Supplementary Material 1

Image Analysis

The location of the tumor was assessed and categorized according to the involvement of the frontal, parietal, temporal, occipital lobes, insula and deep gray matter (both the basal ganglia and thalamus). The presence of an enhancing portion, which was defined as a solid enhancing portion on the contrast-enhanced T1-weighted image, and the presence of a necrotic or cystic portion were evaluated. The T2 hypersignal intensity margin (HSIM) of the tumor was classified on axial T2-weighted images (T2WIs) at a slice where the T2 hyperintense signal area was the largest diameter and was categorized into the following four groups, based on the presence of well-defined HSIM in 1) over 90%, 2) 50–90%, 3) 10–50%, or 4) less than 10% of the margin. Additionally, the presence of a "T2-fluid attenuated inversion recovery (FLAIR) mismatch sign," represented as high signal intensity of the tumor on T2WI and a relatively low signal intensity on FLAIR except for the peripheral rim, which is a specific imaging finding in *isocitrate dehydrogenase (IDH)*-mutant and *chromosome arm* 1p/19q (1p/19q)-nondeleted lower grade glioma suggested by Patel et al. (1), was evaluated.

The regions of interest (ROIs), which were drawn on each resliced image, were multiplied by the MR image section thickness and the intersection gap to obtain the tumor volume per section. The entire tumor volume was calculated by adding the volume measurements of all the sections (2).

Image Analysis of Diffusion Weighted Imaging and Dynamic Susceptibility Contrast-Enhanced Perfusion-Weighted Imaging

The relative cerebral blood volume (CBV) and cerebral blood flow (CBF) were acquired with a software package that utilized a proven tracer kinetic model for the first-pass data (NordicICE, NordicNeuroLab). Realignment was done to minimize patient motion during the dynamic scans. A gamma-variate function estimates the first-pass response as it would appear in the lack of recirculation and was used to fit the 1/T2* curves to decrease the effects of recirculation. To decrease the contrast agent leakage effects, the dynamic curves were mathematically modified (3). After removing recirculation and leakage of the contrast agent, relative CBV and CBF were computed with numeric integration of the curve. To minimize the inconsistency in the relative CBV and CBF in an individual patient, the pixel-based relative CBV and CBF maps were normalized by dividing every value in a specific section by the value in the unaffected white matter of the contralateral side of the tumor to produce normalized CBV (nCBV) and CBF (nCBF) (4). In the same manner, normalized apparent diffusion coefficient (nADC) was used to minimize the bias from differences in the MR scanners.

After acquiring the total voxel values of the nCBV of each tumor, histogram analysis was done with the following measures. The nCBV, nCBF, and nADC histograms were plotted with nCBV on the x-axis with a bin size of 0.1, and the y-axis was demonstrated as a percentage of the total lesion volume by dividing the frequency in each bin by the total number of analyzed voxels. For the quantitative analysis, cumulative nCBV, nCBF, and nADC histograms were acquired from the histograms in which the cumulative number of observations in all of the bins up to the specified bin were mapped on the y-axis as a percentage. The mean nCBV and nCBF ± standard deviation, 95th, 90th, and 85th percentiles of the cumulative nCBV and nCBF were derived from the histograms (5). The mean nADC ± standard deviation and 5th, 10th, and 15th percentiles of the cumulative nADC histograms were derived from the nADC histograms (6-8).

In addition, the tumor signal intensity ratio between T2WI and FLAIR images (e.g., normalized T2 signal intensity, normalized FLAIR signal intensity) was calculated after normalization of the signal intensities on T2WI and FLAIR images by dividing the tumor signal intensities by the contralateral normal white matter signal intensities in each patient to compare and quantify the tumor signal intensity changes between T2WI and FLAIR. The voxel-wise tumor signal intensity ratio between T2WI and FLAIR images was obtained to quantify the "T2-FLAIR mismatch sign."

Supplementary Material 2

Molecular/Genetic Analysis

Immunohistochemical staining was performed using BenchMark XT (an automated immunohistochemical slide staining

system, Roche Diagnostics). Immunohistochemistry was performed on individual whole block sections using antibodies against IDH1 R132H mutant protein (H09, Dianova, 1:50), *epidermal growth factor receptor (EGFR)* SpectrumOrange/CEP7 SpectrumGreen dual-color probes (Abbott Molecular), and LSI 1p36 SpectrumOrange and 19q13 SpectrumGreen probes (Abbott Molecular) to determine the status of *IDH*, *EGFR* gene, and 1p and 19q chromosomes with fluorescence *in situ* hybridization using Vysis probes. *O6-alkylguanine DNA alkyltransferase (MGMT)* methylation-specific polymerase chain reaction, using a methylation EZ kit, was used to assess the methylation status of the *MGMT* promoter.

Supplementary Material 3

Interobserver Agreement

First, we listed patients in increasing order of the ADC_mean values and selected patients in every 3rd order to obtain a group of 26 patients. Another two radiologists (both with 7 years of experience in neuroradiology) drew ROIs of T2 hyperintense lesions on the FLAIR images of the selected group of patients and evaluated the presence of the T2-FLAIR mismatch sign. From these ROIs, the ADC_mean and CBV_mean values were calculated by using the dedicated software, and intraclass correlation coefficient (ICC) was calculated with the data acquired from three independent readers (one for the initial analysis and two additional readers). Interobserver reproducibility was considered poor (ICC, 0.00–0.20), fair to good (ICC, 0.40–0.75), or excellent (ICC, > 0.75) (9). Additionally, Pearson's chi-square test was utilized to identify significant accordance between the readers.

REFERENCES

- 1. Patel SH, Poisson LM, Brat DJ, Zhou Y, Cooper L, Snuderl M, et al. T2-FLAIR mismatch, an imaging biomarker for IDH and 1p/19q status in lower-grade gliomas: a TCGA/TCIA project. *Clin Cancer Res* 2017;23:6078-6085
- 2. Joe BN, Fukui MB, Meltzer CC, Huang QS, Day RS, Greer PJ, et al. Brain tumor volume measurement: comparison of manual and semiautomated methods. *Radiology* 1999;212:811-816
- 3. 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
- 4. Wetzel SG, Cha S, Johnson G, Lee P, Law M, Kasow DL, et al. Relative cerebral blood volume measurements in intracranial mass lesions: interobserver and intraobserver reproducibility study. *Radiology* 2002;224:797-803
- 5. Kim H, Choi SH, Kim JH, Ryoo I, Kim SC, Yeom JA, et al. Gliomas: application of cumulative histogram analysis of normalized cerebral blood volume on 3 T MRI to tumor grading. *PLoS One* 2013;8:e63462
- 6. Kang Y, Choi SH, Kim YJ, Kim KG, Sohn CH, Kim JH, et al. Gliomas: histogram analysis of apparent diffusion coefficient maps with standard- or high-b-value diffusion-weighted MR imaging--correlation with tumor grade. *Radiology* 2011;261:882-890
- 7. Song YS, Choi SH, Park CK, Yi KS, Lee WJ, Yun TJ, 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
- 8. Chu HH, Choi SH, Ryoo I, Kim SC, Yeom JA, Shin H, et al. Differentiation of true progression from pseudoprogression in glioblastoma treated with radiation therapy and concomitant temozolomide: comparison study of standard and high-b-value diffusion-weighted imaging. *Radiology* 2013;269:831-840
- 9. Büsing KA, Kilian AK, Schaible T, Debus A, Weiss C, Neff KW. Reliability and validity of MR image lung volume measurement in fetuses with congenital diaphragmatic hernia and in vitro lung models. *Radiology* 2008;246:553-561