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MAJOR PAPER

Diffusion Tensor Imaging Can Discriminate the Primary Cell Type of Intracranial Metastases for Patients with Lung Cancer

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Purpose: Histopathological differentiation of primary lung cancer is clinically important. We aimed to investigate whether diffusion tensor imaging (DTI) parameters of metastatic brain lesions could predict the histopathological types of the primary lung cancer.

Methods: In total, 53 patients with 98 solid metastatic brain lesions of lung cancer were included. Lung tumors were subgrouped as non-small cell carcinoma (NSCLC) (n = 34) and small cell carcinoma (SCLC) (n = 19). Apparent diffusion coefficient (ADC) and Fractional anisotropy (FA) values were calculated from solid enhanced part of the brain metastases. The association between FA and ADC values and histopathological subtype of the primary tumor was investigated.

Results: The mean ADC and FA values obtained from the solid part of the brain metastases of SCLC were significantly lower than the NSCLC metastases ($P < 0.001$ and $P = 0.003$, respectively). ROC curve analysis showed diagnostic performance for mean ADC values (AUC=0.889, $P = < 0.001$) and FA values (AUC = 0.677, $P = 0.002$). Cut-off value of $> 0.909 \times 10^{-3}$ mm^2/s for mean ADC (Sensitivity = 80.3, Specificity = 83.8, PPV = 89.1, NPV = 72.1) and > 0.139 for FA values (Sensitivity = 80.3, Specificity = 54.1, PPV = 74.2, NPV= 62.5) revealed in differentiating NSCLC from NSCLC.

Conclusion: DTI parameters of brain metastasis can discriminate SCLC and NSCLC. ADC and FA values of metastatic brain lesions due to the lung cancer may be an important tool to differentiate histopathological subgroups. DTI may guide clinicians for the management of intracranial metastatic lesions of lung cancer.

Keywords: *brain metastases, diffusion tensor imaging, fractional anisotropy, apparent diffusion coefficient, lung cancer*

Introduction

Metastatic tumor is the most common brain tumor in adulthood. Among primary tumors that metastasize to the brain, lung cancer accounts for a substantial part, and about 18–24% of brain metastases were from lung cancer.[1] The metastatic lesions demonstrate similar characteristics to the original tumoral tissue.[2] In the treatment planning and estimating the prognosis of patients in lung tumors, the most important factor is the cell type. Therefore, the treatment strategies, clinical course, and prognosis differ between small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC). The treatment goal in a patient with brain metastasis is to establish control of the disease in the CNS, to minimize side effects of chemotherapeutic agents and to sustain the life quality.[3,4]

MRI is the gold standard imaging method for the diagnosis of brain metastasis. Diffusion tensor imaging (DTI) is a noninvasive radiological modality which gives valuable information about character and cellular content of the lesions.[5–11] Apparent diffusion coefficient (ADC) values may help in determining tissue types and characteristics of tumoral lesions. They can be used as an indicator of cellular intensity or aggressive behavior of the tumor.[5] Increased

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cellular densities generally result in lower ADC values, whereas the local cellular damage results in high ADC values.[10] Fractional anisotropy (FA) is a measurement of the structural integrity of the white matter tracts. FA is a quantitative parameter of DTI and shows tissue damage in many diseases including infarct, neurodegenerative disorders and tumor characterization.[6,12–14] There are several studies that tested DTI metrics to differentiate intraaxial from extra-axial lesions, metastases from gliomas, and high-grade gliomas from low-grade gliomas.[12,13,15] However, results of these studies are contradictory. The relationship between FA and tumor cellularity has not been determined yet; both positive and negative correlations have been reported.[7–9,16] To the best of our knowledge, there are no studies that provide histopathological subtype prediction from lung cancer-related brain metastases using DTI parameters.

The aim of our study is to investigate whether DTI parameters of metastatic brain lesions could predict the histopathological types of the primary lung cancer.

Materials and Methods

Patients

We retrospectively examined 61 patients with BM due to the lung cancer who underwent brain MRI in our radiology department. We excluded the patients with radiological evidence of intratumoral hemorrhage (n = 5) and biopsy for the brain lesions (n = 3) in whom DTI parameters would be affected. A total of 53 patients (19 female, 34 male; mean age: 59.33 $\pm$ 8.27 years, age range: 40–78 years) with 98 metastatic brain lesions included the study. All patients included in the study had brain metastases at the time of initial diagnosis and had no history of chemo- and radiation therapy. Histopathological diagnosis was made from transbronchial biopsy with bronchoscopy in 22 patients, transthoracic needle biopsy in 14 patients, brain metastasectomy material in 6 patients, cervical lymph nodes excision in 5 patients, pleural effusion cytology in 3 patients, skin biopsy in 1 patient, biopsy with mediastinoscopy in 1 patient, and bone biopsy in 1 patient. Our institutional review board approved this study, and written infomed consent was obtained for MRI. The procedures properly followed the guidelines of the Helsinki Declaration on human experimentation.

MRI technique

MRI was performed with a 1.5-T system (Magnetom Avanto; Siemens, Erlangen, Germany). First, routine brain MRI protocol included T1-weighted (T1W; TR/TE = 460/14 ms) and T2-weighted (T2W; TR/TE = 2500/80 ms) sequences in the axial and coronal planes, and fluid attenuated inversion recovery (FLAIR) images (TR/TE = 8000/90 ms) in the axial plane with 5-mm-thick sections. The DTI protocol consisted of a single-shot, spin-echo, echo-planar sequence with the fat suppression technique: TR/TE = 2700/89 ms; matrix, 128 × 128; field of view, 230 mm; and slice thickness, 5 mm. DTI was acquired before the administration of contrast media and 30 diffusion-encoding directions were used at b = 1000 s/mm^2. After that, T1W 3D magnetization-prepared rapid gradient echo (TR/TE/TI = 12.5/5/450 ms) volumetric sequences with and without contrast medium (Gadolinium-diethylene triamine pentacetic acid, 0.1 mmol/kg body weight, intravenously) were applied.

The Leonardo console (software version 2.0; Siemens) was used for the post processing of DTI data sets, after which the ADC and color-coded FA maps were reconstructed. T1W 3D-magnetization-prepared rapid gradient-echo (MPRAGE) and T2W images were used as anatomic references for the placement and tracing of the ROIs throughout the whole measurable brain metastases. These images were coupled with corresponding regions of ADC and FA maps at the same section level. The adaptation of the sizes and placement of all ROIs were realized through simultaneous assessment by two experienced radiologists (SSB, IY). Single circular ROIs of 15–60 mm^2 were carefully placed in the center of the solid enhancing region of the tumor to avoid volume averaging with cystic and/or necrotic areas that might influence the quantitative data (Figs. 1 and 2).

Statistical analysis

Statistical analysis was performed using SPSS Statistics V22.0 (IBM, Armonk, NY, USA). Kolmogorov–Smirnov test was used for normality. Mean $\pm$ standard deviations presented as descriptive statistics. In the comparisons of the FA and ADC values from the solid enhanced brain metastases and the lesion sizes in the SCLC and NSCLC groups, the Mann–Whitney U test was used. *P* value of less than 0.05 was considered to indicate a statistically significant difference.

Results

Fifty three patients with 98 metastatic brain lesions were examined. There were 34 patients with 61 metastases in the NSCLC group and 19 patients with 37 metastases in the SCLC group.

There were no statistically significant differences between NSCLC and SCLC groups in terms of gender ($P = 1$), age ($P = 0.07$) and tumor size ($P = 0.811$). These results are summarized in Table 1.

The mean ADC and FA values obtained from solid brain metastases of SCLC were significantly lower than the NSCLC metastases (respectively; $P < 0.001$, $P = 0.003$). The mean ADC and FA values obtained from the metastatic brain lesions were summarized in Table 2.

ROC curve analysis showed high diagnostic performance for mean ADC (area under the curve [AUC] = 0.889, $P = < 0.001$) and for FA (AUC = 0.677, $P = 0.002$). A cut-off value of $> 0.909 \times 10^{-3}$ mm^2/s for mean ADC (Sensitivity = 80.3, Specificity = 83.8, positive predictive values [PPV] = 89.1, negative predictive values [NPV] = 72.1) and > 0.139 for FA values (Sensitivity = 80.3, Specificity = 54.1, PPV = 74.2, NPV = 62.5) revealed in differentiating NSCLC group from SCLC group (Table 3 and Fig. 3).

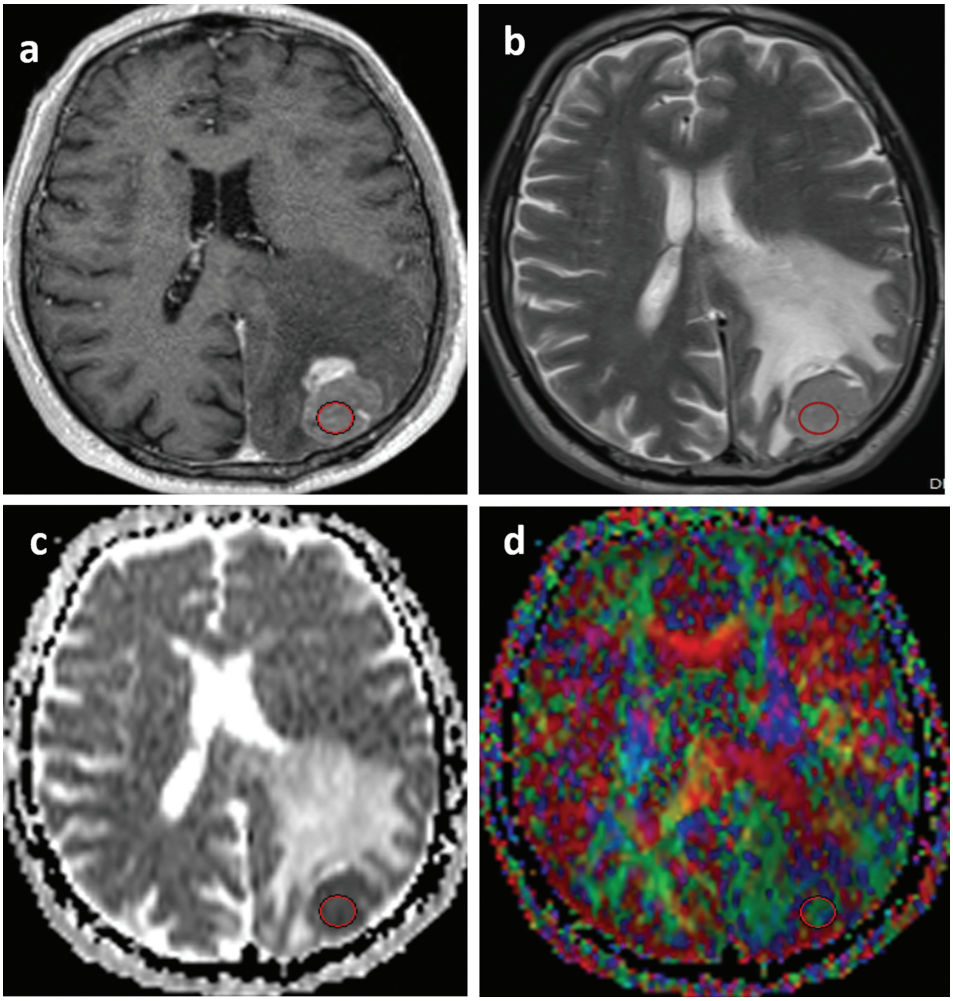

Fig. 1 50-year-old male patient with brain metastases due to the small cell lung cancer. Contrast enhanced axial T1W (**a**), T2W image (**b**), ADC and FA maps (**c** and **d**) show ROI placement. ADC, apparent diffusion coefficient; FA, fractional anisotropy; T1W, T1-weighted; T2W, T2-weighted.

Discussion

In the treatment of patients with brain metastasis, it is aimed to control the disease in the central nervous system, to minimize the side effects related to treatment and to maintain the quality of life. There is 50–60% local recurrence risk after surgical resection of single brain metastases. In addition, complications related to resection such as postoperative neurological worsening, intracranial hemorrhage, permanent paresis, and infections can occur.[3,17] Treatment options of brain metastases are variable, including surgical treatment, complete brain radiation, gamma knife, and systemic chemotherapy, and mostly depend on the cellular subtype and stage of the tumor. It is very important to know the histopathology of the disease in determining the correct treatment approach for brain metastases in lung cancer patients. Improving new, advanced, and non-invasive imaging modalities indicating the histopathological subtypes of lung cancer is important. If the histopathology of the disease can be determined by radiological imaging, this will provide clinicians to choose the right treatment and protect the patient from complications due to unnecessary surgical interventions, especially in cases without histopathological diagnosis yet. This becomes even more considerable when considering the requirement of repeated biopsies due to insufficient sampling in nearly half of the cases and the substantial biopsy-related complication rates.[18] It is well known that surgery is unnecessary for SCLC-related brain metastases. For example, in patients with SCLC, the presence of brain metastases may change the treatment strategy from potentially curative surgical resection to palliative radiation therapy.[3,4,17]

Conventional MRI has a limited capacity in assessing the character of the lesion and the presence and extent of viable tumor tissue and/or tumor necrosis. Therefore, for tumor diagnosis, tumor staging, and determining tumor prognosis invasive techniques including needle or surgical biopsy were required.[19]

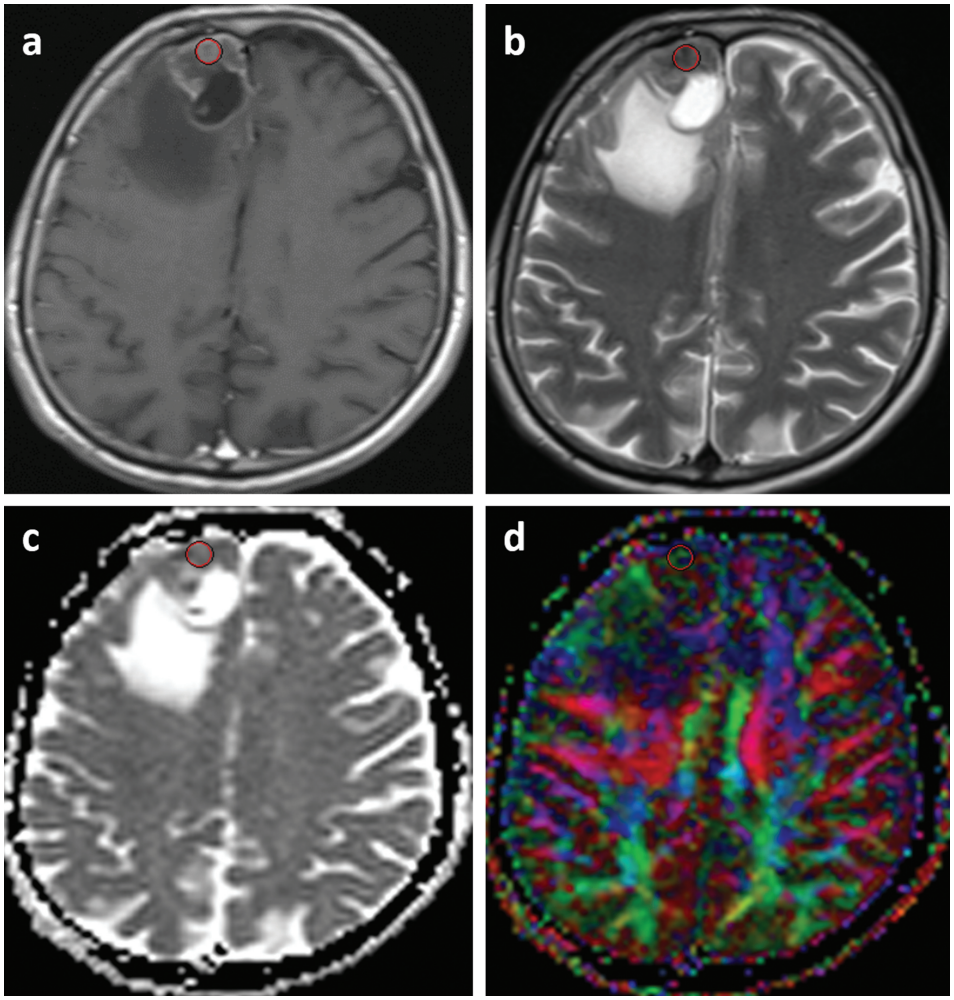

Fig. 2 52-year-old male patient with brain metastases due to the non small cell lung cancer. Contrast enhanced axial T1W (**a**), T2W image (**b**), ADC and FA maps (**c** and **d**) show ROI placement. ADC, apparent diffusion coefficient; FA, fractional anisotropy; T1W, T1-weighted; T2W, T2-weighted.

DTI is a specific MRI technique suited to assess brain parenchyma. The principal of the DTI method depends on microstructure of the tissue.[12] Characteristics of tumors such as necrosis, cystic degeneration and fibrosis vary significantly between tumor types, and these histopathological features can be determined and quantified by DTI.[6,8,20,21] It can be used to distinguish viable tumor from tumor necrosis and/or benign tissue.[19] Most commonly used DTI metrics to analyze the different types of primary and metastatic brain tumors are ADC and FA. Tumor cellularity is the main subject of histological tumor classification.[2] In viable tumor tissue with densely packed tumor cells, low ADC values can be found, whereas in cystic-necrotic tumors and non-tumoral tissue with less cell density, ADC values are expected to be higher. Studies have shown that there was a negative correlation between ADC values and cellularity of brain metastases.[5,11,12,23] FA values are also used as an indicator for showing tissue damage in many diseases like tumors. Studies reported that FA values in brain tumors and peritumoral regions have been affected by histological characteristics of tumors and correlate with cellularity, vascularity, cell density, neuronal and axonal structures, and integrity of fibre tracts. In contrast to ADC, the relationship between FA and cellularity has not been substantiated.[7,12,15,24,25]

It has been reported that ADC values in SCLC metastases compared with NSCLC metastases were significantly lower in different studies. This was explained by the high cellular content of the tumor and big nuclei and little cytoplasm of tumor cells which result in restricted diffusion and lower ADC values.[23,26–28] In our study, compatible with previous studies, in solid SCLC metastases, the mean ADC values were lower than the NSCLC metastases. Lower ADC values may reflect the hypercellularity of these tumors, and decreased intra and extracellular space. These results support the hypothesis that brain metastases of SCLC demonstrate similar histological behavior as the primary tumor.

Table 1 Basic clinical chracteristics of patients with brain metastases due to the lung cancer

	SCLC (n = 19 patients with 37 metastases)	NSCLC (n = 34 patients with 61 metastases)	*P* value
Age (years ± SD)	62.1 ± 8.9	57.8 ± 7.6	0.07
Gender (female/male)	5/14	8/26	1
Size of metastases (millimeter ± SD)	19.5 ± 10.6	17.9 ± 8.7	0.811

NSCLC, non-small cell lung cancer; SCLC, small cell lung cancer; SD, standard deviation.

Table 2 Mean ADC and FA values of solid metastatic lesions

DTI parameters	SCLC met. (n = 38)	NSCLC met. (n = 65)	*P*
ADC (10^{-6} mm^2/s) (mean ± SD)	752 ± 252	1.088 ± 196	0.001
FA (mean ± SD)	0.137 ± 0.04	0.161 ± 0.07	0.003

ADC, apparent diffusion coefficient; FA, fractional anisotropy; NSCLC, non-small cell lung cancer; SCLC, small cell lung cancer; SD, standard deviation.

Table 3 Sensitivity, specificity, positive predictive, and negative predictive values of mean ADC and FA values in differentiation between small cell lung cancer and non-small cell lung cancer with using receiver operating characteristic curve analysis

Diffusion parameters	Cut-off value	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	AUC	*P* values
Mean ADC × 10^{-6} mm^2/s	> 986	80.3	83.8	89.1	72.1	0.889	< 0.001
FA	> 0.139	80.3	54.1	89.1	72.1	0.677	0.002

ADC, apparent diffusion coefficient; AUC, area under the curve; FA, fractional anisotropy; NPV, negative predictive values; PPV, positive predictive values.

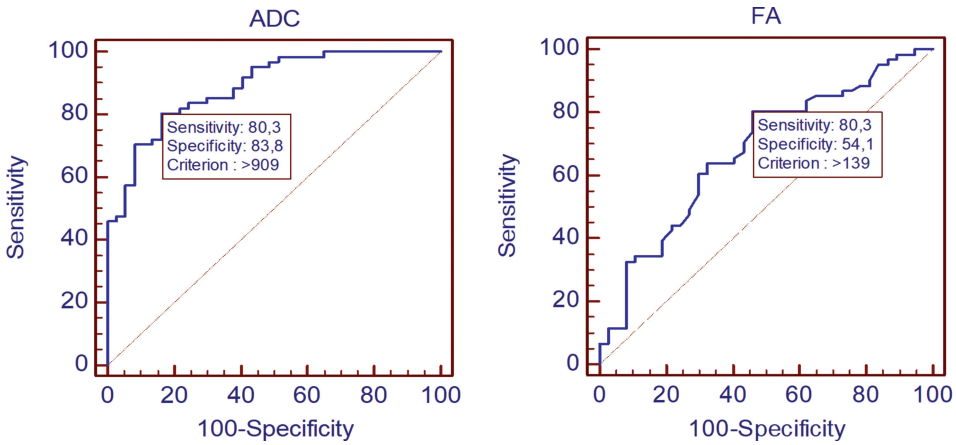

Fig. 3 Receiver operating characteristic curves of the mean ADC and FA values. ADC, apparent diffusion coefficient; FA, fractional anisotropy.

The correlation between the FA values and the tumor cellularity has not been determined yet as both positive and negative correlations have been reported.[6,7,9,12,15,16] Beppu et al. and Inoue et al. reported positive correlation between FA values and glial tumor cellularity.[7,16] On the other hand, in more recent studies, Stadlbauer et al. and Toh et al. suggested that FA is inversely related to tumor cellularity, as confirmedhistologically.[6,9] Tsuchiya et al. investigated the FA values in the differentiation of solitary brain metastasis and high-grade gliomas. However, they did not find any difference between the two groups in both the enhancing part and surrounding region.[15] Lu et al. analyzed the

peritumoral region to differentiate metastases from gliomas.[12] They found higher mean diffusivity values in metastases than gliomas but found no difference in the FA values.[12] The possible explanation for these conflicting reports may be due to the difference of the regions of the tumor analyzed or technical differences in DTI parameters.[8,22] The underlying cause for FA decrease in brain tumors has not been exactly explained yet in the literature. Cruz et al. and Sinha et al. suggested that neoplastic cells and associated peritumoral edema cause changes in the structure of the brain, and this will lead to low FA values in white matter compared to normal brain parenchyma.[24,29] Some researchers found a negative correlation between tumor cellularity and FA values, and attributed this correlation to the reduction in extracellular distance due to tumor infiltration.[12] Hypercellularity causes a decrease in the extracellular space and a decrease in the directionality of diffusion because of the derangement of the microstructures.[6] In our study, the FA values obtained from SCLC metastases were lower than the NSCLC metastases. We thought that the FA decrease in brain metastases of SCLC is related to the decreased extracellular space secondary to high cellularity and decrease in the directionality of diffusion caused by microstructural derangement.[6,26,28]

The major limitation of the current study was small sample size, especially in the SCLC group. Further studies with larger sample sizes may produce more accurate results. The second limitation is the lack of histopathological confirmation of brain metastases in most patients. Histopathological diagnoses were made by investigating the primary lung cancer biopsy specimens in the vast majority of the patients. Sampling of brain metastases is often unnecessary and not practical.

Conclusions

DTI gives important information about tumor cellularity and aggressivity in intracranial metastatic lesions due to lung cancer. SCLC and NSCLC can be discriminated by using ADC and FA values of brain metastasis. ADC and FA values may guide clinicians for the management of intracranial metastatic lesions. In the future, studies with a more patient population with stronger and more significant results will help us in differentiating brain metastases of different histopathological types of lung cancer.

Ethical Approval

This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Ethics Committee of Our University (Date 08.09.2020/No 54022451-050.05.04-).

Conflicts of Interest

The authors declare that there is no conflict of interest.

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