Apparent diffusion coefficient histogram analysis for prediction of prognosis in glioblastoma

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**A R T I C L E   I N F O**

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**ABSTRACT**

Background. – To investigate the potential to predict prognosis of glioblastoma (GBM) patients by analysis of the broader and lower values in the lower distribution of apparent diffusion coefficient (ADC) values in the ADC histogram.

Background. – Presurgical publicly available diffusion-weighted images (DWI) and contrast-enhanced T1-weighted images from 76 GBM patients were analyzed. With applied 2-mixture normal distribution in the ADC histogram of enhanced lesions on T1-weighted images, the mean and width of ADC\textsubscript{L} were analyzed. We dichotomized the lower mean of ADC\textsubscript{L} (L-ADC\textsubscript{L}) and the broader width of ADC\textsubscript{L} (B-ADC\textsubscript{L}) at their own average. B&L-ADC\textsubscript{L} was defined as B-ADC\textsubscript{L} with L-ADC\textsubscript{L}. Progression-free survival (PFS) and overall survival (OS) were determined by using Cox proportional hazards analysis and the Kaplan–Meier method with the log-rank test. The difference between PFS and OS was calculated.

Results. – Six (7.89%) patients had B&L-ADC\textsubscript{L} values. B&L-ADC\textsubscript{L} was strongly associated with poor PFS (hazard risk: 5.747; \( P < 0.002 \)) and OS (hazard risk: 3.331; \( P < 0.018 \)). There were significant differences in PFS (median, 77 vs. 302 days; \( P < 0.001 \)) and OS (median, 199 vs. 472 days; \( P = 0.004 \)) between the patients with and without B&L-ADC\textsubscript{L}. There was no significant difference in the OS–PFS duration difference between the patients with (median, 79 days) and without B&L-ADC\textsubscript{L} (median, 132 days) (\( P = 0.348 \)).

Conclusion. – In this study, B&L-ADC\textsubscript{L} from pretreatment ADC analysis predicted poor PFS. B&L-ADC\textsubscript{L} may indicate higher cellularity and heterogeneity in GBM tumor tissue.

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**Introduction**

Glioma, which is subdivided into tumor grades I to IV by the World Health Organization, is the most common malignant brain tumor \[1,2\]. Glioblastoma (GBM), which is the highest glioma tumor grade, is the most aggressive type. In previous reports, the median progression-free survival (PFS) has ranged from 7.4 to 13.3 months, and the median overall survival (OS) has ranged from 15.5 to 19.8 months, which are quite short \[3,4\]. Although several reports have stated that oxygen 6-methylguanine-DNA-methyltransferase (MGMT) promoter methylation could be a prognostic factor for longer survival and good response to chemotherapy \[5,6\], the median PSF and OS have been reported to be <2 years at 10.9 months and 20.5 months, respectively \[7\].

Previous studies have demonstrated that histogram analysis of the apparent diffusion coefficient (ADC) by magnetic resonance imaging (MRI) was effective for prediction of prognosis in GBM patients \[8–12\]. Pope et al. proposed to analyze the average and proportion in the lower ADC histogram of a 2-mixture normal distribution, and they concluded that the lower mean of the lower distribution was effective for prediction of prognosis in GBM patients \[8–10\].

The tissue heterogeneity of gliomas increases with increasing tumor grade \[13\]. Hempel et al. reported mean kurtosis value for stratifying glioma by assessing tumor heterogeneity \[14\]. In addition, survival should be shorter with increasing grade \[15\]. Hence, we hypothesized that the lower distribution of ADC values of the applied 2-mixture normal distribution in the ADC histogram (ADC\textsubscript{L}), which includes the ADC values that are broader and lower than the means, may indicate GBM tissue heterogeneity and could

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**Abbreviations:** ADC, apparent diffusion coefficient; ADC\textsubscript{L}, the lower distribution of the applied 2-mixture normal distribution in ADC histogram; B-ADC\textsubscript{L}, broader values in ADC\textsubscript{L}; B&L-ADC\textsubscript{L}, broader and lower values in ADC\textsubscript{L}; L-ADC\textsubscript{L}, lower values in ADC\textsubscript{L}; DICOM, Digital Imaging and Communications in Medicine; DWI, diffusion-weighted imaging; GBM, glioblastoma; IQR, interquartile range; MGMT, oxygen 6-methylguanine-DNA-methyltransferase; OS, overall survival; PFS, progression-free survival; TCI, the Cancer Imaging Archive.

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be used to predict poor prognosis. Therefore, the purpose of this study was to investigate the potential to predict prognosis of GBM patients by analysis of the broader and lower values in the ADC$_L$ (B&L-ADCL).

Materials and methods

Patients

Digital Imaging and Communications in Medicine (DICOM) data of the GBM patients were collected by the staff of Henry Ford Hospital, University of California San Francisco, MD Anderson Cancer Center, Emory University, and Thomas Jefferson University Hospital. The data have been published online by the Cancer Imaging Archive (TCIA) (http://www.cancerimagingarchive.net/). Additionally, the clinical information of the GBM patients also has been published online by the Cancer Genome Atlas (https://portal.gdc.cancer.gov/). We collected the DICOM data and clinical information of the GBM patients; therefore, approval from our institutional review board or Health Insurance Portability and Accountability Act was not required for this study. The DICOM data of 262 patients were accessible on the TCIA website. Incomplete diffusion-weighted imaging (DWI) images with b-values of 1000 s/mm$^2$ and of 0 s/mm$^2$ and contrast-enhanced T1-weighted images at baseline (n = 134); geometric mismatches between the DWI and contrast-enhanced T1-weighted images, including motion artifacts (n = 48); severe metal artifacts of the DWI images (n = 2); no clinical information (n = 1); and incomplete survival data (n = 1) were excluded. Finally, a total of 76 patients from December 2008 to September 2013 were enrolled in this study. OS was defined as the number of days between the initial pathological diagnosis and death. PFS was defined as the number of days between the initial treatment and new tumor event [16]. The duration difference between PFS and OS was calculated. Shorter survival was also defined as <25th percentile in PFS or OS. MGMT statuses were obtained from Table S7 (patient characteristics) in the supplemental Information by Brennan et al. report [17]. Since, we only obtained MGMT status in 59% (45 of 76 patients) GBM patients, we analyzed the associations between the results of ADC histogram analysis and overall patients (n = 76) or patients with obtained MGMT status (n = 45). The characteristics of the 76 patients are summarized in Table 1.

### Table 1

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)*</td>
<td>57.5 (50.0, 66.0)</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>47 (61.8)</td>
</tr>
<tr>
<td>Female</td>
<td>29 (38.2)</td>
</tr>
<tr>
<td>Progression-free survival (day)*</td>
<td>195.5 (90.0, 392.0)</td>
</tr>
<tr>
<td>Overall survival (day)*</td>
<td>371.0 (210.8, 553.8)</td>
</tr>
<tr>
<td>Karnofsky performance status 100%</td>
<td></td>
</tr>
<tr>
<td>100%</td>
<td>17 (27.4)</td>
</tr>
<tr>
<td>90%</td>
<td>2 (3.2)</td>
</tr>
<tr>
<td>80%</td>
<td>33 (53.2)</td>
</tr>
<tr>
<td>60%</td>
<td>10 (16.2)</td>
</tr>
<tr>
<td>Not available</td>
<td>15</td>
</tr>
<tr>
<td>Tumor size (cm$^2$)</td>
<td>6.91 ± 4.49</td>
</tr>
<tr>
<td>MGMT status</td>
<td></td>
</tr>
<tr>
<td>Methylated</td>
<td>22 (48.9)</td>
</tr>
<tr>
<td>Unmethylated</td>
<td>23 (51.1)</td>
</tr>
<tr>
<td>Not available</td>
<td>31</td>
</tr>
</tbody>
</table>

KPS: Karnofsky performance status; MGMT: oxygen 6-methylguanine-DNA-methyltransferase.

### ADC histogram analysis

The lesion with the largest diameter was selected in the patients with multiple brain lesions on the contrast-enhanced T1-weighted images. In addition, we assessed the slice on which a target lesion appeared to be the largest on the images. A radiologic technologist with 9 years’ experience manually extracted the entire enhanced lesion without the cystic or necrotic area on contrast-enhanced T1-weighted images by using the image editor tool Paint (Microsoft Corp., Redmond, WA) and the adjust-color threshold function of ImageJ (NIH Image, Bethesda, MD). The tumor size was defined as the area of pixels extracted by the manual procedure.

ADC values were calculated by using software written in C++ (Visual Studio 2013 Community Edition, Microsoft, Redmond, WA) according to eq. 1:

$$\text{ADC value} = -\left[ \ln \left( \frac{S_{b1000}}{S_{b0}} \right) \right] / 1000 \quad (1)$$

where $S_{b1000}$ is the signal intensity at a b-value of 1000 s/mm$^2$, and $S_{b0}$ is the signal intensity at a b-value of 0 s/mm$^2$ on a pixel-by-pixel basis. ADC values with manually extracted regions were used for the histogram analysis with an applied 2-mixture normal distribution [8–10]. The mean and width of ADC$_L$ were calculated by using commercially available software (JMP Pro, version 12.2; SAS Institute, Cary, NC). We dichotomized the mean and width of ADC$_L$ and averaged the tumor size (6.91 cm$^2$) classifiers; therefore, the lower ADC$_L$ (1-ADC$_L$) value was represented as the mean of ADC$_L$ < 1.048 × 10$^{-3}$ mm$^2$/s and the broader value in ADC$_L$ (2-ADC$_L$) was represented as the width of ADC$_L$ > 0.174 × 10$^{-3}$ mm$^2$/s. Additionally, we defined B&L-ADCL as if the mean and width of ADC$_L$ were for B-ADCL and L-ADCL simultaneously.

### Association between results of ADC histogram analysis and shorter survival

The mean and width of ADC$_L$ were divided into four quadrants by the threshold of B&L-ADCL. The proportion of poor prognosis was calculated in each quadrant.

### Statistical analysis

Continuous data were expressed as the means ± standard deviation or as the median and interquartile range (IQR) (25th to 75th percentile; quartile 1, quartile 3). A test of the proportional hazards assumption was used after fitting univariate Cox models, and 95% confidence intervals were generated. PFS, OS, and the duration difference between PFS and OS were estimated by using the Kaplan–Meier method and compared by using the log-rank test. Association between B&L-ADCL or not and MGMT status was analyzed using the Pearson chi-squared test. The mean of ADC$_L$ with a methylated MGMT promoter was compared to that with an unmethylated MGMT promoter by the two-tailed unpaired t-test. All statistical analyses were performed by using JMP Pro, version 12.2 (SAS Institute, Cary, NC), and a P value < 0.05 was considered as indicating statistical significance.

### Results

#### Patient characteristics

Table 1 shows the baseline characteristics in the 76 GBM patients. The mean of ADC$_L$ was $1.048 ± 0.253 × 10^{-3}$ mm$^2$/s, and the width of the ADC$_L$ was $0.174 ± 0.101 × 10^{-3}$ mm$^2$/s. We analyzed six (7.89%) patients as B&L-ADCL. The tumor size was $6.91 ± 4.49$ cm$^2$. Please cite this article in press as: Kondo M, Uchiyama Y. Apparent diffusion coefficient histogram analysis for prediction of prognosis in glioblastoma. J Neuroradiol (2017). https://doi.org/10.1016/j.neurad.2017.11.011.
**PFS and OS of patients with and without B&L-ADC**

In PFS, B&L-ADC was a significant predictor of poor prognosis in the univariate analysis \((P=0.002; \text{Table 2})\). There was a significant difference in PFS between patients with and without B&L-ADC (median, 77 days vs. 302 days; \(P<0.001\; \text{Fig. 1a}\)). For OS, B&L-ADC was also the only significant predictor of poor prognosis in the univariate analysis \((P=0.018; \text{Table 3})\). There was a significant difference in OS between patients with and without B&L-ADC (median, 199 days vs. 472 days; \(P=0.004; \text{Fig. 1b}\)). A representative case with B&L-ADC is described in Fig. 2.

**Table 2**
Cox proportional hazards analysis of potential prognostic factors influencing PFS in all patient.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Univariate analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Hazard risk (95% CI)</td>
</tr>
<tr>
<td>Age &gt; 57.4 years</td>
<td>1.227 (0.773–1.955)</td>
</tr>
<tr>
<td>Gender female</td>
<td>0.721 (0.445–1.148)</td>
</tr>
<tr>
<td>KPS &lt; 80</td>
<td>1.088 (0.523–2.012)</td>
</tr>
<tr>
<td>Tumor size &gt; 6.91 cm(^3)</td>
<td>1.468 (0.921–2.338)</td>
</tr>
<tr>
<td>L-ADC(_{1})</td>
<td>1.453 (0.917–2.302)</td>
</tr>
<tr>
<td>B-ADC(_{1})</td>
<td>1.215 (0.757–1.923)</td>
</tr>
<tr>
<td>B&amp;L-ADC(_{1})</td>
<td>5.747 (2.128–13.148)</td>
</tr>
<tr>
<td>MGMT status</td>
<td>1.074 (0.584–1.977)</td>
</tr>
</tbody>
</table>

ADC\(_{1}\): the lower distribution of the applied 2-mixture normal distribution in ADC histogram; B-ADC\(_{1}\): broader values in ADC; B&L-ADC\(_{1}\): broader and lower values in ADC\(_{1}\); CI: confidence interval; KPS: Karnofsky performance status; L-ADC\(_{1}\): lower values in ADC; MGMT: oxygen 6-methylguanine-DNA-methyltransferase; PFS: progression-free survival.

**Table 3**
Cox proportional hazards analysis of potential prognostic factors influencing OS in all patient.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Univariate analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &gt; 57.4 years</td>
<td>1.236 (0.750–2.045)</td>
</tr>
<tr>
<td>Gender female</td>
<td>1.100 (0.647–1.828)</td>
</tr>
<tr>
<td>KPS &lt; 80</td>
<td>1.353 (0.619–2.629)</td>
</tr>
<tr>
<td>Tumor size &gt; 6.91 cm(^3)</td>
<td>1.408 (0.854–2.343)</td>
</tr>
<tr>
<td>L-ADC(_{1})</td>
<td>1.294 (0.787–2.147)</td>
</tr>
<tr>
<td>B-ADC(_{1})</td>
<td>1.014 (0.593–1.689)</td>
</tr>
<tr>
<td>B&amp;L-ADC(_{1})</td>
<td>3.311 (1.251–7.321)</td>
</tr>
<tr>
<td>MGMT status</td>
<td>1.082 (0.567–2.079)</td>
</tr>
</tbody>
</table>

ADC\(_{1}\): the lower distribution of the applied 2-mixture normal distribution in ADC histogram; B-ADC\(_{1}\): broader values in ADC; B&L-ADC\(_{1}\): broader and lower values in ADC\(_{1}\); CI: confidence interval; KPS: Karnofsky performance status; L-ADC\(_{1}\): lower values in ADC; MGMT: oxygen 6-methylguanine-DNA-methyltransferase; OS: overall survival.

**Fig. 1.** Kaplan–Meier curves of progression-free survival (PFS) and overall survival (OS) determined by apparent diffusion coefficient (ADC) histogram analysis. A. PFS was compared between patients with (red solid line) and without (blue dashed line) broader and lower values in the lower distribution of ADC (B&L-ADC\(_{1}\)). B. OS was also compared.

**Fig. 2.** Apparent diffusion coefficient (ADC) histogram analysis for a 62-year-old man with a glioblastoma. A. Contrast-enhanced T1-weighted image. B. The corresponding contoured enhanced region. C. The corresponding ADC map. D. The ADC histogram obtained by using a 2-mixture normal distribution (red line). In the lower distribution of the ADC (ADC\(_{1}\)), the lower value (mean of ADC\(_{1}\); \(1.039 \times 10^{-3}\) mm\(^2/\)s) had broader values (width of ADC\(_{1}\); 0.293 \(\times 10^{-3}\) mm\(^2/\)s); therefore, we analyzed the broader and lower values (B&L-ADC\(_{1}\)). Oxygen 6-methylguanine-DNA-methyltransferase (MGMT) state was unmethylated. PFS was 80. Progression-free survival (PFS) and overall survival (OS) were 145 days and 313 days, respectively.

**OS–PFS duration difference between the patients with and without B&L-ADC\(_{1}\)**

There was no significant difference in the OS–PFS duration difference between the patients with B&L-ADC\(_{1}\) (median, 79 days; IQR, 0, 228 days) and the patients without B&L-ADC\(_{1}\) (median, 132 days; IQR, 56, 273 days; \(P=0.348\)).

**Distribution of results in ADC histogram analysis and shorter survival**

Sixty-seven percent of patients in the first quadrant of the mean and width of ADC\(_{1}\) had shorter PFS or OS (Fig. 3). Patients in the first quadrant were analyzed as B&L-ADC\(_{1}\). The proportions in other quadrants were < 32% in PFS and OS.
Discussion

In this study, we found that B&L-ADCL was a predictor of poor prognosis in GBM patients and was superior to the use of L-ADCL alone. The median PFS and OS in the GBM patients with B&L-ADCL were quite short at 2.5 months (77 days) and 6.6 months (199 days), respectively. There was no significant difference in the OS–PFS difference between the patients with B&L-ADCL and those without B&L-ADCL. In addition, the P value determined by the log-rank test was smaller for PFS (P < 0.001) than for OS (P = 0.006) in the comparison of the survivals between the patients with and without B&L-ADCL. Consequently, we found that B&L-ADCL was a predictor of short PFS in the GBM patients in this study.

The growth rate of glioma tumor tissue with higher cellularity has been shown to be faster than that of tissue with lower cellularity in mouse models [18]. Schmainda et al. reported that lower ADC values indicated higher tumor cellularity in gliomas [19]. Hence, our results showed that B&L-ADCL values, which indicate higher tumor cellularity, could be predictive of a faster tumor tissue growth rate in GBM patients. In addition, tumor heterogeneity may account for resistance to treatments [20] and has been reported in GBM [21]. Ryu et al. reported that entropy (indicated both intensity and irregularity) of ADC map could potentially be used to measure tumor heterogeneity in gliomas [22]. Consequently, B&L-ADCL calculated on ADC histogram may predict poor PFS because B&L-ADCL appears to indicate a faster GBM tumor tissue growth rate and resistance to treatments.

Although we only dichotomized six patients using B&L-ADCL, we believe it has potential to provide valuable clinical information. In fact, 67% of patients who were analyzed as B&L-ADCL were in < 25th percentile in PFS or OS. In contrast, in the outsize of B&L-ADCL, the largest proportion of patients with poor prognosis was 32%. Those results support our hypotheses that ADC values that are broader and lower than the mean may indicate GBM tissue heterogeneity and could be used to predict poor prognosis as appropriate.

In our results, L-ADCL, alone, which was described as low ADC [8], lower ADCL [9], low ADCL-T [10,11] in previous reports, was not a significant predictor of either PFS or OS in the univariate analysis. Although the results differed from those in a previous report [10] and from those of other previous reports of bevacizumab-treated patients [8,9]; they were consistent with the results of one report [11] and with the results for the patients in the reports above who were not treated with bevacizumab before tumor recurrence [8,9].

In the relationship between MGMT status and GBM patients’ prognosis, a methylated MGMT promoter is a better predictor of outcome not only in alkylating chemotherapy (temozolomide)-treated GBM patients [5] but also in radiotherapy in the absence chemotherapy-treated GBM patients [6]. In contrast, our results found that MGMT status was not a significant prognostic factor in either PFS or OS. Although the reason for this discrepancy is unclear, we perhaps underestimated the potential of MGMT status to predict survival in GBM patients because we only obtained MGMT status in 59% (45 of 76) of patients. In our data for patients with obtained MGMT status (n = 45), the proportion of patients with methylated (n = 22) and unmethylated (n = 23) MGMT promoter was equivalent. Hence, there was no significant association between MGMT status and PFS and OS in the 45 patients. Although we do not know the reason for this, we propose a plausible hypothesis to explain this difference from previous reports [5; 6; 7]. MGMT status is a better prognostic factor, so nonuniform treatment protocols might influence PFS and OS, especially in longer survival. In contrast,
B&L-ADCl may indicate faster tumor tissue growth rate and treatment resistance. Therefore, nonuniform treatment protocols would have less impact on an association between GBM patients’ proges and B&L-ADCl. and we were successful in demonstrating that B&L-ADCl was associated with outcome in all patients (n = 76) as well as in those with obtained MGMT status (n = 45).

In the relationship between MGMT status and ADC histogram parameters, Pope et al. reported that the mean of ADCl was significantly lower in patients with methylated MGMT promoter [9], and they concluded that L-ADCl was a better prognostic factor in bevacizumab-treated patients. In contrast, they reported that PFS and OS in patients with L-ADCl were poor outcome predictors in bevacizumab-treated patients [10]. In our data for patients with obtained MGMT status, the mean of ADCl was also significantly lower in those with methylated MGMT promoter. Hence, we proposed two concerns. First, the mean of ADCl might have potential as an image biomarker for predicting MGMT status. Second, conflicts of predicting outcome using L-ADCl may arise without analyzing the ADCl width. It is possible that the ADCl width is narrow [9] and broad [10]; hence, we believe that it might be clinically important to consider not only the mean but also the width of ADCl.

Choi proposed to predict more accurate prognosis with the combination of MGMT status and ADC values compared with MGMT status alone [12]. Although we agree with the idea of the combination of B&L-ADCl and MGMT status, we were not successful in demonstrating a significant association between “B&L-ADCl or not” and MGMT status. As we mentioned above, MGMT status was not significantly associated with either PFS or OS in our data due to the underestimated potential of MGMT status or nonuniform treatment protocols. Therefore, we could not conclude whether predicting prognosis using the combination of MGMT status and “B&L-ADCl or not” is clinically valuable in this study.

We also did not find a significant association between tumor size and PFS or OS, which differed from the previous findings [16]. For tumor size analysis, Gutman et al. demonstrated major axial length measurement on FLAIR images [16]. In contrast, we manually extracted the entirely enhanced area without the cystic or necrotic tissue on contrast-enhanced T1-weighted images. In addition, Gutman et al. reported that the proportion of contrast-enhanced tumor (hazard ratio [HR] = 7.745) was more associated with OS than was major axial length (HR = 1.016). Because we only measured the actual tumor size on the MR image rather than the proportion of contrast-enhanced tumor, we underestimated the potential to predict poor outcome by tumor size.

There were some limitations in this study that should be considered. The images were obtained by using various instruments and vendors. Kvark et al. reported that ADC values may differ among different MRI systems [23]. However, we dichotomized our data by using the respective averages of the mean and width of ADCl; therefore, the thresholds may have been able to discriminate between small differences in tumor cellularity and heterogeneity. We also extracted the tumor regions manually, and automatic extraction may have provided better reproducibility. Follow-up investigations will be necessary to validate our results.

Conclusion

In conclusion, this study demonstrated that B&L-ADCl is a potential predictor of poor PFS in GBM patients. B&L-ADCl may be an image biomarker of higher cellularity, which is related to faster growth rate and heterogeneity that can cause resistance to treatment in patients with GBM tumors.

**Author’s contributions**

MK has analyzed the data and written the manuscript. YU has performed the statistical analysis and made a critical review of the manuscript.

**Disclosure of interest**

The authors declare that they have no competing interest.

**Appendix A. Supplementary data**

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.neurad.2017.11.011.

**References**


