Glioma: application of whole-tumour textural analysis of diffusion-weighted imaging for the evaluation of tumour heterogeneity

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Aims and objectives

Gliomas are the most common primary malignant brain neoplasms, ranging in grade from low to high[1]. Accurate grading of gliomas is critical for planning therapeutic strategies, assessing prognosis, and monitoring response to therapy [2, 3].

Currently, diffusion-weighted imaging (DWI) provides tumor characterization and has been used to differentiate high- from low-grade gliomas. A few recent reports have suggested that high-grade gliomas exhibit lower apparent diffusion coefficients (ADCs) [2, 4-7] because of higher tumor cellularity. Recently, Kang et al. revealed that the fifth percentile of the cumulative ADC histogram obtained at a high b value DWI was the most promising parameter for differentiating high- from low-grade gliomas [5].

However, fifth percentile of the cumulative ADC histogram reflects only small portion of tumor. Instead, texture analysis parameters such as entropy or homogeneity show entire tumor character and have the advantage of quantifying tumor heterogeneity noninvasively, something that cannot be achieved reliably by simple visual analysis. It is important to assess tumor heterogeneity because tumors with high intratumoral heterogeneity have been shown to have poorer prognosis, which could be secondary to intrinsic aggressive biology or treatment resistance [8].

Until now, some reports have been published regarding tumor heterogeneity in extracranial tumor using CT and MRI texture analysis. In esophageal cancer, B. Ganeshan et al. [9] found patients who had heterogeneous tumors with low uniformity and high entropy values assessed by CT texture analysis demonstrated poorer survival. Francesca Ng et al. [10] reveals CT texture features were associated with 5-year overall survival rate in patients with primary colorectal cancer. In addition, textural parameters reflecting tumor heterogeneity were associated with tumor metabolism, stage and prognosis in lung cancer on non-contrast-enhanced CT [11, 12]. In addition, texture analysis has been used in breast cancer to improve distinction between benign and malignant lesions using contrast-enhanced MRI [13].

To date, there have been a few published reports regarding glioma grading using a texture analysis of imaging data. Most of them were about applications of texture analysis to the characterization of brain tumors, for example, to discriminate glioblastoma multiforme from malignant glioneuronal tumors, and metastasis from gliomas [8, 14-16]. There are only a few reports about gliomas grading using texture analysis. A study of Karoline et al. [17] demonstrated the potential for CT texture analysis to quantify tumor heterogeneity in gliomas and showed a correlation between tumor heterogeneity and
tumor grade. In addition, Ananda et al [18] also revealed textural features extracted on T2-weighted images were highly discriminant between grade I and Grade III gliomas.

To the best of our knowledge, there have been no previous reports examining the ADC textural analysis parameters for the glioma grading. Thus, the purpose of our study was to explore the role of textural analysis of ADC maps based on entire tumor volume in determining the grade of gliomas and to identify the textural ADC parameter with the best diagnostic accuracy in glioma grading.
Methods and materials

This retrospective study was approved by the institutional review board of Seoul National University Hospital. The institutional review board waived the need for written informed consent from the participants.

Patient Selection

Eighty seven patients with astrocytic tumors who had undergone initial MR imaging at Seoul National University Hospital between October 2007 and January 2013 were selected from the radiology report database. Inclusion criteria were as follows: (a) a histopathologic diagnosis of astrocytic tumors according to the World Health Organization criteria, without oligodendroglial components, and (b) MR imaging performed with DW at standard b value prior to surgery or chemoradiotherapy. We excluded 47 patients due to the following reasons: (a) inadequate MR imaging quality due to substantial motion or susceptibility artifacts (n = 8), (b) MR imaging performed at 3 T (n = 38) and (c) too small size of the tumor to perform texture analysis (n = 1).

A total of 40 patients were included in the study. Among the 40 enrolled patients, eight, 10 and 21 exhibited WHO grade II astrocytomas, III anaplastic astrocytomas, and IV glioblastomas, respectively. Grade III astrocytomas and grade IV glioblastomas were classified as high-grade gliomas, while grade II astrocytomas were grouped as low-grade gliomas.

Image Acquisition

All MR images were obtained with a 1.5-T MR imager (Signa HDx or HDxt; GE Medical Systems, Milwaukee, Wis) with an eight-channel head coil. The imaging protocol included axial T2-weighted fast spin-echo (repetition time (TR)/echo time (TE), 5000/131 msec; 25 sections; FA, 90°; section thickness, 5 mm; intersection gap, 1 mm; field of view, 220 x 220 mm; matrix, 448 x 256; one acquired signal; echo train length, 16; voxel resolution, 0.5 x 0.9 x 5.0 mm) and axial T1-weighted spin-echo (TR/TE, 466/11 msec; FA, 70°; section thickness, 5 mm; intersection gap, 1 mm; field of view, 220 x 220 mm; matrix, 320 x 192; voxel resolution, 0.7 x 1.1 x 5 mm) or sagittal T1-weighted 3D inversion recovery fast spoiled gradient echo (TR/TE, 10/4.5 msec; FA, 20°; section thickness, 1 mm; intersection gap, 0 mm; field of view, 220 x 220 mm; matrix, 240 x 240; voxel resolution, 0.9 x 0.9 x 1 mm) sequences with axial and coronal reconstruction.

Echo-planar DW MR imaging (TR/TE, 10000/63 msec; b = 0 and 1000 sec/mm²; 35 sections; bandwidth, 1953 Hz per voxel; section thickness, 3 mm; intersection gap, 1 mm; field of view, 240 x 240 or 220 x 220 mm; matrix, 160 x 160; two acquired signals; voxel
resolution, 1.5 x 1.5 x 3.0 mm) was performed in the axial plane before the injection of contrast material.

DW MR images were acquired in three orthogonal directions and combined into a trace image. By using these data, ADC maps were calculated on a voxel-by-voxel basis with the software incorporated into the MR imaging unit.

T1-weighted sequences were repeated after the intravenous administration of a single dose of 0.1 mmol per kilogram of body weight and a rate of 4 mL/sec of gadopentetate dimeglumine (Magnevist; Bayer Schering Pharma, Berlin, Germany) or gadobutrol (Gadovist, Bayer Schering Pharma, Berlin, Germany).

**Volume Acquisition/ADC histograms**

The MR data for the ADC map were digitally transferred from the PACS workstation to a personal computer and processed with ImageJ (available at http://rsb.info.nih.gov/ij/) [19] and a software program developed in-house using Microsoft Visual C++ (Microsoft, Redmond, Wash).

ROIs that contained the entire tumor were drawn in each section of the ADC maps (Fig 1).
Fig. 1: Images of a 58-year-old woman with grade IV glioma show how ROIs were drawn on (b) ADC 1000 (b = 0 and 1000 sec/mm² map with reference to the (a) axial fast spin-echo T2-weighted MR image (5000/131). # = border of ROI.

References: Department of Radiology, Seoul National University Hospital - Seoul/KR

Tumor boundaries were defined with reference to the high-signal intensity areas thought to represent tumor tissue on the T2-weighted images by one author (S.H.C., a neuroradiologist with eight years of brain MR imaging experience) [20].

Definite areas of cystic, necrotic, or hemorrhagic areas were excluded. The data acquired from each section were summated to derive voxel-by-voxel ADCs for the entire tumor by using the software developed in-house.

ADC histograms were plotted with ADC values on the x-axis with a bin size of 1 x 10⁶ mm²/sec, and the percentage of the total lesion volume calculated by dividing the frequency in each bin by the total number of voxels analyzed on the y-axis. We also performed a cumulative analysis with the ADC histograms, in which the cumulative number of observations in all of the bins up to the specified bin was mapped onto the y-axis expressed as a percentage.

For the cumulative ADC histograms, the fifth percentile ADC value, which is the point at which 5% of the voxel values that form the histogram are found to the left in the histogram were generated [5, 21].

And 3 dimensional height map(3-D height map) of ADC signal intensity was generated using a software program developed in-house using Microsoft Visual C++ (Microsoft, Redmond, Wash) for representative ADC maps of grade II, III and IV, respectively.

Textural Analysis

Textural analysis from Gray Level Coocurrence Matrices (GLCM) is a way of extracting second order statistical texture features in the images (refer). In this study, we used 4 textural parameters for the quantitative analysis of 3-D textural parameters, GLCM entropy and GLCM homogeneity as well as skewness and kurtosis of image histogram. 3-D ROIs were analyzed with in-house software based on C++ with MFC (Microsoft Foundation Classes; Microsoft, Seattle, WA, USA), which was run on a personal computer.

For ROIs in the ADC map, textural parameters were determined as shown below: GLCM entropy, a parameter indicating both intensity and irregularity, GLCM homogeneity, indicating how close the image is to an uniform distribution of the grey levels. Higher entropy and lower homogeneity represent increased heterogeneity [22, 23].

Histopathologic Analysis
Immunohistochemistry was used to measure the Ki-67 labeling index. The routinely used formalin-fixed, paraffin-embedded tissue blocks were sectioned at 4-µm thickness and then used for immunohistochemistry.

The areas with the highest cellularity on inspection were selected and the Ki-67 labeling index was evaluated by the avidin-biotin complex immunohistochemical technique.

**Statistical Analysis**

All statistical analyses were performed with MedCalc software (version 12.6.1.0 for Microsoft Windows 2000/XP/Vista/7; MedCalc Software, Mariakerke, Belgium) and GraphPad InStat (version 3.05, 32 bits for Win 95/NT; GraphPad Software, San Diego, Calif). Results with P values less than .05 were considered to be significant.

To compare the textural parameters and histogram parameters of high- and low-grade gliomas, the unpaired Student t test and reciever operating characteristic (ROC) analysis were applied. In addition, one-way analysis of variance with post-hoc test and ROC analysis were performed to compare the parameters of each grade.

After determining the parameter demonstrating the highest diagnostic accuracy obtained through the above analyses, we planned to suggest a potential diagnostic algorithm that can differentiate the three different WHO glioma grades. Leave-one-out method was used and the Cochran's Q test was performed to compare the accuracies.

With a Pearson linear regression model, the mean ADC and the fifth percentile ADC values described above were correlated with the Ki-67 labeling index.
Images for this section:

**Fig. 1:** Images of a 58-year-old woman with grade IV glioma show how ROIs were drawn on (b) ADC 1000 (b = 0 and 1000 sec/mm² map with reference to the (a) axial fast spin-echo T2-weighted MR image (5000/131). # = border of ROI.

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Results

Table 1 summarizes the ADC texture and histogram parameters of low- and high-grade gliomas.

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<tr>
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<th>High grade (n=32)</th>
<th>p-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Entropy</td>
<td>6.261±0.412</td>
<td>6.861±0.539</td>
<td>0.006</td>
</tr>
<tr>
<td>Homogeneity</td>
<td>0.0303±0.0015</td>
<td>0.0315±0.0013</td>
<td>0.022</td>
</tr>
<tr>
<td>Skewness</td>
<td>0.082±0.176</td>
<td>0.582±0.669</td>
<td>0.045</td>
</tr>
<tr>
<td>Kurtosis</td>
<td>0.477±1.659</td>
<td>0.945±2.358</td>
<td>0.527</td>
</tr>
</tbody>
</table>

ADC (x10^-6mm^2/sec)

<table>
<thead>
<tr>
<th></th>
<th>Low grade (n=8)</th>
<th>High grade (n=32)</th>
<th>p-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>1327±322</td>
<td>1300±289</td>
<td>0.81</td>
</tr>
<tr>
<td>Fifth percentile</td>
<td>1030±185</td>
<td>836±235</td>
<td>0.037</td>
</tr>
</tbody>
</table>

Table 1: ADC texture and histogram parameters of low- and high-grade gliomas.
Note.-Values are the mean ± standard deviation. * Significant difference between two groups (P<.05). The difference between two groups was evaluated by using unpaired student’s t-test.

References: Department of Radiology, Seoul National University Hospital - Seoul/KR
In terms of the comparisons of multiple textural parameters, the entropy, homogeneity and skewness were significantly different between low- and high-grade gliomas. Entropy value was observed significantly higher in high grade gliomas than low grade tumors (6.861±0.539 vs 6.261±0.412, P=0.006). In addition, homogeneity was significantly higher in high grade gliomas than low grade tumors (0.0315±0.0013 vs 0.0303±0.0015, P=0.022). Higher skewness was observed in high grade gliomas than low grade tumors (0.582±0.669 vs 0.082±0.176, P=0.045). No significant difference was found between low- and high-grade gliomas with respect to kurtosis (P=0.527). In cumulative histogram
analysis, fifth percentile of cumulative histogram showed significant differences between high and low grade gliomas (836±235 vs 1030±185, \( P = 0.037 \)).

In table 2, ADC texture and histogram parameters of the grade II, III and IV gliomas are summarized.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Grade II (n=8)</th>
<th>Grade III (n=10)</th>
<th>Grade IV (n=22)</th>
<th>( p)-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Entropy</td>
<td>6.261±0.4120</td>
<td>6.295±0.4963</td>
<td>7.119±0.3165</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Homogeneity</td>
<td>0.0303±0.0015</td>
<td>0.0315±0.0014</td>
<td>0.0312±0.0013</td>
<td>0.074</td>
</tr>
<tr>
<td>Skewness</td>
<td>0.082±0.176</td>
<td>0.265±0.572</td>
<td>0.733±0.671</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Kurtosis</td>
<td>0.477±1.659</td>
<td>0.898±2.068</td>
<td>0.967±2.532</td>
<td>0.872</td>
</tr>
</tbody>
</table>

**Table 2:** ADC texture and histogram parameters of the grade II, III and IV gliomas.

Note.-Values are the mean ± standard deviation. * Significant difference between three groups (\( P < .05 \)), \( p\)-values were calculated using a one-way analysis of variance.

**References:** Department of Radiology, Seoul National University Hospital - Seoul/KR

Entropy proved to be significantly different significantly between grades II and IV (6.261±0.4120 vs 7.119±0.3165, \( P < 0.001 \)) and between grades III and IV (6.295±0.4963 vs 7.119±0.3165, \( P < 0.001 \)). Skewness differed significantly between grades II and IV (0.082±0.176 vs 0.733±0.671, \( P < 0.05 \)), but did not show a significant difference between grades III and IV (0.265±0.572 vs 0.733±0.671, \( P > 0.05 \)). However, no significant difference was observed among the grade II, III and IV gliomas with respect to homogeneity, kurtosis, mean ADC and fifth percentile ADC value (\( P > 0.05 \)).
Table 3 summarized the results of ROC analyses of entropy, homogeneity and fifth percentile ADC used to distinguish high- from low-grade gliomas (Fig. 2).

<table>
<thead>
<tr>
<th></th>
<th>Entropy</th>
<th>Homogeneity</th>
<th>Fifth percentile ADC</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC*</td>
<td>0.830 (0.676, 0.930)</td>
<td>0.738 (0.575, 0.864)</td>
<td>0.750 (0.588, 0.873)</td>
</tr>
<tr>
<td>Sensitivity(%)‡</td>
<td>78.1 (25/32)</td>
<td>56.3 (18/32)</td>
<td>59.4 (19/32)</td>
</tr>
<tr>
<td>Specificity(%)‡</td>
<td>87.5 (7/8)</td>
<td>75 (6/8)</td>
<td>87.5 (7/8)</td>
</tr>
<tr>
<td>Accuracy(%)‡</td>
<td>80 (32/40)</td>
<td>60 (24/40)</td>
<td>65 (26/40)</td>
</tr>
<tr>
<td>Cutoff value</td>
<td>&gt;6.501</td>
<td>&gt;0.031</td>
<td>≤859</td>
</tr>
<tr>
<td>P-value for ROC curve</td>
<td>0.0001</td>
<td>0.0124</td>
<td>0.0027</td>
</tr>
<tr>
<td>P-value for Cochran’s Q test of diagnostic accuracy</td>
<td>0.146</td>
<td></td>
<td></td>
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</table>

**Table 3:** ROC results for Entropy, Homogeneity and Fifth percentile of ADC histogram for glioma grading (low- vs. high-grade) Note.-* Data in parentheses are 95% confidence intervals. ‡Sensitivity and specificity for identifying high-grade tumors. **References:** Department of Radiology, Seoul National University Hospital - Seoul/KR
Fig. 2: ROC curves for texture parameters and Fifth percentile of ADC histogram for glioma grading (low- vs. high-grade)

References: Department of Radiology, Seoul National University Hospital - Seoul/KR

The entropy cutoff value of 6.501 exhibited a sensitivity, specificity and accuracy of 78.1% (25/32), 87.5% (7/8) and 80% (32/40), respectively. The sensitivity, specificity and accuracy were 56.3% (18/32), 75% (6/8) and 60% (24/40), respectively, by using the homogeneity cutoff value of 0.031. The fifth percentile ADC cutoff value of $859 \times 10^{-6}$ mm$^2$/sec exhibited sensitivity, specificity and accuracy of 59.4% (19/32), 87.5% (7/8) and 65% (26/40), respectively. There was no significant difference among the diagnostic accuracies of the entropy, homogeneity and fifth percentile ADC ($P= 0.146$) (Fig. 2). However, in leave-one-out method, entropy showed the highest diagnostic accuracy among the significant parameters including entropy, homogeneity and fifth percentile of ADC histogram (72.5% vs. 45% vs. 47.5% respectively). In addition, accuracy of entropy differed significantly from ones of homogeneity and fifth percentile of ADC histogram ($Cochran's Q = 13.059, P = 0.001$).

We performed ROC analyses of entropy for the differentiation between grade III and IV gliomas. The entropy cutoff value of 6.792 exhibited a sensitivity, specificity and accuracy of 81.8% (18/22), 90% (9/10) and 84.4% (27/32), respectively.
The entropy and the fifth percentile ADC values of the tumor revealed a significant relationship with Ki-67 labeling index ($R^2 = 0.1072, P = 0.039; R^2 = 0.2150, P = 0.003$, respectively) (Fig. 3).

**Fig. 3:** The correlation study of the Ki-67 labeling index (a) with the Entropy and (b) with fifth percentile of ADC using a linear regression model. The relationships were noted significantly. ($R^2 = 0.1072, P = 0.039; R^2 = 0.2150, P = 0.003$, respectively).

**References:** Department of Radiology, Seoul National University Hospital - Seoul/KR

Figure 4, 5 and 6 show representative ADC maps and histograms of grade II, III and IV, respectively.
Fig. 4: Images of a 43-year-old male with a grade II astrocytoma. (A) T2-weighted image, (B) ADC map, with corresponding (C) histogram of ADC, (D) cumulative ADC histogram and (E) 3-D height map of ADC signal intensity. The entropy value of ADC was 6.168.

References: Department of Radiology, Seoul National University Hospital - Seoul/KR
Fig. 5: Images of a 30-year-old male with a grade III anaplastic astrocytoma. (A) T2-weighted image, (B) ADC map, with corresponding (C) histogram of ADC, (D) cumulative ADC histogram and (E) 3-D height map of ADC signal intensity. The entropy value of ADC was 6.792.

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Fig. 6: Images of a 62-year-old male with a grade IV glioblastoma. (A) T2-weighted image, (B) ADC map, with corresponding (C) histogram of ADC, (D) cumulative ADC histogram and (E) 3-D height map of ADC signal intensity. The entropy value of ADC was 7.05.

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Fig. 5: Images of a 30-year-old male with a grade III anaplastic astrocytoma. (A) T2-weighted image, (B) ADC map, with corresponding (C) histogram of ADC, (D) cumulative ADC histogram and (E) 3-D height map of ADC signal intensity. The entropy value of ADC was 6.792.

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<tbody>
<tr>
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<td>1327±322</td>
<td>1177±334</td>
<td>1355±255</td>
<td>0.27</td>
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<tr>
<td>Fifth percentile</td>
<td>1030±185</td>
<td>881±261</td>
<td>815±226</td>
<td>0.088</td>
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Table 3: ROC results for Entropy, Homogeneity and Fifth percentile of ADC histogram for glioma grading (low- vs. high-grade) Note. - * Data in parentheses are 95% confidence intervals. †Sensitivity and specificity for identifying high-grade tumors.

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Conclusion

The results of our study suggest that the high entropy and high homogeneity of cumulative ADC histograms based on entire tumor volumes could be used to differentiate high-from low-grade gliomas, whereas the high entropy may be useful for the discrimination between grade III and grade IV gliomas. The diagnostic accuracy of the ADC entropy was significantly higher than that of the fifth percentile of ADC histogram in distinguishing high- from low-grade gliomas and ADC entropy was useful for differentiation of grade IV glioma from grade III glioma. Our study also showed the correlation of ADC entropy with glioma grade. Tumors are heterogeneous on both genetic and histopathological levels with intratumoral spatial variation in the cellularity, angiogenesis, extravascular extracellular matrix, and areas of necrosis [8]. Previous studies have also shown that increased tumor heterogeneity is associated with poor outcomes and adverse biological features such as intrinsic aggressive biopsy or treatment resistance for a range of tumors [9, 10, 12, 17].

The heterogeneity induced by ADC map texture analysis of gliomas is most likely related to irregular tumor vascular proliferation and tumor necrosis. Heterogeneous tumor vascularity in high grade glioma was established and may be used to differentiate high grade glioma from low glioma in many previous studies [4, 20, 24]. Heterogeneous tumor vascular proliferation leads to localized tumor hypoxia and necrosis in some area and localized angiogenesis and tumor proliferation in other area. In addition, these studies did not demonstrate significant difference of CBV between grade II and grade III gliomas, but the difference of CBV between grade III and IV was significant because of lack microvascular proliferation and absent necrosis of grade III glioma in histopathologic studies [4, 25]. In addition, Kang et al [5] found that grade IV gliomas showed a higher mean ADC than either grade II or grade III gliomas due to inclusion of microscopic areas of necrosis and partial volume-averaging effect of adjacent areas of necrosis. Our results also revealed the difference of entropy between grade III and IV was bigger than grade II and III, which supports increased ADC entropy in high grade glioma can be explained by irregular vascular proliferation.

Ki-67, a nuclear antigen specific for proliferating cells [27], is used for the evaluation of tumor proliferation and its positive relationships with higher cell density and tumor grade have been well-known in the astrocytic gliomas [28]. A few studies showed that minimum or fifth percentile values of ADC histogram correlated well with the Ki-67 labeling index, but relationship between mean ADC and the Ki-67 labeling index was insignificant in high-grade gliomas [29, 30]. Our results demonstrated fifth percentile values of ADC histrogram had a negative correlation with the Ki-67 labeling index in gliomas including low grade gliomas and entropy had a positive relationship with Ki-67 labeling index. Because an elevated Ki-67 labeling index correlates with tumor aggressiveness and entropy reflects
spatial irregularity, it is reasonable to explain the positive relationship between entropy and Ki-67 labeling index.

In addition, entropy may be representative of entire tumors. In previous studies, specific value such as minimum or fifth percentile of the cumulative ADC histogram was used to distinguish high- from low grade gliomas. However, specific feature values reflect only small portion of tumor. Instead, texture analysis parameters such as entropy or homogeneity show entire tumor character and have the advantage of quantifying tumor heterogeneity noninvasively.

Apart from the intrinsic limits of any retrospective study, our study has several limitations. First, only a small number of low-grade gliomas (n= 8) was included; however, it is well known that low-grade gliomas account for 10-15% of all adult primary intracranial tumors [24], which is very similar to our study setting. Further prospective study that includes a larger population is warranted to strengthen the statistical power. Second, tumor boundary was defined with reference to high signal intensity on T2W images and tumor infiltration as well as peri-tumoral edema was included in the ROIs. However, the differentiation between these two components is impossible in the imaging studies. Third, despite the exclusion of any visible foci of suspected artifacts on the ADC map from the ROI measurements [5, 31], the possibility of including extreme ADCs resulting from DW MR imaging and ADC map misregistration artifacts remains. Texture analysis parameters obtained from ADC map can be presumed to be less affected by these artifacts and, therefore, seems to be a more reliable histogram parameter than specific percentile of cumulative ADC histogram such as minimum or fifth percentile.

In conclusion, this study reveals that the entropy of ADC histogram could be used for distinguishing high- from low-grade gliomas, and grade IV from III gliomas with diagnostic accuracies of 80% and 84.4%, respectively.
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