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Three-dimensional analysis of apparent diffusion coefficient histograms in evaluating effect of radiotherapy on primary central nervous system lymphoma

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Abstract

Background : To retrospectively evaluate the usefulness of 3-dimensional analysis of apparent diffusion coefficient (ADC) histograms as an indicator of response to radiotherapy in primary central nervous system lymphoma (PCNSL).

Materials and Methods : Eight consecutive patients with diffuse large B-cell PCNSL who underwent chemoradiotherapy were included. Diffusion-weighted images (b values of 0 and 1,000 sec/mm^2) were obtained. The region of interest comprised the entire tumor. A range of ADC histogram parameters, including the minimum, maximum, skewness, and kurtosis values obtained prior to chemoradiotherapy were investigated in relation to overall and progression-free survival.

Results : The progression-free survival rate was significantly higher in patients with a higher minimum ADC value ($p = 0.017$), lower maximum ADC value ($p = 0.017$), lower kurtosis value ($p = 0.025$), or lower skewness value ($p = 0.025$). No significant correlation was observed between any other ADC histogram parameter and overall survival.

Conclusion : These results indicate that ADC histogram parameters offer a useful biomarker in predicting the outcome of radiotherapy in PCNSL.

Introduction

Primary central nervous system lymphoma (PCNSL), a rare type of non-Hodgkin lymphoma, affects the cerebral parenchyma but presents no evidence of systemic disease[1)]. Histologically, the most common type is diffuse large B-cell lymphoma[2)], which accounts for approximately 1% of non-Hodgkin lymphomas and 3% of primary brain tumors[1)]. Diffuse large B-cell lymphoma is characterized by a high incidence (approximately 30%) of ocular involvement[3)]. The rates of occurrence of this disease have shown an increase in patients with acquired immunodeficiency syndrome and other types of disease that compromise the immune system[4)].

Diffusion-weighted images (DWIs) obtained in magnetic resonance imaging (MRI) show the diffusion of water molecules, which reflects the Brownian movement of these particles on a T2-weighted image. The apparent diffusion coefficient (ADC), which is calculated from DWIs, can quantitatively reflect the degree of diffusion in the region of interest[5)]. Recent advances in MRI technology have enabled the quantification of the functional information provided by ADC values[6)]. Several

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studies have investigated prediction of tumor malignancy based on ADC parameters. One showed that ADC parameters were effective in predicting the prognosis in cases of glioblastoma[5]. Others showed that ADC measurements within contrast-enhancing regions in PCNSL may provide noninvasive insight into clinical outcome[7], and that ADC values reflect high proliferative activity in PCNSL[8]. However, tumors generally consist of various components. Therefore, the ADC value will depend on the region measured. Radiotherapy (RT) is considered an important therapy in the treatment of PCNSL[9][10]. We hypothesized that the proportion of the various components in the tumor might influence the therapeutic outcome of RT. The purpose of the present study, therefore, was to investigate the association between the prognosis for PCNSL and 3-dimensional (3D) analysis of ADC histogram parameters obtained prior to RT.

Methods and Materials

Patients

This retrospective study was approved by the institutional review board (SH4055) and the informed consent was waived.

The patients were selected from the database of the radiation oncology section of this institute between January 2012 and January 2015. These comprised 12 consecutive patients with a histological diagnosis of PCNSL who had undergone RT at Tokyo Medical University Hospital. Finally, 8 patients (5 men and 3 women) with a histological diagnosis of PCNSL were included in the study. The remaining 4 were excluded as they showed a complete response to high dose methotrexate (HD-MTX). None of the patients were human immunodeficiency virus carriers. Table 1 shows the characteristics of these patients. The median age was 73 years (range, 49 to 86 years). The histological type in all cases was a diffuse large B-cell lymphoma. All underwent MRI before biopsy. After HD-MTX, 2 patients (25.0%) showed a partial response, 5 (62.5%) stable disease, and 1 (12.5%) progressive disease according to the Response Evaluation Criteria in solid Tumors (RECIST) (version 1.1).

Table 1 Patient characteristics

Characteristic	Patients (*n*)
Age (y)	
≤ 60	3
> 60	5
Sex	
Male	5
Female	3
Performance status	
0	2
1	3
2	2
3	1
Lactate dehydrogenase (U/L)	
≤ 222	5
< 223	3
Histology	
Diffuse large B-cell lymphoma	8
Effect of chemotherapy before radiotherapy	
Partial response	2
Stable disease	5
Progressive disease	1
Radiation dose (Gy)	
50	1
45	7

Treatment

All 8 patients underwent chemotherapy with HD-MTX, followed by 3D conformal RT. The interval between diagnosis and the start of RT was within 2 months for all but 1 patient. The total median radiation dose was 45 Gy (range, 45 to 50 Gy), which was delivered over 25 sessions at a rate of 1.8 to 2 Gy per day. A radiation dose of almost 30 Gy was first given to the entire brain, and the remaining dose to the locality of the tumor prior to RT. Three-dimensional conformal RT was used to administer more than 95% of the prescribed dose of radiation to more than 95% of the target volume.

Magnetic resonance imaging studies

Magnetic resonance imaging was performed at least 3 times, at before biopsy, before RT, and after RT. Tumor response was evaluated based on the RECIST at 1 to 3 months after RT. All MRI examinations were performed with a 1.5 T Superconductive MRI system (Avanto, Siemens, Erlangen, Germany). They included routine sequences, such as T1- and T2-weighted images, and DWIs. The image parameters were as follows : axial T1-weighted spin-echo (TR/TE, 574/11 ms) ; axial T2-weighted fast spin-echo (TR/TE, 4,000/91 ms) ; axial fluid-attenuated inversion recovery (TR/TE/TI, 9,000/102 ms) ; axial DWI echo-planar imaging (TR/TE, 3,500/80 ms ; b-value, 0 and 1,000 s/mm^2 ; matrix size, 256 × 256 × 24 ; FOV, 230 mm ; slice thickness, 5.0 mm ; gap, 10% ; average, 6 ; bandwidth 1,240 Hz/Px.) ; and axial, sagittal, and coronal contrast-enhanced T1-weighted spin-echo (TR/TE, 574/11 ms).

ADC histogram analysis

An abnormal enhancement area on contrast-enhanced T1-weighted images[11-13] was taken to indicate the presence of a tumor. The entire tumor was contoured on all

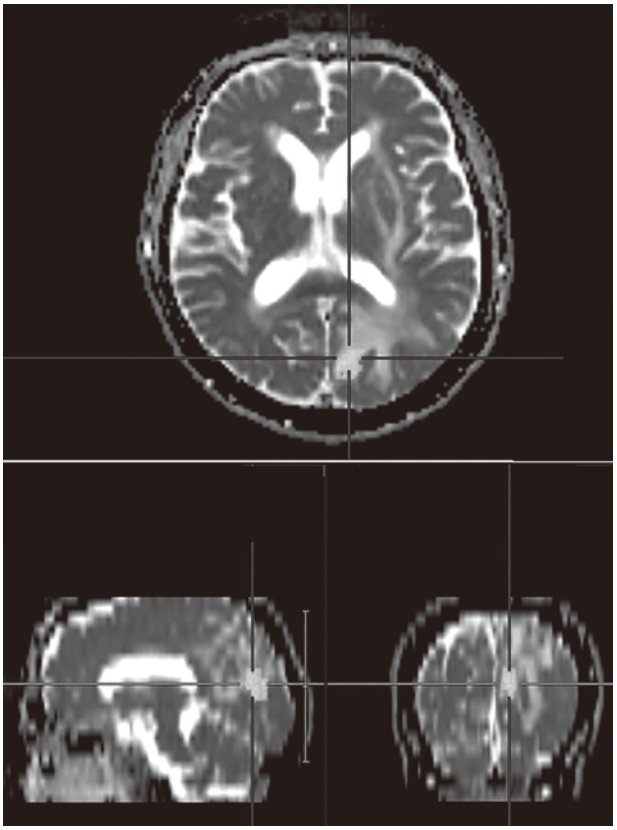

Fig. 1 Entire tumor was contoured on all slices on ADC map.

slices of the ADC map (Fig. 1) on MRI before biopsy, upon agreement between a radiation oncologist (RM) and a diagnostic radiologist (ZA). The data acquired on each slice were summated to derive voxel-to-voxel ADCs for the entire tumor. The minimum, maximum, median, mode, mode 50u, 5th, 75th, 90th percentile, skewness, and kurtosis values were derived from the ADC histogram. All statistical 3D analyses of the ADC histograms were performed using MATLAB software (The MathWorks, Inc., MA, USA).

Statistical analysis

Overall survival was measured from the beginning of RT to the date of death or October 2015. Progression-free survival (PFS) was calculated from the beginning of RT to the date of recurrence or last follow-up. Recurrence was defined by MRI. The survival curve was analyzed by the Kaplan-Meier method. Statistical differences were evaluated by the log-rank test. A p-value of 0.05 or less was considered significant. Age (≧ 60 vs. < 60 yr), sex, and 3D analysis of ADC histogram parameters (minimum, maximum, median, mode, mode 50u, 5th, 75th, 90th percentile, skewness, and kurtosis) were entered into the log-rank test. Mode 50u indicates ADC values of every 50 units. The statistical analysis was performed using EZR ver. 10 statistical software (Jichi Medical University, Japan)[14].

Results

Table 2 shows the results of the 3D analysis of the ADC histogram parameters. The median values for minimum, maximum, median, mode, mode 50u, 5th, 75th, and 90th percentile, skewness, and kurtosis of the ADC before biopsy were 536.5, 2,500, 955.5, 1,250, 1,250, 677.5, 1,214, 1,398, 1.03, and 0.75 × 10^{-6} mm^2/s, respectively.

Between 1 and 3 months after RT, 2 patients (25.0%) showed a complete response, 5 (62.5%) a partial response, and 1 (12.5%) stable disease according to RECIST.

The patients were observed for a median time of 5 months (range : 1 to 28 months) from the first day of RT, and 3 of the 8 patients were observed for more than 19 months. The PFS rate for all patients was 43% at 1 year after RT. The PFS rate was significantly higher in patients with a higher minimum ADC value (p = 0.017), lower maximum ADC value (p = 0.017), lower kurtosis value (p = 0.025), or lower skewness value (p = 0.025) (Fig. 2), when the boundary value was set as the median value. No significant correlation was observed between the other ADC histogram parameters and PFS. No significant correlation was observed between any of the

Table 2 Three-dimensional analysis of apparent diffusion coefficient histogram parameters

Patient	1	2	3	4	5	6	7	8
Minimum (× 10^{-6} mm^2/s)	532	696	567	541	569	18	371	397
Maximum (× 10^{-6} mm^2/s)	2,955	1,498	2,447	2,487	1,189	2,513	2,876	3,311
Median (× 10^{-6} mm^2/s)	919	992	1,277	877	843	797	1,124	1,139
Mode (× 10^{-6} mm^2/s)	964	1,328	1,261	793	876	746	784	884
Mode 50u (× 10^{-6} mm^2/s)	1,250	1,250	1,250	800	900	800	1,250	1,250
5th percentile (× 10^{-6} mm^2/s)	675	743	827	713	646	591	680	674
75th percentile (× 10^{-6} mm^2/s)	1,172	1,256	1,426	1,131	924	934	1,422	1,680
90th percentile (× 10^{-6} mm^2/s)	1,421	1,375	1,518	1,329	967	1233	1,763	2,399
Skewness (× 10^{-6} mm^2/s)	1.91	0.21	–0.2	1.53	–0.15	1.88	1.1	0.95
Kurtosis (× 10^{-6} mm^2/s)	5.63	–1.44	0.26	2.95	–0.09	4.81	1.24	–0.31

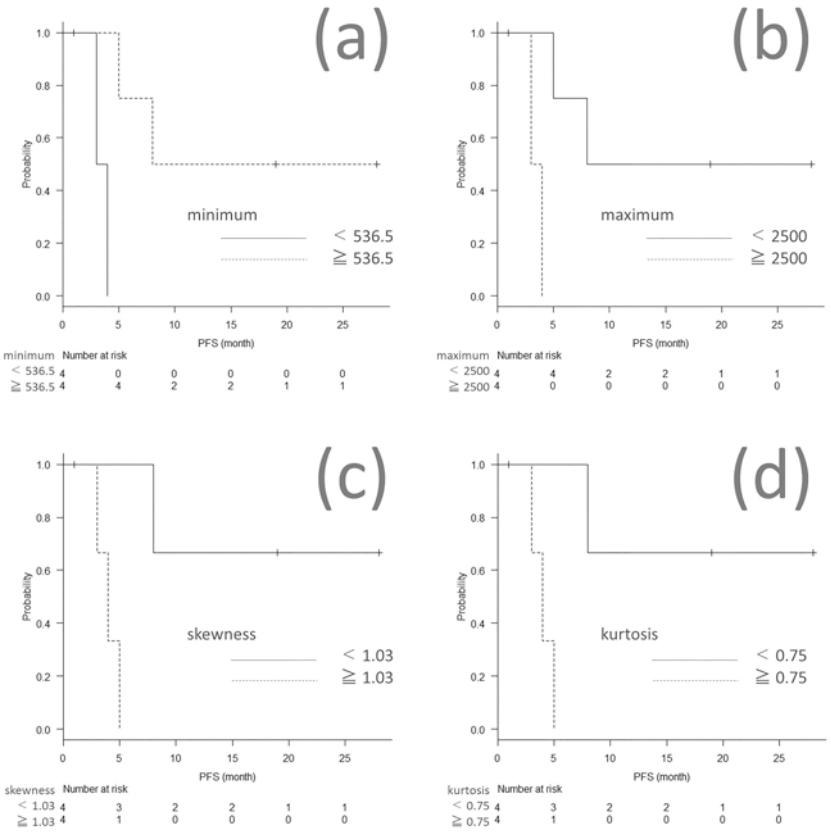

Fig. 2 Progression-free survival was calculated by Kaplan-Meier method. Statistically significant differences are shown for 4 ADC map parameters : (a) minimum ADC values ; (b) maximum ADC values ; (c) skewness of ADC values ; (d) kurtosis of ADC values ; *p*-values were 0.017, 0.017, 0.025, and 0.025, respectively.

ADC histogram parameters and overall survival. No significant correlation was observed between age, sex, performance status, lactate dehydrogenase value, and PFS.

Discussion

A review of the treatment of 1,180 immunocompetent patients with PCNSL in 50 publications[15] reported the following median survival times : 2 months with biopsy only ; 1.5 months with surgery ; 16 months with RT ; 13 months with chemotherapy ; and 16 months with combined treatment comprising chemotherapy and RT. This indicates that RT plays a major role in the treatment of PCNSL. In the present study, 7 out of 8 tumors responded to RT, while 1 tumor remained stable. The 1-year PFS rate was only 43%, however, indicating that while early-stage PCNSL responds well to RT, it tends to recur at a later stage. The survival rate was very low compared to that of systemic large B-cell lymphoma. These clinical data suggest that the nature of PCNSL is different from that of malignant lymphoma arising in the extra-CNS area, although it shows the same histological characteristics as large B-cell lymphoma.

A prognostic model of PCNSL was established based on 338 newly diagnosed consecutive patients at the Memorial Sloan-Kettering Cancer Center[16]. The data revealed age 50 years or younger and a Karnofsky performance score of 1 to 3 to be significant prognostic factors in terms of overall and failure-free survival. Another study which analyzed 378 PCNSL patients in 23 institutions identified the following 5 risk factors : age, over 60 years ; a performance status of more than 1 ; increased serum level of lactate dehydrogenase ; high cerebrospinal fluid protein concentration ; and involvement of a deep lesion of the brain[17]. The same study, which was based on different populations, also demonstrated that the 2-year overall survival rate correlated with the number of risk factors. The 2-year overall survival rate was as follows : 80% for favorable patients with no or 1 risk factor ; 57% for intermediate patients with 2 to 3 risk factors ; and 24% for unfavorable patients with 4 to 5 risk factors. In the present study, a higher minimum ADC value, lower maximum ADC value, lower kurtosis value, and lower skewness value were identified as prognostic factors for PFS. These results suggest that the effect of RT is related to the homogeneity of the tumor cells. Recent studies have shown that ADC histogram parameters reflect high proliferative activity in PCNSLs[8], and that they are very useful in pre-treatment estimation of their biological

properties[18]. These parameters, derived from the ADC histogram, enable a distinction to be made between patients in whom the prognosis is expected to be favorable and those in whom it is not. Moreover, these parameters differ in concept from the prognostic factors described above, and appear to be independent of these well-known parameters.

In the present study, the entire tumor was contoured on all slices on the ADC map. No discrepancies between the 2 physicians (a radiation oncologist and a diagnostic radiologist) were found in this analysis. To increase the accuracy of such data we believe that it may be helpful to fuse such ADC images with enhanced-T1- or T2-weighted images[11-13].

One recent study analyzed clinical results in 52 PCNSL patients who underwent combination therapy comprising rituximab, methotrexate, procarbazine and vincristine, followed by reduced-dose whole-brain RT[19]. The results were highly favorable, revealing a PFS of 3.3 years. The ADC values showed no correlation with response to treatment in that study. However, the others showed that ADC parameters were effective in predicting the prognosis in cases of PCNSL[7)20]. One study showed that ADC histogram parameters were useful predictors for PFS and response to HD-MTX in PCNSL[21]. However, some cases of a complete response to HD-MTX were included in that study. Whereas the treatment method used in the present study differed from that of this earlier study, and while the sample size was smaller here, the results do indicate that ADC histogram parameters allow the prognosis for PCNSL to be predicted. To our knowledge, this is first study to demonstrate that ADC histogram parameters can be used in determining the prognosis for PCNSL, even in cases where there is not a complete response to HD-MTX.

This study has several limitations. The sample size was small, and it was a retrospective non-randomized controlled study. As the tumor boundary values were set relatively for the analysis, they cannot be universally applied to other groups. Further study is necessary, however, to determine the validity of ADC histogram parameters as prognostic factors for PCNSL.

In conclusion, the present study demonstrated that 3D analysis of ADC histogram parameters was useful in predicting the prognosis of PCNSL. The present results also indicate that PFS is likely to be significantly higher in patients with a higher minimum ADC value, lower maximum ADC value, lower kurtosis value, or lower skewness value.

Conflict of interest notification

The authors declare no conflict of interest with regard to this report. This manuscript has not been published, nor is it under consideration for publication elsewhere.

This retrospective study was approved by the institutional review board (SH4055) and the informed consent was waived.

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拡散係数の3次元ヒストグラム解析による中枢神経原発リンパ腫に対する放射線療法の効果予測

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【要旨】 背景：中枢神経原発リンパ腫に対する放射線治療の効果の指標として、拡散係数の3次元ヒストグラム解析の有用性を遡及的に評価する。

対象と方法：対象は8人の化学放射線療法を受けた中枢神経原発リンパ腫患者。病理はびまん性大細胞型B細胞リンパ腫。すべての患者で拡散強調画像（B値は0と1,000秒/mm^2）が撮像されている。計測の関心領域は腫瘍全体とした。化学放射線療法の前に得られた拡散強調画像のヒストグラムにおける最小値、最大値、歪度および尖度と全生存率および無増悪生存率との関係を調査した。

結果：無増悪生存率は、最小値が大きい患者（$p = 0.017$）、最大値が小さい患者（$p = 0.017$）、尖度値が小さい患者（$p = 0.025$）、または歪度値が小さい患者（$p = 0.025$）で良好であった。他のヒストグラムパラメーターと全生存期間の間に有意差はみられなかった。

結論：拡散係数の3次元ヒストグラム解析は中枢神経原発リンパ腫に対する放射線治療の効果を予測する上で有用な画像バイオマーカーとなる可能性がある。

〈キーワード〉 中枢神経原発リンパ腫、PCNSL、見かけの拡散係数、ヒストグラム解析、放射線治療