kim HS. Clinical value of vascular permeability estimates using dynamic susceptibility contrast MRI: improved diagnostic performance in distinguishing hypervascular primary CNS lymphoma from glioblastoma. AJNR Am J Neuroradiol 2018;39:1415-1422
12. Emblem KE, Bjørnerud A, Mouridsen K, et al. T(1)- and T(2)(*)-dominant extravasation correction in DSC-MRI: part II-predicting patient outcome after a single dose of cediranib in recurrent glioblastoma patients. J Cereb Blood Flow Metab 2011;31:2054-2064
13. Wang S, Martinez-Lage M, Sakai Y, et al. Differentiating tumor progression from pseudoprogression in patients with glioblastomas using diffusion tensor imaging and dynamic susceptibility contrast MRI. AJNR Am J Neuroradiol 2016;37:28-36
14. Young RJ, Gupta A, Shah AD, et al. MRI perfusion in determining pseudoprogression in patients with glioblastoma. Clin Imaging 2013;37:41-49
15. Wen PY, Macdonald DR, Reardon DA, et al. Updated response assessment criteria for high-grade gliomas: response assessment in neuro-oncology working group. J Clin Oncol 2010;28:1963-1972
16. Yin J, Sun H, Yang J, Guo Q. Comparison of K-means and fuzzy c-means algorithm performance for automated determination of the arterial input function. PLoS One 2014;9:e85884
17. Yan LF, Sun YZ, Zhao SS, et al. Perfusion, diffusion, or brain tumor barrier integrity: which represents the glioma features best? Cancer Manag Res 2019;11:9989-10000
18. Wong AM, Yan FX, Liu HL. Comparison of three-dimensional pseudo-continuous arterial spin labeling perfusion imaging with gradient-echo and spin-echo dynamic susceptibility contrast MRI. J Magn Reson Imaging 2014;39:427-433
19. Sanz-Requena R, Prats-Montalban JM, Marti-Bonmati L, et al. Automatic individual arterial input functions calculated from PCA outperform manual and population-averaged approaches for the pharmacokinetic modeling of DCE-MR images. J Magn Reson Imaging 2015;42:477-487
20. Rosen BR, Belliveau JW, Vevea JM, Brady TJ. Perfusion imaging with NMR contrast agents. Magn Reson Med 1990;14:249-265
21. Ostergaard L, Weisskoff RM, Chesler DA, Gyldensted C, Rosen BR. High resolution measurement of cerebral blood flow using intravascular tracer bolus passages. Part I: mathematical approach and statistical analysis. Magn Reson Med 1996;36:715-725
22. Kim JH, Choi SH, Ryoo I, et al. Prognosis prediction of measurable enhancing lesion after completion of standard concomitant chemoradiotherapy and adjuvant temozolomide in glioblastoma patients: application of dynamic susceptibility contrast perfusion and diffusion-weighted imaging. PLoS One 2014;9:e113587
23. Sourbron S, Ingrisch M, Siefert A, Reiser M, Herrmann K. Quantification of cerebral blood flow, cerebral blood volume, and blood-brain-barrier leakage with DCE-MRI. Magn Reson Med 2009;62:205-217
24. Boxerman JL, Schmainda KM, Weisskoff RM. Relative cerebral blood volume maps corrected for contrast agent extravasation significantly correlate with glioma tumor grade, whereas uncorrected maps do not. AJNR Am J Neuroradiol 2006;27:859-867
25. Kim JY, Yoon MJ, Park JE, Choi EJ, Lee J, Kim HS. Radiomics in peritumoral non-enhancing regions: fractional anisotropy and cerebral blood volume improve prediction of local progression and overall survival in patients with

glioblastoma. Neuroradiology 2019;61:1261-1272
26. Hauck WW, Miike R. A proposal for examining and reporting stepwise regressions. Stat Med 1991;10:711-715
27. Thust SC, van den Bent MJ, Smits M. Pseudoprogression of brain tumors. J Magn Reson Imaging 2018;48:571-589
28. Cha J, Kim ST, Kim HJ, et al. Differentiation of tumor progression from pseudoprogression in patients with posttreatment glioblastoma using multiparametric histogram analysis. AJNR Am J Neuroradiol 2014;35:1309-1317
29. Park HH, Roh TH, Kang SG, et al. Pseudoprogression in glioblastoma patients: the impact of extent of resection. J Neurooncol 2016;126:559-566
30. Boxerman JL, Ellingson BM, Jeyapalan S, et al. Longitudinal DSC-MRI for distinguishing tumor recurrence from pseudoprogression in patients with a high-grade glioma. Am J Clin Oncol 2017;40:228-234
31. Neska-Matuszewska M, Bladowska J, Sasiadek M, Zimny A. Differentiation of glioblastoma multiforme, metastases and primary central nervous system lymphomas using multiparametric perfusion and diffusion MR imaging of a tumor core and a peritumoral zone-Searching for a practical approach. PLoS One 2018;13:e0191341
32. Essig M, Shiroishi MS, Nguyen TB, et al. Perfusion MRI: the five most frequently asked technical questions. AJR Am J Roentgenol 2013;200:24-34
33. Soliman HM, ElBeheiry AA, Abdel-Kerim AA, Farhoud AH, Reda MI. Recurrent brain tumor versus radiation necrosis; can dynamic susceptibility contrast (DSC) perfusion magnetic resonance imaging differentiate? Egypt J Radiol Nucl Med 2018;49:719-726
34. Song YS, Choi SH, Park CK, et al. True progression versus pseudoprogression in the treatment of glioblastomas: a comparison study of normalized cerebral blood volume and apparent diffusion coefficient by histogram analysis. Korean J Radiol 2013;14:662-672
35. Hu LS, Baxter LC, Smith KA, et al. Relative cerebral blood volume values to differentiate high-grade glioma recurrence from posttreatment radiation effect: direct correlation between image-guided tissue histopathology and localized dynamic susceptibility-weighted contrast-enhanced perfusion MR imaging measurements. AJNR Am J Neuroradiol 2009;30:552-558
36. Jain R, Narang J, Schultz L, et al. Permeability estimates in histopathology-proved treatment-induced necrosis using perfusion CT: can these add to other perfusion parameters in differentiating from recurrent/progressive tumors? AJNR Am J Neuroradiol 2011;32:658-663
37. Jain R. Perfusion CT imaging of brain tumors: an overview. AJNR Am J Neuroradiol 2011;32:1570-1577
38. Kwon YW, Moon WJ, Park M, et al. Dynamic susceptibility contrast (DSC) perfusion MR in the prediction of long-term survival of glioblastomas (GBM): correlation with MGMT promoter methylation and 1p/19q deletions. Investig Magn Reson Imaging 2018;22:158-167
39. Binabaj MM, Bahrami A, ShahidSales S, et al. The prognostic value of MGMT promoter methylation in glioblastoma: a meta-analysis of clinical trials. J Cell Physiol 2018;233:378-386
40. Brandes AA, Franceschi E, Tosoni A, et al. MGMT promoter methylation status can predict the incidence and outcome of pseudoprogression after concomitant radiochemotherapy in newly diagnosed glioblastoma patients. J Clin Oncol 2008;26:2192-2197