Turk Neurosurg, 2021

Original Investigation

DOI: 10.5137/1019-5149.JTN.32084-20.4

Received: 21.08.2020
Accepted: 16.02.2021

Published Online: 16.09.2021

Diffusion-Weighted Imaging of Brain Metastasis: Correlation of MRI Parameters with Histologic Type

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ABSTRACT

AIM: To compare the diffusion properties of brain metastases as imaging biomarkers in various types of tumours, to determine their histology and origin.

MATERIAL and METHODS: Magnetic Resonance Imaging (MRI) and diffusion-weighted imaging (DWI) were used to retrospectively study the data of 143 patients suffering from brain metastases. Four categories of primary tumours with metastases to the brain were included: lung carcinoma (n=102, 71.3%); breast carcinoma (n=27, 18.8%); colon carcinoma (n=8, 5.6%); and others (n=6, 4.2%). The Apparent Diffusion Coefficient (ADCmin) values, as well as the normalised ADC ratio (nADC), were determined. The lesions on the DWI were categorised as follows: type 1, with negative findings on DWI; type 2, which were isointense with the normal cortical grey matter; type 3, which were hyperintense compared to the normal cortical grey matter.

RESULTS: The diffusion type, mean ADCmin, and mean nADC showed statistically significant differences in different types of metastases. In the subgroup analysis, it was found that type 3 was the diffusion type found most extensively in the brain metastases of small cell carcinoma (SCLC) (n=52, 65.8%, p<0.000). Furthermore, the mean ADCmin and nADC values were the least for the brain metastases of the SCLC (552.0 ± 134.2 and nADC = 0.8 ± 0.1, p<0.000, respectively). The value of the mean ADCmin was low in the human epidermal growth factor receptor 2 (HER-2) negative groups than in the HER-2 positive groups at 786.8 ± 299.1 vs 844.8 ± 141.3 (p<0.006).

CONCLUSION: Our findings indicated that there is a correlation between diffusion parameters as imaging biomarkers of the solid component of brain metastases of primary tumours and the tumour histology.

KEYWORDS: Brain, Metastases, Diffusion, MRI

INTRODUCTION

The detection of brain metastases is important for the initial staging and prognosis of patients with systemic malignancy. The primary tumours that widely metastasize to the brain are pulmonary (39–56%), breast (13–30%), skin (8–11%), gastrointestinal (6–9%) and renal (2–6%) (2,5,6,8,9,18,27,29,31). The primary tumour is not detected in 2 to 14% of the cases of brain metastases (5,6,18,27). When multiple cerebral lesions are observed in patients with known primary cancer, they possibly indicate metastases. The metastases are usually present at the junction of the grey and white matter and the border zones of the main arterial vascular regions; however, the metastases of different tumours depict different characteristics on brain magnetic resonance imaging (MRI), such as diffusion properties (1,7,11,12,14,19,24,25).

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Diffusion-weighted MR imaging (DWI) is often performed for diagnosing acute infarction of the brain due to its capability to reveal cytotoxic oedema that is observed due to the change in the water diffusion of damaged cells. The DWI function depends on the differential rates of diffusion or the Brownian motion of water. Hence, it is often used in the field of neuro-oncology for the diagnosis and follow-up of patients suffering from brain tumours. Diffusion restriction is indicated by the low values of Apparent Diffusion Coefficient (ADC), which is linked to cytotoxic oedema, hypercellularity or dense contents (haemorrhage and protein), increase in the number of cells and ratio of nucleus/cytoplasm, and the accumulation of macromolecules. The transfer of water molecules is restricted by a decrease in the extracellular space, which leads to restricted diffusion in the malignant masses. According to previous studies, highly cellular tumours display more restriction of diffusion and low values of ADC (11,33). ADC values acquired from DWI are particularly related to tumour cellularity, treatment response, glioma grade, and survival (4,21,33).

Very few studies have examined the ADC characteristics of metastatic brain lesions from various primary tumours, which might help in differentiating the origin of different brain metastases (1,7,11,14,19,24). Hayashida et al. demonstrated that well-differentiated adenocarcinomas were usually hypointense, while small- and large-cell neuroendocrine carcinomas showed hyperintensity on DWI (11). According to Duygulu et al., restricted diffusion was seen in metastatic lesions of the breast, colon, lung, and testis carcinomas (7). In several studies, it was noted that the primary tumours of small cell carcinoma (SCLC) had a tendency of low ADC values compared to that of other tumours (17,20). Koyama et al. demonstrated high diagnostic capabilities of DWI and ADC values of primary tumours on chest MRI, while quantitatively differentiating between non-small cell carcinoma (NSCLC) and SCLC compared to short tau inversion recovery (STIR) and contrast ratios. ADC values of primary tumours of SCLC were considerably smaller compared to those of NSCLC (17). The tumour cellularity of SCLC might be the reason for this finding, which is a critical factor affecting ADC values in viable tumour tissue.

The aim of this study was to compare the diffusion properties of brain metastases from different types of tumours to predict their origin and histologic type.

MATERIAL and METHODS

The diffusion MRI results were retrospectively examined in 227 patients suffering from brain metastases from March 2015 to June 2019. A 1.5 T Avanto Siemens scanner was used to obtain all MRI scans (Erlangen, Germany). In addition, we also performed the conventional MR imaging and DWI. Furthermore, sagittal T1 weighted localizing sequence (TR/TE/excitations.15/6/1), fast spin-echo T2-weighted (TR/TEeff/excitation, 5670/99/2; echo-train length 7), axial T1-weighted (398/10/1), fluid-attenuated inversion recovery (FLAIR) (TR/TEeff/inversion time, 7370/84/2276; echo-train length 17) sequences, and axial, sagittal, and coronal contrast-enhanced T1-weighted sequences were obtained. The section thickness of the T1-weighted, T2-weighted, and FLAIR sequences was 5 mm, with an intersection gap of 1 mm, a 22-cm field of view (FOV), and 256-512 matrix. A spin-echo, EPI sequence was used to perform the DWI. The following parameters were used: TR/TE 4700/104; diffusion gradient encoding in three orthogonal directions; b 0. 500, 1000 s/mm^2; matrix size, 128 pixels; section thickness, 5 mm; FOV, 220 mm and section gap, 1 mm. Prior to contrast-enhanced imaging, DWI scans were performed.

Lesions equal to or greater than 1 cm in size were used to obtain a very good resolution of ADC maps. An expert radiologist manually created five uniform regions of interest (ROI) that included over 20 pixels corresponding to the enhanced part of the lesions on the contrast-enhanced T1 weighted images, to determine the signal intensity (SI) of the ADC values. The ROIs were marked on solid areas, to prevent averaging the volume with cystic or degenerative regions that might have an impact on the quantitative data. The smallest value of the five ROI measurements was considered as the representative value in every case. The same technique was used for a corresponding region in the contralateral white matter. The ADC_{min} values were recorded (Figure 1A-C). The ratio of the mean ADC_{min} of the tumour was divided by the mean ADC_{min} of the corresponding contralateral region to obtain the normalised ADC ratio (nADC). The visual categorization of the lesions on DWI was as follows: type 1, negative results on DWI; type 2, isointense with the normal-appearing cortical grey matter; type 3, hyperintense compared to the normal-appearing cortical grey matter (Figure 2A-C). The categorization was similar to that in Jung's study (14). However, the mean score was not calculated in our study; rather, only the percentage of patients with this type was recorded. Lung carcinomas were further classified as small cell adenocarcinoma and squamous cell carcinomas. Sub-grouping of breast carcinomas was made in accordance with the human epidermal growth factor receptor 2 (HER-2) status, oestrogen (ER), and progesterone (PR) positivity. When the value was more than 3+, it was considered to be positive for HER-2. When the value was 0 or 1, it was considered as negative for HER-2 expression. The status of ER and PR was considered positive when the expression was 10% or more. Biopsy or surgery of the primary tumour was performed to determine the histopathology.

The Shapiro-Wilk test was first performed to check the normal distribution of the data. The difference between groups was then examined by performing a t-test and a Mann-Whitney U test for parametric and non-parametric values, respectively. A chi-square test was used to compare the categorical values. The groups were compared using the one-way analysis of variance (ANOVA test) and the Kruskal-Wallis test in lesions with normal and non-normal distribution, respectively. A Bonferroni correction was used for multiple comparisons between the intrinsic subgroups. SPSS version 22 for Windows was used to perform all statistical analyses on a personal computer. A p value <0.05 was considered statistically significant.

The ethics committee of the research and education hospital in our city provided the approval for this retrospective study protocol (GOKA/2019/2/10 is the protocol number).

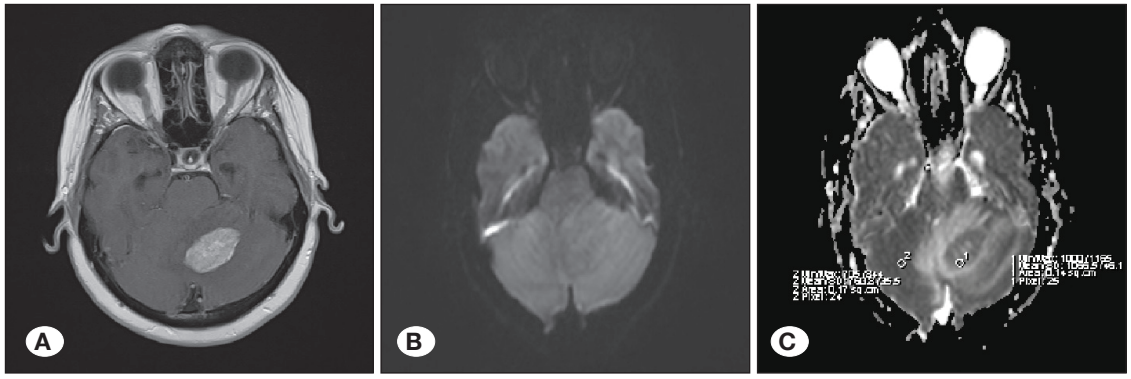

Figure 1A-C: Representative MR images in which the ROI within a tumour and the related contralateral normal-appearing white matter are presented for computing apparent diffusion coefficient values for the brain metastases. Contrast enhancement of the left cerebellar metastasis in patients with breast carcinoma is demonstrated on contrast-enhanced T1 weighted images (1). Negative findings are seen on diffusion-weighted imaging (DWI) **(B)**. ADC map with ROIs inside the tumour and the relevant contralateral normal-appearing white matter **(C)**.

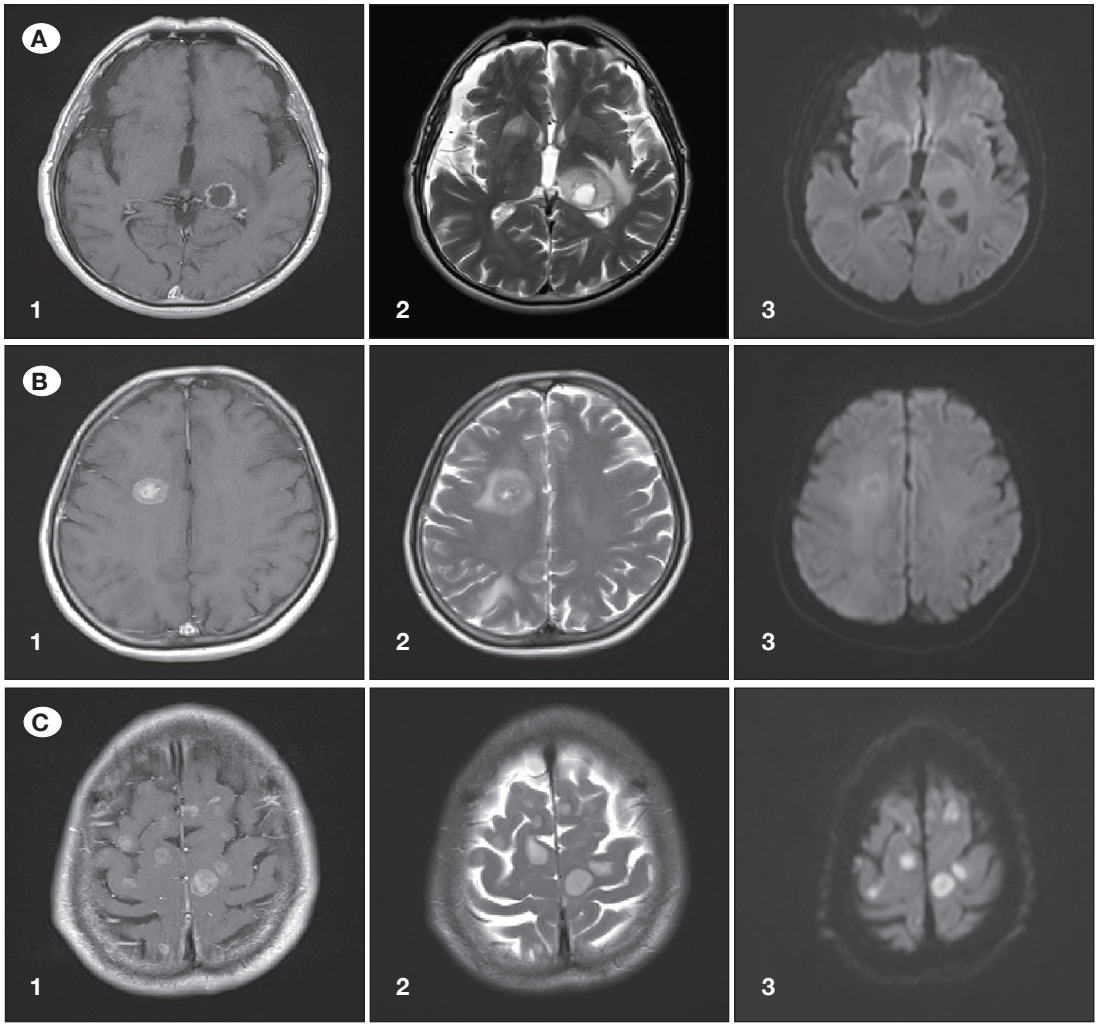

Figure 2: Representative MR images that demonstrate visual scores on the basis of DWI results attained for brain metastases of NSCLC **(A1, A2, A3)**, breast carcinoma **(B1, B2, B3)**, and SCLC **(C1, C2, C3)**. Contrast-enhanced T1 weighted images show enhanced tumour in the left thalamus **(A1)**, right frontal lobe **(B1)**, and left frontal lobe **(C1)**. T2 weighted images show peritumoral brain oedema if present **(A2,B2,C2)**. Brain metastases are not detectable on DWI in type 1 **(A3)**. DWI images show iso-signal intensity in type 2 **(B3)** and high signal intensity in type 3 **(C3)** respectively, relative to normal-appearing cortical grey matter.

RESULTS

There were a total of 227 patients, of which 45 had the largest tumour size of less than 1 cm, 28 were diagnosed with haemorrhagic metastasis, and 11 patients had metastases to the pia mater. These patients were not included in the study; thus, a sample of 143 patients was considered for the study. The patients were in the age group of 27 to 85 years, while their mean age was 59.5 ± 10.7 years. Males comprised 62.2% of the patients in the study (n=89). The following were the primary tumours that had metastasized to the brain: lung carcinoma (n=102, 71.3%), breast carcinoma (n=27, 18.8%), colon carcinoma (n=8), renal cell carcinoma (n=1), rhabdomyosarcoma (n=1), pancreatic carcinoma (n=1), prostatic carcinoma (n=1), cardiac sarcoma (n=1), and ovarian carcinoma (n=1).

We classified the patients into four groups according to the primary disease: lung carcinoma (group 1), breast carcinoma (group 2), colon carcinoma (group 3), and others (group 4). The age, dominancy, sex, and the number of metastatic lesions in all groups is depicted in Table I. The variation in age and sex between the groups was statistically significant. This variation was due to the mean age and sex of patients suffering from breast carcinoma. The dominancy and the number of all metastases between the groups did not show statistically significant differences. The tumours were located in the regions of anterior circulation, posterior circulation, and even circulation in 59.8%, 28.4%, and 12.5% of the cases, respectively. In 30% of the cases, there was a solitary metastasis (n=43).

The total number of metastatic lesions included in the study were 348 (Table II). There were no differences in the localization (supratentorial or infratentorial), distribution (anterior or posterior circulation), and the size of the measured lesions. There were statistically significant differences in the mean ADC_{min}, mean nADC, and diffusion type of the metastatic lesions between the groups. The mean ADC_{min} value and mean nADC were the lowest in the patients with lung carcinoma, and the differences were thought to be caused by these patients. In all four groups, the most common type of diffusion was type 1. The most common type 1 and type 3 diffusions were seen in 91.7% of the patients with colon carcinoma and 33.6% of the patients with lung carcinoma. Only one patient with colon carcinoma had a type 3 lesion. In patients with breast carcinoma, the number of metastatic lesions with type 3 was very low (n=3). In group 4, only two patients had lesions with type 2 diffusion, which were pancreatic carcinoma and rhabdomyosarcoma in the thigh. Other patients showed type 1 diffusion.

Lung carcinoma was also subgrouped into three categories, namely, SCLC, squamous cell carcinoma, and adenocarcinoma (Table III). Statistically significant differences were observed between the groups in the diffusion type of the lesion. The most widely noted diffusion type in brain metastases of the SCLC was Type 3 (n=52, 65.8%). Furthermore, statistically significant differences were noted between the values of ADC_{min} and nADC of the lesions that were the smallest among cases with brain metastases of SCLC.

For 69 lesions in 24 patients, the overall status of ER/PR/HER-2 was known (Tables IV – VI). It was found that the mean ADC_{min} values of metastatic lesions of HER-2 positive and HER-2 negative patients had statistically significant differences. In the HER-2 negative groups, the mean ADC_{min} value was smaller (Table IV). Statistically significant differences were noted in the diffusion types of lesions between the PR positive and PR negative patient groups. Type 1 had the highest percentage in the PR negative patient group (82.9%) (Table IV). It was also found that the value of mean ADC_{min} was lower in metastatic lesions in the ER-positive and PR-positive patients compared to that in the ER-negative and PR-negative patients; however, this difference was not statistically significant (Tables IV and V).

Table I: Characteristics of all Patients

	Lung (n=102) (71.3%)	Breast (n=27) (18.8%)	Colon (n=8) (5.6%)	Other tumours (n=6) (4.2%)	p
Age (mean ± std)	61.2 ± 9.3	52.1 ± 12.1	60.8 ± 11.6	62.5 ± 13.6	**0.002**
Sex n (%)					
Man	83 (81.4)	0 (0.0)	3 (37.5)	3 (50.0)	**0.000**
Woman	19 (18.6)	27 100.0)	5 (62.5)	3 (50.0)	
Dominancy of lesions n (%)					
Anterior	61 (59.8)	15 (55.6)	3 (37.5)	4 (66.7)	
Posterior	29 (28.4)	9 (33.3)	2 (25.0)	2 (33.3)	0.446
Even	12 (11.8)	3 (11.1)	3 (37.5)	0 (0.0)	
The number of metastases n (%)					
1	33 (32.4)	5 (18.5)	3 (37.5)	2 (33.3)	0.531
2 and more	69 (67.6)	22 (81.5)	5 (62.5)	4 (66.7)	

Table II: Characteristics of Metastatic Lesions

	Lung (n=256)	Breast (n=72)	Colon (n=12)	Other tumours (n=8)	p
Diffusion type of the lesion					
1	89 (34.8)	50 (69.4)	11 (91.7)	6 (75.0)	
2	81 (31.6)	19 (26.4)	0 (0.0)	2 (25.0)	**0.000**
3	86 (33.6)	3 (4.2)	1 (8.3)	0 (0.0)	
Localisation of the lesion n (%)					
Supratentorial	200 (78.1)	50 (69.4)	8 (66.7)	7 (87.5)	0.407
Infratentorial	56 (21.9)	22 (30.6)	4 (33.3)	1 (12.5)	
Dominancy of the lesion n (%)					
Anterior	157 (61.3)	41 (56.9)	7 (58.3)	7 (87.5)	0.407
Posterior	99 (38.7)	31 (43.1)	5 (41.7)	1 (12.5)	
The size of lesion (mm) (mean ± std)	17.4 ± 9.3	17.4 ± 6.7	22.3 ± 9.1	18.5 ± 8.3	0.137
The mean ADCmin (mean ± std)	731.7 ± 217.3	816.6 ± 231.2	854.0 ± 190.7	901.1 ± 153.6	**0.001**
The mean ADCmin lesion/ the mean ADC white matter (mean ± std)	1.0 ± 0.3	1.1 ± 0.3	1.1 ± 0.2	1.3 ± 0.2	**0.001**

Table III: Characteristics of Metastatic Lesions in Types of Lung Cancer

	SCLC (n=79)	Adenocarcinoma (n=80)	Squamous cell carcinoma (n=52)	p
Diffusion type of the lesion				
1	3 (3.8)	46 (57.5)	23 (44.2)	
2	24 (30.4)	25 (31.3)	16 (30.8)	**0.000**
3	52 (65.8)	9 (11.3)	13 (25.0)	
Localisation of the lesion n (%)				
Supratentorial	63 (79.7)	59 (73.8)	40 (76.9)	0.669
Infratentorial	16 (20.3)	21 (26.3)	12 (23.1)	
Dominancy of the lesion n (%)				
Anterior	56 (70.9)	46 (57.5)	30 (57.7)	0.154
Posterior	23 (29.1)	34 (42.5)	22 (42.3)	
The size of lesion (mm) (mean ± std)	15.3 ± 6.9	18.4 ± 9.3	17.2 ± 9.5	**0.065****
The mean ADCmin (mean ± std)	552.0 ± 134.2	825.7 ± 225.4	805.1 ± 186.0	**a-b:0.000*** **a-c:0.000*** b-c:1.000*
The mean ADCmin lesion/ the mean ADC white matter (mean ± std)	0.8 ± 0.1	1.1 ± 0.3	1.1 ± 0.2	**a-b:0.000*** **a-c:0.000*** b-c:1.000*

*One-way ANOVA (post-hoc Bonferroni test) **Kruskal–Wallis Test*

Table IV: Her-2 Status of Metastatic Lesions in Breast Carcinoma

	Her-2 (+) (n=37)	Her-2 (-) (n=32)	p
Diffusion type of the lesion			
1	29 (78.4)	20 (62.5)	
2	8 (21.6)	11 (34.4)	0.249
3	0 (0.0)	1 (3.1)	
Localisation of the lesion n (%)			
Supratentorial	27 (73.0)	21 (65.6)	0.690
Infratentorial	10 (27.0)	11 (46.4)	
Dominancy of the lesion n (%)			
Anterior	21 (56.8)	18 (56.3)	1.000
Posterior	16 (43.2)	14 (43.8)	
The size of lesion (mm) (mean ± std) (median)	17.6 ± 6.7 (15.0)	17.9 ± 6.8 (15.0)	0.620*
The mean ADCmin (mean ± std) (median)	844.8 ± 141.3 (851.0)	786.8 ± 299.1 (720.5)	**0.006***
The mean ADCmin lesion/ the mean ADC white matter (mean ± std) (median)	1.2 ± 0.1 (1.17)	1.1 ± 0.4 (1.09)	0.069*

**Mann Whitney U test.*

Table V: Oestrogen Receptor Status in Patients with Breast Carcinoma

	ER(+) (n=35)	ER(-) (n=34)	p
Diffusion type of the lesion			
1	26 (74.3)	23 (67.6)	
2	8 (22.9)	11 (32.4)	0.44
3	1 (2.9)	0 (0.0)	
Localisation of the lesion n (%)			
Supratentorial	24 (68.6)	24 (70.6)	1.00
Infratentorial	11 (31.4)	10 (29.4)	
Dominancy of the lesion n (%)			
Anterior	21 (60.0)	18 (52.9)	0.72
Posterior	14 (40.0)	16 (47.1)	
The size of lesion (mm) (mean ± std)	18.8 ± 7.3	16.7 ± 5.9	0.25
The mean ADCmin (mean ± std)	778.8 ± 135.6	858.1 ± 292.1	0.27
The mean ADCmin lesion/ the mean ADC white matter (mean ± std)	1.1 ± 0.1	1.2 ± 0.4	0.69

**Mann Whitney U test.*

Table VI: Progesterone Receptor Status in Patients with Breast Carcinoma

	PR(+) (n=28)	PR(-) (n=41)	p
Diffusion type of the lesion			
1	15 (53.6)	34 (82.9)	
2	12 (42.9)	7 (17.1)	**0.024**
3	1 (3.6)	0 (0.0)	
Localisation of the lesion n (%)			
Supratentorial	17 (60.7)	31 (75.6)	0.29
Infratentorial	11 (39.3)	10 (24.4)	
Dominancy of the lesion n (%)			
Anterior	13 (46.4)	26 (63.4)	0.25
Posterior	15 (53.6)	15 (36.6)	
The size of lesion (mm) (mean ± std)	18.3 ± 7.7	17.3 ± 5.9	0.93
The mean ADCmin (mean ± std)	770.1 ± 123.8	850.5 ± 275.1	0.23
The mean ADCmin lesion/ the mean ADC white matter (mean ± std)	1.1 ± 0.1	1.2 ± 0.3	0.46

**Mann Whitney U test.*

We evaluated the correlation between the type of diffusion and the mean ADC_{min} values in the measured lesions. The mean ADC_{min} values were 899.9 ± 191.7 (n=157, median: 877.0, min: 556.0, max: 2296.0) in type 1 lesions; 739.8 ± 146.1 (n=102, median: 723.0, min: 407.0, max: 1219.0) in type 2 lesions; and 532.5 ± 132.3 (n=90, median: 534.0, min: 224.0, max: 782.0) in type 3 lesions. We also compared the median ADC values of the three types of lesions. The Bonferroni-corrected Mann–Whitney U test showed a statistically significant difference in the median ADC values between the three groups. We accepted $p<0.001$ in every comparison. As expected, the lesions without restricted diffusion had higher median ADC_{min} values and those with restricted diffusion had lower median ADC values. We compared the nADC in the three types of lesions. The mean nADCs of the lesions were 1.2 ± 0.2 (median: 1.2, min: 0.8, max: 3.2) in type 1; 1.0 ± 0.2 (median: 1.0, min: 0.5, max: 1.8) in type 2; and 0. ± .1 (median: 0.7, min: 0.3, max: 1.0) in type 3 lesions. The difference in the median values of nADC was statistically significant between three groups, as seen in the Bonferroni-corrected Mann–Whitney U test. We accepted $p<0.001$ in every comparison. Overall, the results showed that the lesions without restricted diffusion had higher nADC values compared to those of lesions with restricted diffusion.

DISCUSSION

Brain metastases are often seen in patients with primary malignancy. However, almost 30% of the brain metastases are detected during the diagnosis of the primary tumour or prior to the invent of the primary tumour. All patients with malignant disease are asked to undergo MRI of the brain if metastases are strongly suspected based on their clinical history. Until now, no characteristic properties of carcinogenic lesions in the brain have been defined for computed tomography (CT) or MRI images that can distinguish between brain metastases and primary brain tumours. It has been suggested that low T2 signal intensities would be seen in mucinous metastases, and high signal on unenhanced TI imaging would be seen in metastases from melanoma (3,26). However, the features of the signals might differ and change over time due to haemorrhage or an increase in melanin and paramagnetic ions like in melanomas.

It has been reported that distinct localizations of brain metastases from different primary tumours are seen on MRI. For instance, brain metastases from breast cancer are seen more often in the cerebellum, while metastases from NSCLC are mainly found in the parietooccipital lobes (28). Schroeder et al. studied the distribution of brain metastases from different tumours (30). They showed that in a group of 369 patients, the type of primary tumour was significantly related to the spatial distribution of brain metastases. Remarkably, brain metastases from skin cancer exhibited an almost specific affinity to the supratentorial space. The multivariate statistical analyses showed that there was a significant build-up of brain metastases from skin cancer in a frontal location, while that from the breast and gastrointestinal cancer occurred in a cerebellar location (30). The most widespread localization in our study was in the anterior circulation region in all groups; however, there was no statistically significant difference in the spread across the locations. This might be because our study did not include patients with haemorrhagic and millimetric metastases.

In some of the earlier studies, the DWI properties of various cerebral metastases have been presented. Several methods of measuring ADC were used, which limits the comparability of the studies. Hayashida et al. evaluated the DWI of 26 metastatic brain lesions in patients with different primary tumours and classified them according to the histological type (11). They found that signal intensity on DWI can predict the histology of metastases. In their study, well-differentiated metastatic lesions to the brain from adenocarcinomas [i.e., tumours within lung (n=4), ovary (n=1), and uterus (n=1)] tended to be hypointense. SCLC (i.e., tumours within the lung, n=3) and large-cell neuroendocrine carcinomas (tumour within the lung, n=1) showed hyperintensity on DWI. The mean nADC value was considerably higher in well-differentiated compared to that of weakly differentiated adenocarcinomas and lesions other than adenocarcinomas. Of three small cell carcinomas, two exhibited the lowest nADC among 26 tumours. Jung et al. measured ADC_{min} and nADC in 74 lesions from primary lung cancer (14). They found that the ADC_{min} parameters were not related to the histology of the tumours [i.e., adenocarcinoma (n=56), SCLC (n=11), and squamous cell carcinoma (n=7)]. A total of 948 lesions from 159 patients were examined by Meyer et al. The most widely prevalent tumours were lung and breast carcinomas and malignant melanomas. The findings showed that SCLC had the smallest ADC values (mean value, 0.86 ± 0.27) compared to those of the brain metastases from NSCLC (mean value, 1.17 ± 0.49), breast carcinoma (0.97 ± 0.21), and malignant melanoma (0.99 ± 0.36) (24). Zakaria et al. analysed the ADC_{min} and ADC_{mean} of brain metastases. The ADC values of melanoma (n=5) and SCLC (n=6) were smaller compared to those of the metastases from other carcinomas, for example breast cancer (n=10), ovarian cancer (n=4) and colorectal cancer (n=4). The authors also examined the cellularity of some tumours and determined that ADC_{min}, ADC_{mean} and mean cellularity had a negative correlation (33). In our study, there was a statistically significant difference in the mean ADC_{min} and nADC values between the different histologic types of lung cancer. Similar to that in Meyer et al. and Zakaria et al.'s study SCLC in our study showed lower ADC_{min} values (552.0 ± 134.2) (24,33). The cause of lower ADC values might be due to the higher number of patients compared to those in other studies. In addition, we found that the type of diffusion was significantly different in SCLC from adenocarcinomas and squamous cell carcinomas, and it was correlated with low ADC values. The percentage of type 3 diffusion was 65.8% in SCLC, which was equal to the proportion of high-intensity tumours on DWI observed in Hayashida et al.'s study (11). Our findings support previous studies showing the tendency of low ADC values and hyperintensity of SCLC on DWI. The reason for their high signal intensity remains unknown. In our study, some patients with SCLC also had type 1 diffusion (n=27, 34.2%). DWI studies on primary lung carcinomas demonstrated differences between the ADC values of SCLC and NSCLC. SCLC demonstrated statistically significant lower ADC values than NSCLC (20). The hypercellularity of the tumour is the most likely mechanism. There might be two different types of genetic subgroups of SCLC due to the range of ADC values and the different types of diffusion detected in our study.

Duygulu et al. studied brain metastasis in 76 patients with different primary tumours. They classified the patients into two groups based on the restricted diffusion (7). In their study, metastases of the lung (n=10, 66.6%) (5 SCLC, 5 NSCLC), breast (n=3, 20%), colon (n=1, 100%), and testicular carcinomas (n=1, 100%) showed restriction of diffusion. The mean ADC_{min} value of metastatic lesions showing restricted diffusion was 720 ± 160 mm^2/sn, and that of lesions not showing restricted diffusion was 780 ± 210 mm^2/sn. Similarly, in our study we detected the restricted diffusion type 3 in metastatic lesions from the lungs (n=86, 33.6%) and breast (n=3, 4.2%), and colon carcinoma (n=1, 8.3%). However, in our study, the mean ADC_{min} value in metastatic lesions showing restricted diffusion was lower (532.5 ± 132.3 mm^2/sn), and the mean ADC_{min} value in metastatic lesions not showing restricted diffusion was higher (899.9 ± 191.7 mm^2/sn) compared to the values in their study. In addition, they found no correlation between mean ADC_{min} values of the solid components of the tumours with restricted diffusion. However, in our study, the ADC_{min} values were significantly correlated with the diffusion properties of brain metastases. We also detected a statistically significant correlation between restricted diffusion and the histopathological type of tumour. In their study, the ADC_{min} values were lowest in SCLC, but no correlation was found between them. This might be because the number of lesions was higher in our study than in their study.

The metastatic lesion from the sarcoma in the study by Hayashida was isointense with the normal grey matter; however, its nADC value was small (11). It was thought that the low nADC value was because of the low SI on T2-weighted images. In our study, the metastases from cardiac sarcoma were hypointense, and those from rhabdomyosarcoma of the thigh was isointense compared to the grey matter on diffusion MRI, and their nADC values were high. The ADC values of the primary tumours were examined by Hassanien et al. in musculoskeletal soft tissue mass (10). The researchers recommended that DWI and quantitative ADC mapping to routine MR examination should be performed so that soft tissue tumours can be examined, particularly in uncertain cases. The mean ADC values of benign tumours were significantly higher compared to those of malignant soft tissue tumours. There were variations in the ADC values of malignant soft tissue sarcoma in accordance with the histology. The smallest values were seen for low-grade sarcoma and malignant fibrous histiocytoma, while the highest values were found for high-grade myxofibrosarcoma. According to Hayashida et al. (11), restricted diffusion was seen in one of four patients (25%) with colon carcinoma compared to one in 11 patients (8.3%) in our research. Further studies for the evaluation of the DWI characteristics of brain metastases from colon carcinoma are required.

In some recent studies, the impact of biological heterogeneity and immunohistochemical factors of tumours on prognosis, therapeutic decisions, and imaging parameters was examined. However, only one study focused on brain metastases from lung carcinomas, and two focused on brain metastases from breast carcinomas. Jung et al. studied the

hypothesis that the signal intensity of brain metastasis from lung cancer (n=74 patients) on DWI differs based on the genetic background of the lesion (14). The status of mutations in ALK, EGFR, and KRAS was considered for categorizing 56 patients with adenocarcinoma. The findings showed that there was a significant relationship between the ADC values of adenocarcinomas on DWI and the EGFR mutation status. Such patients are believed to respond well to non-invasive treatment with tyrosine kinase inhibitors, and the treatment can be planned accordingly if the mutation status is known. Unfortunately, for the purpose of our study, there were no available data about the genetic mutations of lung cancers. It was demonstrated by Ahn et al. that all ADC variables in 34 patients with brain metastases from breast cancer reported on ADC histogram parameters showed a declining trend in the ER/PR positive group than in the ER/PR negative group. No significant relationships were observed between the ADC values of brain metastases and HER-2 status (1). The mean ADC value in the HER-2 positive group in Meyer et al.'s study was 1.00 ± 0.21, while that in the HER-2 negative group was 0.97 ± 0.19. No statistically significant differences were noted between the breast cancer subtypes in 279 lesions in 26 patients (24). The relationship between immunohistochemical markers and ADC values in the primary breast lesion was examined in several past studies. Kim et al. (16) studied 77 breast cancer masses on diffusion MRI (16). The median ADC values of primary breast cancer in the ER-positive group were significantly lower compared to those in the ER-negative group. The median ADC value of 192 patients with breast carcinoma was reported by Martincich et al. (23). The tumours were classified by the authors into four groups: luminal A, luminal B, HER-2 enriched, and triple-negative. It was found that ADC values had a weak statistically significant relationship with the percentage of ER-positive cells. The median values of ADC were significantly higher in the ER-negative tumours than in the ER-positive tumours. The highest median ADC value was seen in the HER-2 enriched tumours. However, there was no statistically significant difference between the median ADC values in the HER-2 enriched tumours and in the triple-negative tumours. Furthermore, the authors reported that a large proportion of the tumours in the most aggressive breast cancer subgroups showed DWI values similar to those usually seen in benign lesions. Kamitani et al. found significantly lower mean ADC values in ER-positive cancers than in ER-negative cancers and significantly lower mean ADC values in PR positive cancers than in PR negative cancers in patients with invasive ductal carcinoma. No relationship was found between HER-2 scores and ADC (15). The mean ADC values in 83 patients with breast carcinoma were examined by Tezcan et al. The study found no relationship between ADC values and ER positivity or HER-2 positivity (32). The ADC values of PR positive carcinomas were found to be considerably lower than those of PR negative cancers (p=0.03). The ADC_{mean} in the ER-positive group and the HER-2 negative group was found to be considerably smaller compared to that in the ER-negative group and the HER-2 positive group in the study by Jeh et al. (13). A statistically significant difference in the mean ADC_{min} values of metastatic lesions between patients in the HER-2 positive and HER-2 negative groups was seen in our study, with HER-2 positive groups exhibiting considerably higher values. This was consistent with the findings in the study by Jeh et al. (13). The difference in the diffusion types of lesions between patients in the PR positive and negative groups was found to be statistically significant. The percentage of type 1 was the highest the PR negative patients (82.9%). Their ADC_{min} values were lower in the metastatic lesions in the ER-positive and PR-positive patients in comparison to those in lesions with negative receptors; however, this difference was not statistically significant. A statistically significant correlation was reported between ER positivity and ADC value in some studies, which was less in the ER-positive group (1,13,15,16,23), and also between PR positivity and ADC values, which was less in the PR positive group (1,15,32). The molecular diffusion of water through perfusion has an impact on the ADC value. It was found in a study on experimental models that ERs obstructed the angiogenic pathway and decreased the perfusion, which had an impact on the ADC value (22). This might lead to a declining trend in ADC values in the brain metastases and primary tumours of breast carcinomas. HER-2 overexpression is known to cause angiogenesis, which increases the ADC values; however, this overexpression also leads to cell proliferation, thus reducing the ADC values. Therefore, because of these contradictory effects of HER-2 overexpression on ADC values, a non-significant relationship might emerge between the HER-2 status and ADC values of brain metastases in breast cancer (1). Nonetheless, a significant inverse relationship and smaller ADC values in HER 2 negative groups compared to those in the HER-2 positive groups have not been reported in any study in the past, as previously discussed.

There are several limitations to our study. Firstly, the study is retrospective in nature. Secondly, the DWI features of only three primary tumours were present in adequate numbers to perform a statistical comparison. The largest groups of primary cancer in our study were the lung and breast carcinomas. Third, no correlation between the histopathological parameters, such as tumour cellularity and DWI findings of the brain metastases was performed. Fourth, the grades of lung cancer pathology (i.e., well, moderately, or poorly differentiated) and EGFR mutation status in adenocarcinoma were not available, which might have an impact on the results of the DWI parameters. An advantage of our research is that it included a greater number of patients compared to previous studies in the literature. Furthermore, tumours less than 1 cm in size were not included so that the ADC values could be accurately determined on a 1.5 Tesla MRI, which improved the accuracy of the ADC measurements and the assessment of the diffusion type.

CONCLUSION

A limited number of studies related to the diffusion properties and immunohistochemical features of brain metastasis are available in the literature. In clinical practice, the DWI properties of brain metastases might be important in predicting the primary cancer site and immunohistochemical type if they are unknown. Our study showed the lowest ADC_{min} values and the restricted diffusion in the metastatic brain lesions of SCLC

compared to those in other tumours. These findings indicate a different microstructure of the solid component of these tumours and support previous studies in the literature. Further studies, including histochemical factors, are necessary to establish the mechanism of diffusion changes at the microstructural level.

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