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Impairment of Cerebral Interstitial Fluid Dynamics after Whole-Brain Radiotherapy and Its Association with Leukoencephalopathy Development

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Purpose: To evaluate changes in cerebral interstitial fluid dynamics following whole-brain radiotherapy (WBRT) for brain metastases using the diffusion tensor imaging analysis along the perivascular space (DTI-ALPS) index, and to investigate the relationship between these changes and the subsequent development of radiation-induced leukoencephalopathy (LEP).

Materials and Methods: A retrospective analysis was conducted on 50 patients who underwent WBRT for brain metastases. Baseline and post-WBRT DTI-ALPS indices were compared using paired t-tests. Univariate and multivariate linear regression analyses were performed to assess the relationship between changes in the DTI-ALPS index and clinical- and treatment-related factors. In a subset of 33 patients, univariate and multivariate logistic regression analyses were conducted to explore the association between the percentage change in the DTI-ALPS index and the development of LEP at 6-month follow-up, after adjustment for relevant clinical- and treatment-related factors.

Results: The mean DTI-ALPS index decreased significantly following WBRT (baseline: 1.487±0.257; post-WBRT: 1.353±0.229; $p<0.001$). A higher baseline DTI-ALPS index was significantly associated with a greater decline in the index post-WBRT ($p=0.023$). In the logistic regression analysis, a greater percentage reduction in the DTI-ALPS index was the only factor significantly associated with LEP development at 6 months ($p=0.048$).

Conclusion: WBRT is associated with impaired cerebral interstitial fluid dynamics, as reflected by a significant reduction in the DTI-ALPS index. A greater decline in the DTI-ALPS index was predictive of LEP development, suggesting its potential utility as a biomarker for early diagnosis of radiation-induced LEP.

Key Words: Whole-brain radiotherapy, leukoencephalopathy, glymphatic system, neurofluids

INTRODUCTION

Whole-brain radiotherapy (WBRT) remains the most widely used treatment for brain metastases due to its broad availability and effectiveness in symptom palliation, treating not only detectable but also occult lesions.[1] However, as advancements in cancer therapy have led to improved prognoses for patients with brain metastases, concerns about WBRT-associated long-term toxicities have increased.[2] One of the most common and serious complications of WBRT is radiation-induced leukoencephalopathy (LEP), which typically presents as delayed cognitive impairment accompanied by diffuse white matter T2 hyperintensities (WMH) on imaging, affecting up to 50% of patients following WBRT.[2-4]

First described in 2012, the glymphatic system is believed to play a key role in maintaining central nervous system homeostasis.[5] More recently, the broader concept of "neurofluids"—encompassing all components of intracranial fluids, including blood, cerebrospinal fluid, and interstitial fluid—has garnered

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increasing research attention for its role in supporting neuroglial function.[6,7] The proposed pathophysiological mechanisms underlying radiation-induced LEP, including neuroinflammation, increased blood-brain barrier permeability, impaired arterial compliance, and glial proliferation,[8-12] are closely related to factors that affect neurofluid dynamics and glymphatic function.[13,14] Therefore, it is reasonable to hypothesize that impairments in the glymphatic system and neurofluid dynamics could be associated with the various pathophysiological responses observed after WBRT.

To date, however, only two studies have explored the relationship between brain irradiation and the impairment of interstitial fluid dynamics. One of the studies utilized the diffusion tensor image analysis along the perivascular space (DTI-ALPS) method, while the other adopted the diffusion-weighted image analysis along the perivascular space (DWI-ALPS) method, a simplified version of the DTI-ALPS.[15,16] DTI-ALPS is a non-invasive, indirect approach used to evaluate glymphatic function or cerebral interstitial fluid dynamics in vivo.[17] This technique has been employed in various studies to investigate the relationship between cerebral interstitial fluid dynamics and various pathologies, with findings consistent with those from more invasive techniques such as intrathecal tracer injections.[18,19] However, both studies used a case-control design,[15,16] which limits their ability to assess temporal changes in glymphatic function or cerebral interstitial fluid dynamics following brain irradiation.

This study aimed to longitudinally assess changes in cerebral interstitial fluid dynamics after WBRT in patients with multiple brain metastases using the DTI-ALPS method. We also examined the relationship between changes in the DTI-ALPS index and various clinical- and treatment-related factors. Finally, we explored the association between changes in the DTI-ALPS index and the development of LEP following WBRT. We hypothesized that the DTI-ALPS index would progressively decrease after WBRT, and that this decline would correlate with the radiation dose received during treatment. Additionally, we hypothesized that reductions in the DTI-ALPS index would be significantly associated with the development of LEP, even after adjusting for other clinical- and treatment-related factors.

MATERIALS AND METHODS

Study population

This retrospective, longitudinal, observational study was conducted at a single institution—Gangnam Severance Hospital—and approved by the Institutional Review Board (IRB approval number: 3-2024-0157). Due to the retrospective design and minimal risk associated with this electronic linkage-based research, the IRB waived the requirement for informed consent.

We reviewed electronic medical records from January 2011 to April 2024 and identified 540 patients who underwent WBRT for multiple brain metastases. However, due to the unavailability of raw DTI data required to calculate the DTI-ALPS index, not all patients were eligible for inclusion. Complete pre- and post-WBRT DTI data were available for only 52 patients. Of these, two were excluded due to the presence of metastatic lesions or peritumoral edema in the periventricular white matter—the site of the regions of interest (ROI) placement for DTI-ALPS index calculation. Thus, a total of 50 patients were included in the final analysis.

Two subgroups, which were not mutually exclusive, were analyzed. The first subgroup included 28 patients who underwent at least two follow-up DTI scans post-WBRT. This group was used to assess changes in the DTI-ALPS index at three time points: baseline, post-WBRT, and the last follow-up. The "last follow-up" refers to the last available brain magnetic resonance imaging (MRI) examination obtained after WBRT for each patient. The second subgroup comprised 33 patients who underwent 6-month follow-up brain MRI scans, including T2-weighted fluid-attenuated inversion recovery (T2 FLAIR) sequences. In this group, radiation-induced LEP was evaluated using T2 FLAIR imaging, and its relationship with changes in the DTI-ALPS index, as well as other clinical- and treatment-related factors, was investigated (Fig. 1).

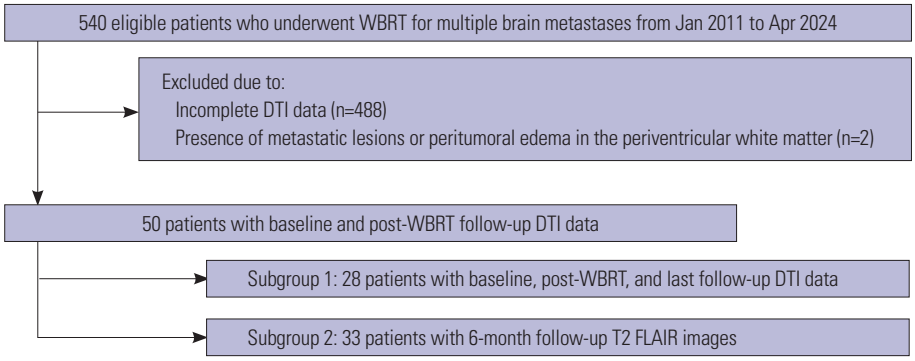

Fig. 1. Flowchart of the study population. WBRT, whole-brain radiotherapy; DTI, diffusion tensor imaging; T2 FLAIR, T2-weighted fluid-attenuated inversion recovery.

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Evaluation of clinical factors

Patient histories of hypertension and diabetes mellitus (DM) at the time of baseline MRI acquisition were collected through a review of electronic medical records. Additionally, we examined whether patients had received systemic chemotherapy or undergone local treatment for brain metastases prior to WBRT. In patients with lung cancer, the use of tyrosine-kinase inhibitors was specifically investigated.

Radiation treatment

All patients received WBRT at a total dose of 25–30 Gy, delivered in daily fractions of 2.5–3.0 Gy using intensity-modulated radiation therapy. When clinically indicated, a simultaneous integrated boost approach was applied to deliver higher doses than the standard WBRT dose to the gross tumor volume. Radiation therapy planning was based on computed tomography (CT) scans acquired with patients immobilized in a thermoplastic mask. Contrast-enhanced T1-weighted magnetic resonance and CT images were rigidly co-registered based on mutual information.

In patients without hippocampal metastases, hippocampal-avoidance WBRT was conducted, with the hippocampal-avoidance region defined as a 5-mm three-dimensional (3D) margin around the hippocampus.

Image acquisition

Baseline brain MRI was performed within 1 month before WBRT, and post-WBRT MRI was acquired approximately 1–3 months following treatment completion. All brain MRI examinations were conducted using a 3T scanner (MAGNETOM Vida, Siemens Healthineers, Erlangen, Germany). Imaging sequences included pre- and post-contrast-enhanced sagittal 3D magnetization-prepared rapid acquisition with gradient echo imaging, axial T2 FLAIR imaging, axial susceptibility-weighted imaging (SWI), and DTI. DTI data were acquired using an echo-planar imaging sequence with the following parameters: field of view, 224×224 mm; acquisition matrix, 112×112; voxel size, 2×2×2 mm; repetition time, 3800 ms; echo time, 65 ms; one image with b=0 s/mm^2 and 64 images with b=1000 s/mm^2.

Image data analysis

The DTI-ALPS index was calculated as previously described.[17] Three ROIs were manually placed in the projection, association, and subcortical fiber areas at the level of the lateral ventricle in the left hemisphere on color fractional anisotropy DTI maps, with reference to SWI images. Each site was evaluated for metastatic lesions or peritumoral edema prior to ROI placement.

In Subgroup 1 (patients with two or more post-WBRT follow-up brain MRIs), only the first and last follow-up MRIs were used to assess changes in the DTI-ALPS index. In Subgroup 2, the development of radiation-induced LEP was defined as any increase in the periventricular Fazekas score on 6-month follow-up T2 FLAIR images, compared to that of baseline MRI.[20-22]

Statistical analysis

Categorical data are presented as frequencies (percentages), while continuous data are expressed as the mean±standard deviation or median with interquartile range (IQR), depending on the distribution assessed using the Kolmogorov–Smirnov test.

Changes in the DTI-ALPS index between baseline and post-WBRT MRI were analyzed using a paired t-test. To evaluate longitudinal changes in the DTI-ALPS index, DTI-ALPS indices at baseline, post-WBRT, and the last follow-up were compared using the Friedman test in Subgroup 1.

Univariate and multivariate linear regression analyses were performed sequentially to investigate the relationship between changes in the DTI-ALPS index and various clinical- and treatment-related factors. The dependent variable was the percentage change in the DTI-ALPS index following WBRT. Independent variables included age, sex, hypertension, DM, primary lung cancer, prior systemic therapy, tyrosine-kinase inhibitor treatment, radiation boost, WBRT dose, total radiation dose, hippocampal avoidance, post-WBRT MRI scan interval, and baseline DTI-ALPS index. Since the WBRT dose was uniformly either 25 Gy or 30 Gy across all patients, it was considered a categorical variable. Variables with a p-value<0.1 in the univariate analysis were included as covariates in the multivariate analysis.

To explore the relationship between the development of radiation-induced LEP and percentage changes in the DTI-ALPS index, as well as other clinical- and treatment-related factors, patients with and without LEP in Subgroup 2 were compared using the Mann–Whitney U test and Fisher's exact test. Factors analyzed included baseline Fazekas score and the same set of variables used in the preceding linear regression analysis. Additionally, univariate and multivariate logistic regression analyses were performed using the same variables, with those showing a p-value<0.1 in the univariate analysis included in the subsequent multivariate analysis.

All statistical analyses were performed using SPSS (version 28.0, IBM Corp., Armonk, NY, USA) and MedCalc (version 22.032, MedCalc Software Ltd., Ostend, Belgium). A two-tailed p-value<0.05 was considered statistically significant.

RESULTS

Clinical and treatment characteristics

This study included 50 patients, 30 males and 20 females (age range, 29–79 years; mean age, 59.5±11.2 years). The most common primary malignancy was lung cancer (n=31), followed by breast cancer (n=10) and colorectal cancer (n=3). Prior to WBRT, 41 patients had received systemic therapy. The remaining nine patients, who had not undergone prior systemic therapy, were diagnosed with de novo brain metastasis at the time of their initial cancer diagnosis. All patients were receiving systemic therapy at the time of WBRT. Eight patients were treated with tyrosine-kinase inhibitors for their lung cancer.

No patient had received local treatment for brain metastases, such as Gamma knife surgery or surgical resection, prior to WBRT. The WBRT dose was either 25 Gy in 10 fractions (n=27, 54%) or 30 Gy in 10 fractions (n=23, 46%). A total of 38 patients (76%) underwent hippocampal-avoidance WBRT. Additionally, 38 patients (76%) received a simultaneous radiation boost to the tumor, with a median dose of 3500 cGy (range, 3000–4000 cGy). Table 1 summarizes the patient and treatment characteristics, while Supplementary Table 1 (only online) presents the details for Subgroups 1 (patients with two or more follow-up MRI scans) and Subgroups 2 (patients with 6-month follow-up FLAIR images available).

Table 1. Patient and Treatment Characteristics (n=50)

Characteristic	Value
Age (yr)	59.5±11.2 (29–79)
Sex (male: female)	30:20
Hypertension	11 (22)
Diabetes mellitus	4 (8)
Primary malignancy	
Lung cancer	31 (62)
Breast cancer	10 (20)
Colon cancer	3 (6)
Liver cancer	1 (2)
Soft tissue sarcoma	2 (4)
Malignant melanoma	1 (2)
Thyroid cancer	1 (2)
Uterus cancer	1 (2)
WBRT dose	
25 Gy	27 (54)
30 Gy	23 (46)
Radiation boost	38 (76)
Hippocampal avoidance	38 (76)
Prior systemic therapy	41 (82)
Tyrosine-kinase inhibitor treatment	8 (16)
Time interval (days)	
Baseline MRI–WBRT start	15 (IQR: 9–27)
WBRT completion–post-WBRT MRI	35 (IQR: 27–50)

MRI, magnetic resonance imaging; WBRT, whole-brain radiotherapy; IQR, interquartile range.
Data are presented as mean±standard deviation (range), n (%), or IQR.

The median interval between baseline MRI and the start of WBRT was 15 days (IQR: 9–27), while the median interval between WBRT completion and the post-WBRT MRI was 35 days (IQR: 27–50, range: 16–86). In Subgroup 1, the median interval between WBRT completion and the last follow-up MRI was 254 days (IQR: 142–376). In Subgroup 2, the median interval between WBRT completion and the 6-month follow-up MRI was 172 days (IQR: 157–197).

Changes in the DTI-ALPS index after WBRT

The mean post-WBRT DTI-ALPS index (1.353±0.229) was significantly lower than the mean baseline DTI-ALPS index (1.487±0.257; $p<0.001$). In Subgroup 1, the median DTI-ALPS indices at baseline, post-WBRT, and the last follow-up were 1.451 (IQR: 1.283–1.647), 1.343 (IQR: 1.227–1.433), and 1.266 (IQR: 1.089–1.412), respectively, showing a statistically significant decline over time ($p<0.001$) (Fig. 2).

Relationship between changes in the DTI-ALPS index and clinical- and treatment-related factors

In univariate analysis, a higher baseline DTI-ALPS index was the only factor significantly associated with a greater post-WBRT decrease in the DTI-ALPS index (β=-11.768, $p=0.023$). Multivariate regression analysis was not conducted, as no other factors, including WBRT dose, total radiation dose, and post-WBRT MRI scan interval, were significantly associated with index changes in the univariate analysis (Table 2).

Association between changes in the DTI-ALPS index and the development of LEP following WBRT

Among the 33 patients in Subgroup 2, 10 (30.3%) exhibited LEP on 6-month follow-up T2 FLAIR imaging. All LEP cases showed an increased extent of symmetric, diffuse WMH on FLAIR images compared to baseline MRI, consistent with the character-

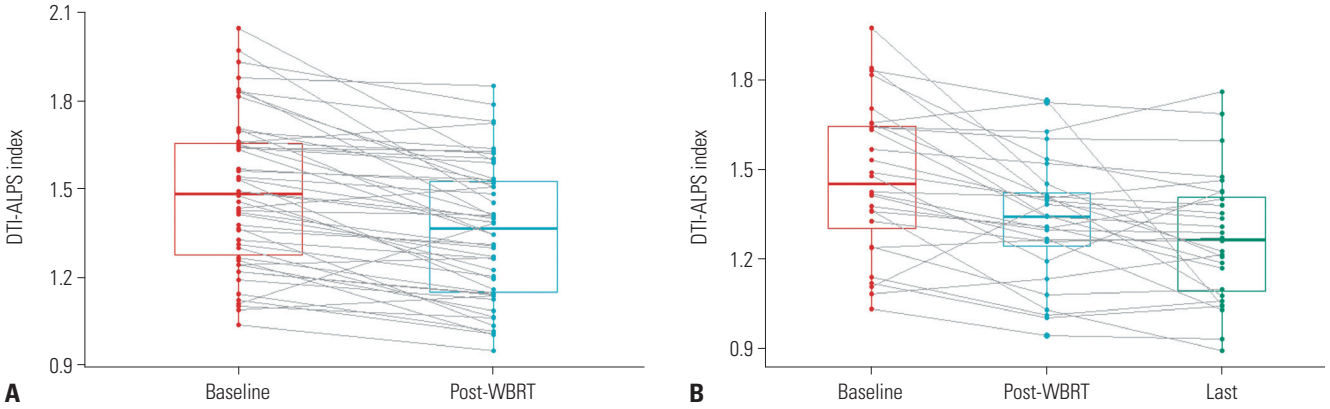

Fig. 2. (A) Changes in DTI-ALPS index before and after WBRT in 50 patients. (B) Changes in DTI-ALPS index before and after WBRT, and at the last follow-up, in 28 patients of Subgroup 1. DTI-ALPS, diffusion tensor imaging analysis along the perivascular space; WBRT, whole-brain radiotherapy.

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istic findings of radiation-induced LEP.[22] Compared to patients without radiation-induced LEP, those with LEP were older (p=0.023) and demonstrated a significantly greater percentage decrease in the DTI-ALPS index (p=0.022). Although patients with LEP tended to have higher baseline Fazekas scores, this difference was not statistically significant (p=0.076). Supplementary Table 2 (only online) presents further detailed results.

Univariate logistic regression analysis identified age (β=0.100, p=0.041), primary lung cancer (β=2.284, p=0.044), prior systemic therapy (β=-1.492, p=0.095), percentage change in the DTI-ALPS index (β=-0.097, p=0.048), and baseline Fazekas score (β=1.271, p=0.032) as factors potentially associated with the development of radiation-induced LEP (p<0.1). In the multivariate logistic regression analysis including these covariates, only the percentage change in the DTI-ALPS index was significantly associated with the development of radiation-induced LEP (β=-0.194, p=0.048) (Table 3). Fig. 3 shows representative cases.

Table 2. Univariate Linear Regression Analysis for the Percentage Change in the DTI-ALPS Index after WBRT

Variable	Coefficient	Standard error	p
Age	-0.157	0.119	0.191
Sex	0.349	2.737	0.899
Hypertension	-3.988	3.186	0.217
Diabetes mellitus	-2.235	4.933	0.652
Primary lung cancer	-1.799	2.751	0.516
Prior systemic therapy	-1.616	3.483	0.645
Tyrosine-kinase inhibitor treatment	2.413	3.641	0.511
Radiation boost	-2.457	3.120	0.435
WBRT dose (25 Gy vs. 30 Gy)	-1.013	2.687	0.708
Total radiation dose	0.001	0.004	0.866
Hippocampal avoidance	-1.247	3.135	0.693
Post-WBRT MRI scan interval	-0.057	0.077	0.463
Baseline DTI-ALPS index	-11.768	4.996	0.023

DTI-ALPS, diffusion tensor imaging analysis along the perivascular space; WBRT, whole-brain radiotherapy; MRI, magnetic resonance imaging.

DISCUSSION

This study is the first reported longitudinal investigation to assess the impact of WBRT on cerebral interstitial fluid dynamics. We observed a significant impairment in cerebral interstitial fluid dynamics following WBRT, evidenced by a decline in the DTI-ALPS index. This decline was detectable as early as approximately 1–3 months post-WBRT and persisted over time. Moreover, a higher baseline DTI-ALPS index was associated with a greater decrease in the index after WBRT. Notably, a greater decline in the DTI-ALPS index on MRI at 1 month post-WBRT was associated with the development of LEP observed on the 6-month follow-up MRI.

Our findings align with previous studies reporting impaired cerebral interstitial fluid dynamics following radiation therapy. Taoka, et al.[16] observed significantly lower DWI-ALPS indices in 22 patients who had received WBRT for brain tumors compared to 105 healthy controls. Similarly, Zheng, et al.[15] employed the DTI-ALPS method to assess the effects of radiation therapy on the glymphatic clearance system in 109 patients with nasopharyngeal cancer, including 74 who had undergone radiation therapy and 35 who had not, though the radiation was not directed at the brain. Their findings also revealed a lower DTI-ALPS index in the irradiated group. Furthermore, among the irradiated patients, those with radiation encephalopathy had significantly lower DTI-ALPS indices compared to those

Table 3. Univariate and Multivariate Logistic Regression Analyses for the Development of Radiation-Induced LEP on 6-Month Follow-Up T2 FLAIR Images in Subgroup 2

Variable	Univariate analysis			Multivariate analysis		
	Coefficient	Standard error	p	Coefficient	Standard error	p
Age	0.100	0.049	0.041	0.110	0.076	0.146
Sex	-0.760	0.806	0.346			
Hypertension	1.050	0.927	0.258			
Diabetes mellitus	0.154	1.288	0.905			
Primary lung cancer	2.284	1.134	0.044	2.292	1.591	0.150
Prior systemic therapy	-1.492	0.894	0.095	-2.572	1.801	0.153
Tyrosine-kinase inhibitor treatment	1.504	1.012	0.137			
Radiation boost	1.371	1.147	0.232			
WBRT dose (25 Gy vs. 30 Gy)	0.087	0.758	0.909			
Total radiation dose	0.001	0.001	0.430			
Hippocampal avoidance	-0.194	0.838	0.817			
Baseline DTI-ALPS index	0.058	1.370	0.966			
Percentage change in DTI-ALPS index	-0.097	0.049	0.048	-0.194	0.098	0.048
Baseline Fazekas score	1.271	0.592	0.032	0.244	1.014	0.810

DTI-ALPS, diffusion tensor imaging analysis along the perivascular space; LEP, leukoencephalopathy; T2 FLAIR, T2-weighted fluid-attenuated inversion recovery; WBRT, whole-brain radiotherapy.

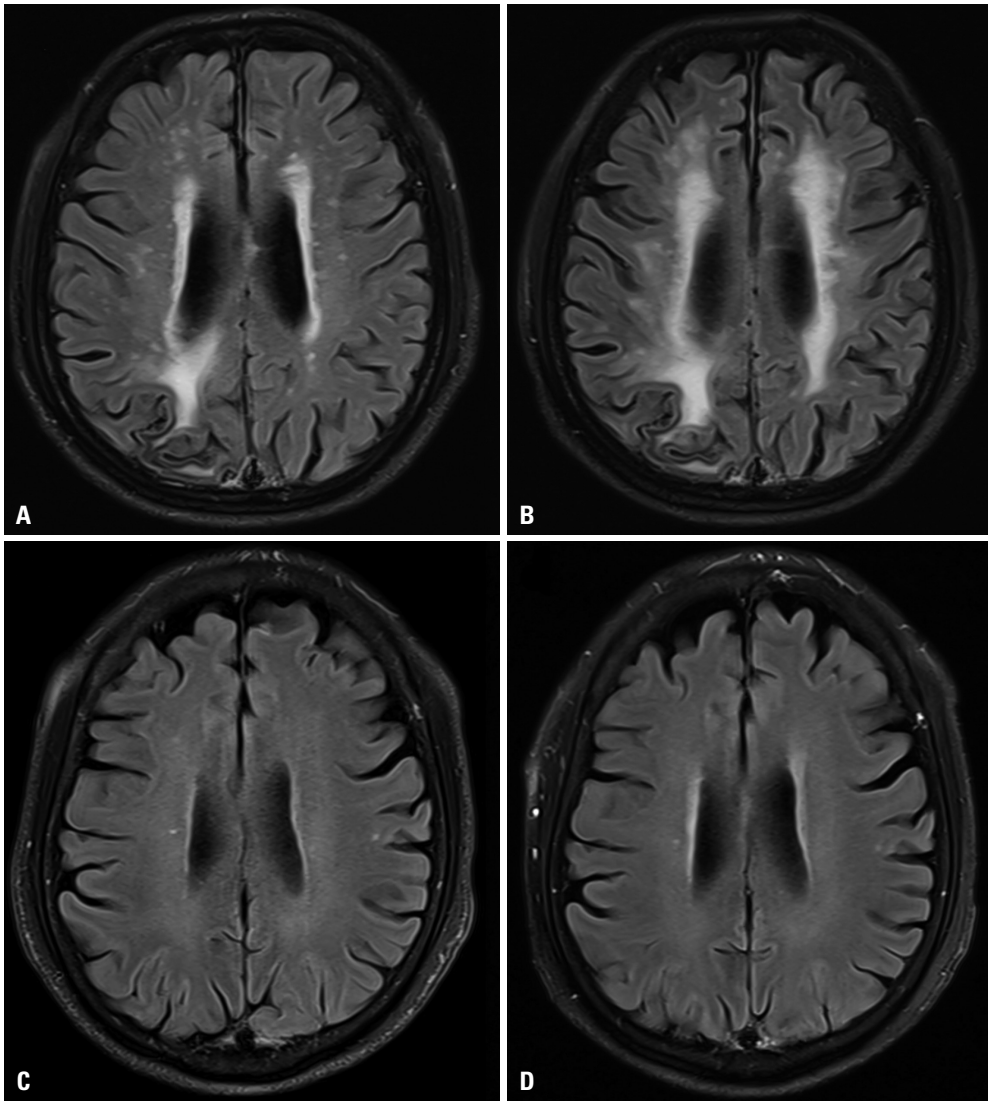

Fig. 3. Representative cases illustrating the association between radiation-induced LEP on 6-month follow-up imaging and changes in the DTI-ALPS index. A 75-year-old male patient with lung cancer underwent WBRT for multiple brain metastases (not shown in these slices). The DTI-ALPS index decreased by 21.1%, from 1.703 at baseline to 1.344 at 1 month post-WBRT. Compared to the baseline FLAIR image (A), the development of LEP is evident on the 6-month follow-up FLAIR image (B). A 66-year-old male patient with lung cancer underwent WBRT for multiple brain metastases (not shown in these slices). The DTI-ALPS index decreased by 1.19%, from 1.426 at baseline to 1.409, 1 month post-WBRT. Compared to the baseline FLAIR image (C), no LEP was observed on the 6-month follow-up FLAIR image (D). DTI-ALPS, diffusion tensor imaging analysis along the perivascular space; WBRT, whole-brain radiotherapy. LEP, leukoencephalopathy; DTI-ALPS, diffusion tensor imaging analysis along the perivascular space; WBRT, whole-brain radiotherapy; FLAIR, fluid-attenuated inversion recovery.

without.

The observed impairment of cerebral interstitial fluid dynamics following WBRT may be attributed to several post-radiation changes in the brain parenchymal microenvironment, including reduced vascular density, small vessel dysfunction, and decreased cerebral blood flow, all of which resemble features of small vessel disease (SVD).[23-25] These vascular alterations could impair interstitial fluid dynamics, as arterial pulsation is known to be a key driver of glymphatic flow.[14,26,27] Additionally, the pro-inflammatory state induced by radiation, along with reactive changes in microglia and astrocytes, could be another major factor contributing to impaired interstitial fluid dynamics.[13,28] These vascular changes and neuroinflammation may exacerbate each other, and the resulting impairment of interstitial fluid dynamics may cause the accumulation of pro-inflammatory cytokines, creating a vicious cycle.[13]

Interestingly, our findings revealed that the degree of decline in the DTI-ALPS index following WBRT was correlated exclusively with the baseline DTI-ALPS index, rather than with clinical- or treatment-related factors such as age or radiation dose. This contrasts with previous studies, which identified older age and higher radiation doses as significant contributors to increased damage severity.[9,16] This discrepancy may be due to the limited sample size or the relatively narrow range of radia-

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tion doses administered in our cohort. Regarding the timing of the post-WBRT MRI, the linear regression analysis demonstrated that the specific variability within the post-WBRT scan interval did not significantly affect the percentage change in the DTI-ALPS index, thus supporting the robustness of our reported immediate post-WBRT changes. Additionally, the observed association between a higher baseline DTI-ALPS index and a greater post-WBRT decline may be explained by a floor effect. Patients with lower baseline indices may have already exhibited impaired interstitial fluid dynamics, thereby limiting the extent to which further deterioration could be observed following WBRT. Alternatively, this finding may reflect a functional reserve effect. In this context, individuals with more efficient glymphatic function or interstitial fluid dynamics, as indicated by a higher baseline DTI-ALPS index, may show a more pronounced decline simply because they possess a larger functional reserve. This suggests that a greater decline does not necessarily indicate inherent fragility but rather reflects the magnitude of the functional capacity that was affected. Further studies with larger sample sizes and more varied treatment conditions are warranted to clarify these relationships.

Our findings highlight the importance of personalized approaches to WBRT, particularly in modulating radiation dose. Notably, baseline DTI-ALPS index appears to influence the degree of post-radiation changes in interstitial fluid dynamics. This underscores the need for treatment regimens that minimize radiation-induced damage. Exploring strategies like hippocampal avoidance or overall dose reduction, when clinically feasible, may help preserve cognitive functions without compromising tumor control. Although no statistically significant association was found between radiation boost and changes in the DTI-ALPS index or LEP development, a theoretical risk remains. Given the key role of perivascular spaces in the glymphatic theory and their sensitivity to radiation-induced vascular and inflammatory changes, radiation oncologists might consider minimizing exposure to these regions when feasible.[10,23,24] Advanced techniques such as stereotactic radiosurgery or fractionated stereotactic radiotherapy may help limit unintended damage, particularly in patients with preserved interstitial fluid dynamics at baseline.

The development of LEP was evaluated only at the 6-month follow-up MRI due to the limited follow-up duration. The incidence of LEP at 6 months in this study was 30.3% (10/33), consistent with previous reports indicating a cumulative incidence of approximately 30% by 6 months and up to 100% by 3 years for radiation-induced LEP.[29] We found that a greater decline in the DTI-ALPS index as early as 1–3 months post-WBRT was significantly associated with the development of LEP at the 6-month follow-up. A similar relationship between the DTI-ALPS index and LEP severity was also reported in a prior study involving patients undergoing radiation therapy for nasopharyngeal cancer.[15] Although radiologic LEP does not necessarily coincide with cognitive impairment or other neurological symptoms, a previous study reported that radiologic LEP may precede the onset of clinical manifestations.[30] Furthermore, radiologic LEP typically presents as abnormal white matter changes resembling the WMH commonly observed in SVD. Notably, radiation-induced LEP is thought to share key pathophysiological mechanisms with SVD.[24] Therefore, the presence of radiologic LEP, even in the absence of clinical symptoms, may reflect an early stage of radiation-induced brain injury. In this context, despite the lack of comprehensive neurological evaluations in our cohort, we consider the identification of radiologic LEP alone to be clinically meaningful. Collectively, our findings support a strong association between changes in the DTI-ALPS index and the pathophysiology of radiation-induced LEP, suggesting that the DTI-ALPS index could serve as a promising biomarker for the early diagnosis of this condition.

We also explored whether a greater burden of SVD prior to WBRT may predispose patients to developing LEP. Our analysis demonstrated a trend toward higher baseline Fazekas scores in patients who developed LEP, although the difference was not statistically significant in the Mann–Whitney U test. This trend is consistent with previous studies highlighting the prognostic value of pre-treatment WMH burden. For example, Chan, et al.[31] reported that higher baseline Fazekas scores significantly predicted global cognitive decline following WBRT. Similarly, univariate logistic regression in our study showed a significant association between baseline Fazekas score and LEP development. However, this association lost significance in multivariate analysis after adjusting for other factors, including the percentage change in the DTI-ALPS index, which remained the only significant predictor. These findings suggest that SVD may contribute to the risk of LEP through mechanisms involving impaired interstitial fluid dynamics. Furthermore, given the growing evidence linking SVD to dysfunction of interstitial fluid dynamics,[18,32] along with our finding that LEP development and the DTI-ALPS index are significantly associated, it is plausible that SVD, LEP, and interstitial fluid dynamics are closely interconnected. In this context, the DTI-ALPS index may serve as a marker of this shared pathophysiology and as a potential predictor of clinical outcomes following WBRT. Further studies involving larger and more diverse patient populations are warranted to elucidate these relationships and to validate the prognostic value of the DTI-ALPS index in the setting of WBRT.

This study has several limitations. First, due to the poor prognosis of patients with brain metastases, the number of eligible patients with DTI data from both baseline and post-WBRT was inevitably small. Second, we assessed the development of radiation-induced LEP solely based on radiological findings, without incorporating cognitive function tests such as the Mini-Mental State Examination. Although radiologic LEP has been reported to precede clinical symptoms and may reflect underlying pathological changes of radiation-induced LEP, the lack of objective cognitive assessments limits our ability to directly correlate imaging abnormalities with functional outcomes.[24,30]

This limitation may affect the clinical interpretation of our results, particularly regarding their relevance to cognitive dysfunction following WBRT. Third, other potential factors related to radiation-induced LEP, such as brain parenchymal atrophy or the degree of brain metastasis control, were not considered in this study. Finally, the DTI-ALPS index was calculated based on manually placed ROIs, which may introduce observer variability. Despite this potential limitation, previous studies have reported good to excellent interobserver reliability for the index, with intraclass correlation coefficients of ≥0.77.[19,33] Moreover, all DTI data in this study were acquired using consistent imaging parameters and the same scanner model, which may have helped to minimize variability. Nonetheless, observer-dependent variation remains a potential limitation, particularly due to the manual nature of ROI placement.

In conclusion, cerebral interstitial fluid dynamics were impaired following WBRT, as indicated by a reduction in the DTI-ALPS index. A greater decline in the DTI-ALPS index was associated with the development of LEP, suggesting its potential utility as a promising biomarker for the early diagnosis of radiation-induced LEP.

DATA AVAILABILITY

The datasets generated and/or analyzed in this study are available from the corresponding author upon reasonable request.

AUTHOR CONTRIBUTIONS

Conceptualization: Bio Joo. Data curation: Mina Park, Sung Jun Ahn, Jina Kim, and Sun Ho Min. Formal analysis: Bio Joo. Investigation: Yeona Cho and Bio Joo. Methodology: Yeona Cho and Bio Joo. Resources: Yeona Cho and Bio Joo. Supervision: Sang Hyun Suh and Yeona Cho. Validation: Bio Joo. Visualization: Bio Joo. Writing—original draft: Bio Joo. Writing—review & editing: Bio Joo and Yeona Cho. Approval of final manuscript: all authors.

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