

Differentiation between solitary brain metastasis and high-grade glioma by diffusion tensor imaging

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Abstract. We tested our hypothesis that fractional anisotropy (FA) maps of diffusion tensor imaging could be used to differentiate between a solitary brain metastasis and a high-grade glioma. In seven patients with a solitary metastasis and seven patients with a high-grade glioma, FA values of enhancing and non-enhancing parts of the tumour were compared. Additionally, we visually assessed FA maps. No significant difference in the FA values of either the enhancing or non-enhancing part was found between the two groups. In the visual assessment, displacement of subcortical white-matter fibres was found in five of the seven metastasis patients, but in only one glioma patient. Additionally, discrimination between tumour and oedema was possible in three of the seven metastasis patients, but not in any glioma patient. Although FA values are not helpful in differentiating between the two groups, visual differences in FA values can allow the differentiation. Displacement of white-matter fibres is another finding suggestive of metastasis.

Metastases and high-grade gliomas are the most common intra-axial brain tumours. In many clinical settings, especially in patients with multiple lesions, the diagnosis of brain metastasis is usually straightforward and uncomplicated. However, it is often difficult to differentiate a solitary brain metastasis from a high-grade glioma based on the imaging findings alone, and applied MRI techniques, such as MR spectroscopy [1] and perfusion imaging [2], have been reported to be of value in this regard.

Diffusion tensor imaging (DTI) is an MRI technique that is capable of visualizing the anisotropy of proton motion. Water proton diffusion can be quantified in several ways by using such parameters as fractional anisotropy (FA), mean diffusivity (MD), and eigenvalues of the diffusion tensor (λ_1 , λ_2 , and λ_3) [3, 4]. The advent of DTI has also made it possible to depict major white matter tracts by means of fibre tracking. We hypothesized that changes on FA maps, which are more easily obtained compared with diffusion tensor tractograms and provide information on changes in anisotropy in an objective manner, can be used to make the differential diagnosis between a solitary brain metastasis and a high-grade glioma.

Materials and methods

Study subjects

Seven patients with a solitary brain metastasis (four men and three women; age range 55–70 years; mean age 60 years) and seven patients with a histologically proved grade III or IV glioma according to the WHO classification (four men and three women; age range 17–70 years; mean age 49 years) examined during a 24 month period by MRI that included DTI were retrospectively entered into this study. We excluded two patients examined during the

same period who had intratumoural or peritumoural haemorrhage that may have introduced measurement errors. This was done because a haematoma could have its own FA value different from that of tumour and peritumoural tissue. As the number of excluded patients was rather small, we considered that this did not significantly affect this study. Metastatic lesions were diagnosed as solitary on the basis of the post-contrast T_1 weighted MRI findings. The diagnosis of the brain metastasis was confirmed pathologically in five patients and was made clinically in the other two patients based on the history and MRI findings. The primary lesions responsible for the metastases included lung cancer (four patients), colon cancer (one patient), and uterus cancer (one patient). The remaining patient's lesion was adenocarcinoma of unknown primary. The diagnosis of high-grade glioma was made pathologically in every patient. There were four patients with glioblastoma, two with anaplastic astrocytoma, and one with anaplastic oligodendroglioma. The DTI was performed prior to therapy in all of the metastasis and high-grade glioma patients.

MRI techniques

All MR examinations were performed with a 1.5 T clinical imager (EXCELART XP SPIN Edition; Toshiba Medical Systems, Tochigi, Japan) equipped with a self-shielding gradient system (30 mT m⁻¹ maximum gradient strength and 130 T m⁻¹ s⁻¹ slew rate). Each MR examination consisted of fast spin-echo T_2 weighted and fluid-attenuated inversion-recovery (FLAIR) sequences, pre- and post-contrast spin-echo T_1 weighted sequences, and DTI. To obtain the post-contrast T_1 weighted scans, we injected each patient with a standard dose (0.1 mmol kg⁻¹) of gadolinium-based contrast material.

DTI was performed using an inversion-recovery-prepared single-shot echo-planar diffusion-weighted (DW) sequence. Axial DW images were collected with identical section position and thickness (5 mm) by applying diffusion gradients ($b=0$ and 1000 s mm⁻²) sequentially

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in six directions (xx, yy, zz, xy, xz, and yz). Other parameters for DTI were a repetition time/echo time/inversion time (TR/TE/TI) of 8400/120/2200 ms, a field-of-view of 260 mm × 260 mm, an acquisition matrix of 128 × 128, twenty 5 mm sections with 1.5 mm gap, and three excitations. We generated FA maps from the data thus obtained by using software incorporated in the MR imager.

Image assessment

We measured the FA values of the enhancing part and the surrounding region with T_2 prolongation that probably included oedema and/or tumour infiltration on the FA maps. We applied a region-of-interest (ROI) consisting of more than 10 pixels to each of the two regions on an image display screen (Figure 1). The ROI was placed within the white matter carefully comparing the FA maps with conventional T_2 weighted, FLAIR, and pre- and post-contrast T_1 weighted images of the identical section. In the same manner, we also measured the FA values of the white matter of the centrum semiovale on the contralateral side of the lesion. The measurement was repeated three times by different observers and the values were averaged. The statistical analysis was performed by using the unpaired Student's *t*-test with statistical significance set at $p < 0.05$.

We also visually assessed the FA maps in regard to the following: (1) intensity of the enhancing part and non-enhancing surrounding part of the tumour on FA maps; (2) changes in subcortical white-matter fibres and other major tracts adjacent to the tumour; and (3) other prominent findings. The assessment was performed independently by two neuroradiologists, and when there was disagreement between them, the final judgment was made by consensus.

Results

Measurement of FA values

The results of the FA measurements in the enhancing and non-enhancing parts of the tumour are summarized in Table 1. Measurements of the two parts were not performed in one patient with brain metastasis (brain metastasis case 4) because the tumour was cystic and associated with little oedema. The FA values in both the solitary brain metastasis group and high-grade glioma group were lower in both the enhancing part and non-enhancing part than in normal white matter. The FA values of the enhancing part was smaller in the brain metastases (0.14 ± 0.05) than in the gliomas (0.16 ± 0.05), but the difference was not statistically significant ($p = 0.23$). The difference between the FA values of the non-enhancing part of brain metastases (0.16 ± 0.05) and glioma (0.20 ± 0.09) was also not significant ($p = 0.18$). Nor was the difference in FA values between the enhancing part and non-enhancing part significant in either the brain metastases or the gliomas ($p = 0.56$ and $p = 0.16$, respectively).

Visual assessment of FA maps

The results of the visual assessments of the FA maps of the two groups are summarized in Tables 2 and 3. All of the metastases were located supratentorially. Subcortical white-matter fibres displaced by tumour and/or oedema were depicted in five of the seven patients with brain metastasis (Figure 2). In three of the seven patients, the tumour and oedema showed diffuse hypointensity owing to decreased FA values. However, the tumour and oedema could be discriminated in three patients, because the tumour was clearly hyperintense (brain metastasis case 5)

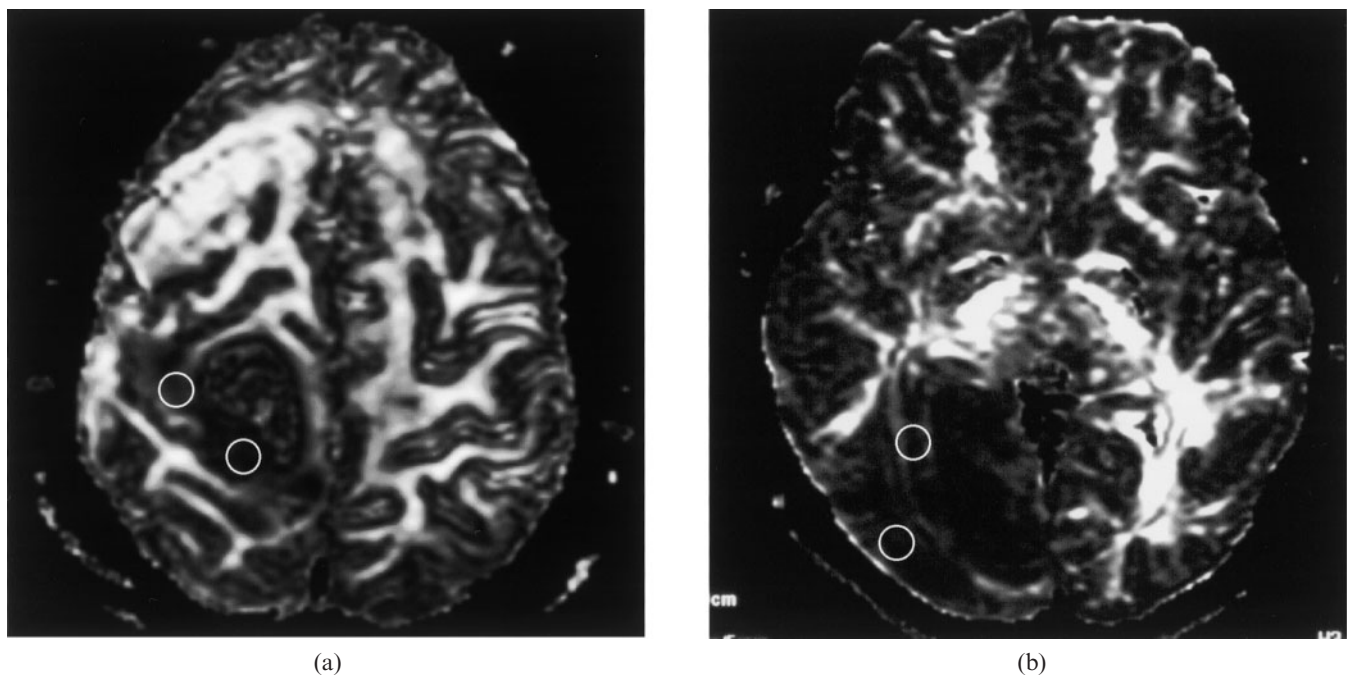


Figure 1. (a) Fractional anisotropy (FA) map shows regions of interest (ROIs) placed in an enhancing part and a surrounding region in a patient with metastatic adenocarcinoma. This image is identical to Figure 2c. (b) FA map shows two ROIs placed similarly in Figure 1a in a patient with glioblastoma. This image is identical to Figure 3c.

Table 1. Fractional anisotropy (FA) values of the tumour, peritumoural region, and normal white matter in 14 patients with solitary metastasis or high-grade glioma

Case no.	Brain metastasis				Case no.	High-grade glioma			
	Age/Sex	Enhancing part	Non-enhancing part	Normal white matter		Age/Sex	Enhancing part	Non-enhancing part	Normal white matter
1	58/M	0.11	0.19	0.62	1	64/F	0.12	0.15	0.62
2	58/F	0.17	0.13	0.57	2	70/F	0.19	0.17	0.57
3	57/M	0.15	0.12	0.5	3	61/M	0.17	0.25	0.51
4	70/M	NA	NA	0.51	4	51/M	0.2	0.37	0.64
5	55/F	0.22	0.12	0.64	5	17/M	0.07	0.12	0.6
6	60/F	0.08	0.18	0.62	6	47/F	0.2	0.15	0.59
7	65/M	0.09	0.22	0.62	7	30/M	0.16	0.17	0.56
Average ± SD		0.14 ± 0.05	0.16 ± 0.05	0.58 ± 0.06			0.16 ± 0.05	0.20 ± 0.09	0.58 ± 0.04

NA, indicates not available owing to cystic nature and lack of oedema. SD, standard deviation.

Table 2. FA map findings in seven patients with solitary metastasis

Case no.	Age/Sex	Location	Diagnosis	Findings
1	58/M	Temporal lobe	Lung carcinoma	Displacement of white matter-fibres and corticospinal tract
2	58/F	Frontal lobe	Lung carcinoma	Diffusely decreased FA
3	57/M	Frontal lobe	Colon carcinoma	Diffusely decreased FA, displacement of white matter-fibres
4	70/M	Parietal lobe	Lung carcinoma	Displacement of white matter-fibres
5	55/F	Parietal lobe	Uterus carcinoma	Diffusely decreased FA, discrimination between tumour and oedema
6	60/F	Frontal lobe	Adenocarcinoma of unknown origin	Displacement of white matter-fibres, discrimination between tumour and oedema
7	65/M	Parietal lobe	Lung carcinoma	Displacement of white matter-fibres and corpus callosum fibres, discrimination between tumour and oedema

FA, fractional anisotropy.

Table 3. FA map findings in 7 patients with high-grade glioma

Case no.	Age/Sex	Location	Diagnosis	Findings
1	64/F	Frontal lobe	AA	Diffusely decreased FA
2	70/F	Pareital lobe	GBM	Diffusely decreased FA
3	61/M	Frontal lobe	GBM	Diffusely decreased FA
4	51/M	Brainstem	GBM	Diffusely decreased FA
5	17/M	Temporal lobe	AA	Diffusely decreased FA
6	47/F	Occipital lobe	GBM	Diffusely decreased FA, optic fibres passing through
7	30/M	Frontal lobe	AO	Diffusely decreased FA, displacement of white matter-fibres

FA, fractional anisotropy; AA, anaplastic astrocytoma; GBM, glioblastoma; AO, anaplastic oligodendroglioma.

or hypointense (brain metastasis cases 6 and 7) compared with the oedema (Figure 2). By contrast, in all seven patients with glioma the enhanced part and surrounding region showed diffuse hypointensity owing to decreased FA values. Thus, the tumour and surrounding oedema could not be discriminated visually in any of the glioma patients (Figure 3). Displacement of the white-matter fibres was noted in only one glioma patient (high-grade glioma case 7).

Discussion

DTI has been applied to the imaging of brain tumours in several ways. Some groups have used FA and MD maps to assess involvement of white matter tracts by gliomas

and suggested that they were useful for surgical planning [5–8]. More recently, one of the clinical applications of DTI, fibre tracking, has been reported to be of value for demonstrating the relationship between the tumour and major white matter pathways, such as the corticospinal tract [9]. In contrast to these studies, the present study was performed to determine whether DTI is capable of being useful for differential diagnosis between a solitary brain metastasis and a high-grade glioma. Most previous studies on the clinical use of DTI employed FA and MD, which represent the directionality and magnitude, respectively, of proton anisotropy. We thought that FA would be an effective index, because FA maps not only quantitatively reflect anisotropy changes but also visualize white matter pathways that may be affected by brain neoplasms.

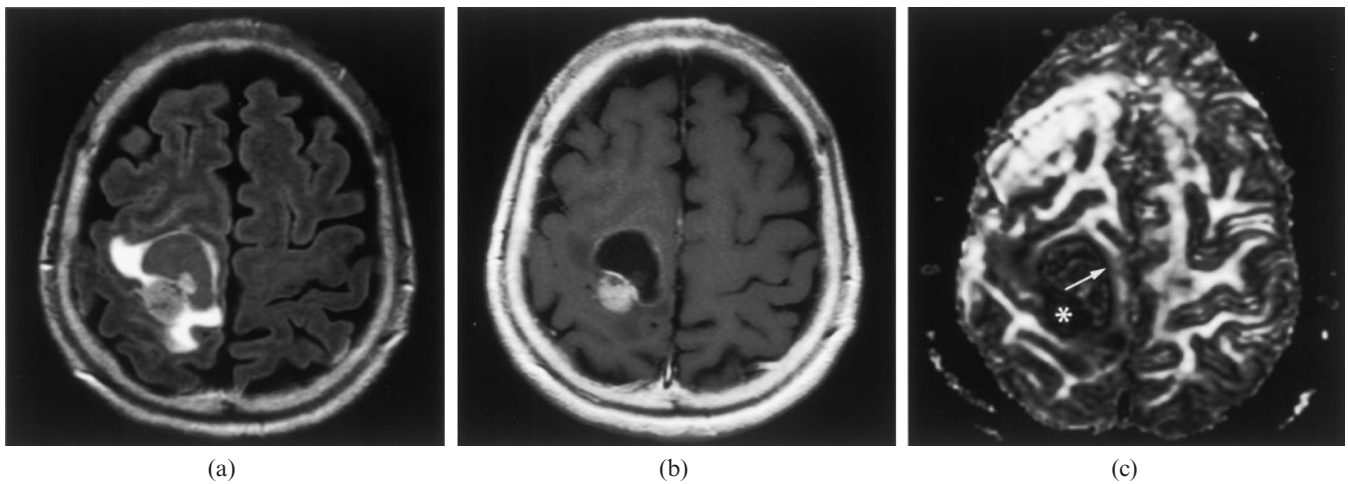


Figure 2. A 60-year-old woman with surgically confirmed adenocarcinoma of unknown origin (brain metastasis case 6). (a) Axial fluid attenuated inversion recovery (FLAIR) image (8000/120/2300/1 [repetition time/echo time/inversion time/number of excitations (TR/TE/TI/NEX)]) shows a hyperintense mass with cystic component surrounded by moderate degree of oedema. (b) Axial post-contrast T_1 weighted image (540/15/1.4 [TR/TE/NEX]) shows enhancement of the solid part as well as that of the cyst wall. (c) Fractional anisotropy (FA) map shows lower FA of the solid part (*, 0.08) than that of the peritumoural oedematous part (0.18). Displaced white-matter fibres are also visible (arrow).

The same as in previous reports [10–13], the FA values in both tumour tissue and peritumoural region were lower than in normal white matter. However, we found no significant difference in FA values between the enhancing tumour regions of brain metastases and high-grade gliomas. Sinha et al [10] explained the decrease in FA values within brain tumour by a loss of structural organization, while Beppu et al [12] pointed to a positive correlation between FA values and both the cellularity and vascularity of tumours. Although no histopathological analysis was performed in our study, we think that such changes are present in tumour tissue and may be responsible for the decrease in the FA values. Our study, however, showed that such FA changes are not reliable for making the differential diagnosis between brain metastasis and high-grade glioma. Tumour infiltration is thought to be present in the peritumoural areas that show

hyperintensity on T_2 weighted images of high-grade gliomas. Areas adjacent to metastatic brain tumours show vasogenic oedema and are usually well demarcated from the tumour. We, therefore, speculated that there might be a difference in the FA values of the peritumoural region between the two types of tumours, but, again, no significant difference was found. Lu et al [11] conducted a study similar to our own and also found no difference in FA values but stated that the MD in the peritumoural region was significantly greater in brain metastases than in high-grade gliomas. They attributed the difference between the two parameters to possible representation of tumour infiltration by the FA. However, both the study by Lu et al [11] and our own found that the FA in the peritumoural region is unreliable as a means of differentiating between brain metastases and high-grade gliomas. The MD in the peritumoural tissue of primary

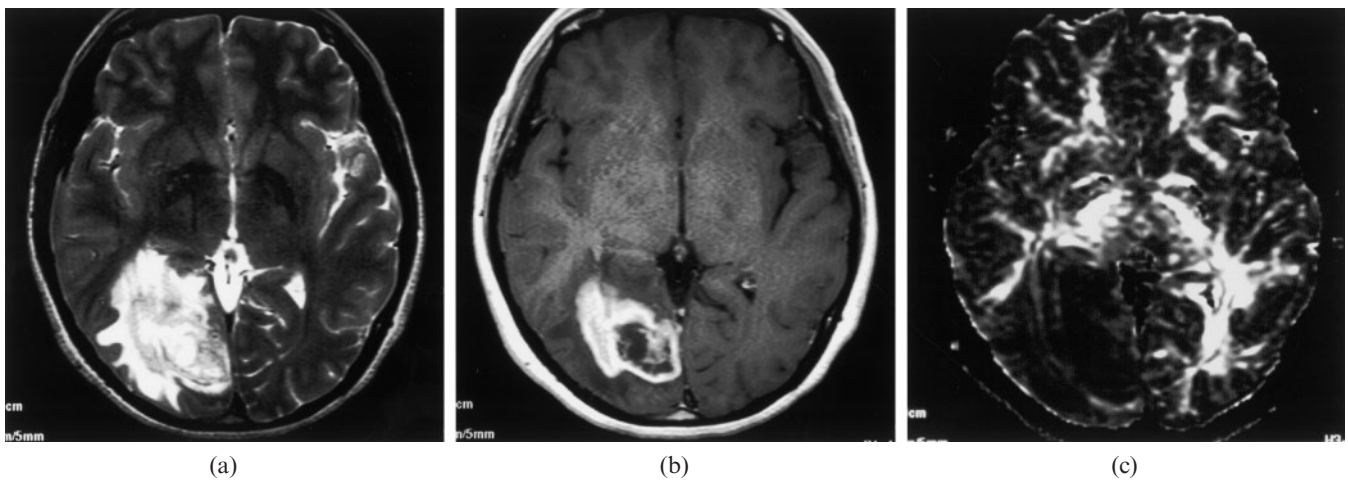


Figure 3. A 47-year-old woman with pre-treatment glioblastoma (high-grade glioma case 6). (a) Axial T_2 weighted image (4240/105/1 [repetition time/echo time/number of excitations (TR/TE/NEX)]) shows a heterogeneously hyperintense mass surrounded by a hyperintense region. (b) Post-contrast T_1 weighted image (540/15/1.4 [TR/TE/NEX]) shows enhancement of the solid part. (c) Fractional anisotropy (FA) map shows diffuse hypointensity due to decreased FA. The enhancing part (0.2) and non-enhancing part (0.15) are hard to discriminate.

brain tumours has been reported to decrease after dexamethasone treatment [14], and the difference between the two kinds of tumours in this respect seems worthy of evaluation.

The visual assessment revealed that both the enhancing and peritumoural non-enhancing regions of both kinds of tumours showed hypointensity owing to decreased FA in most cases. Interestingly, the two regions could be discriminated on the FA maps of three patients with metastasis, but not in any of the patients with glioma. Although there were no significant quantitative differences, there seemed to be a larger variance in the FA between the two regions in metastatic tumours. On the other hand, FA maps clearly visualize subcortical white-matter fibres and adjacent fibre tracts, and they revealed displacement of the fibres in five of the seven patients with brain metastasis, but in only one of the seven patients with glioma. In the other glioma patients, hypointensity owing to decreased FA was observed in the subcortical white matter and it extended to the cortex. Metastatic brain tumours arise within the brain parenchyma and usually grow by expansion, displacing the surrounding brain tissue, whereas high-grade gliomas extend by infiltration. We think that these differences in tumour growth may be a cause of the difference in findings on FA maps.

There are several limitations to this study. First, the patient population was relatively small. Second, our results may also have been influenced by the size and location of the tumours. The visual assessment and the placement of the ROIs for the measurements of FA values were subjective, and we did not set clear criteria for ROI placement to measure the FA values in the peritumoural region. The reasons for selecting FA as the index in this study have been stated above. To overcome these issues, we are continuing this study in a larger series including other parameters such as MD as quantitative indices.

In conclusion, solitary brain metastases and high-grade gliomas cannot be reliably differentiated either visually or quantitatively on the basis of FA changes. However, a diagnosis of brain metastasis is suggested when FA maps outline the tumour or when they demonstrate displacement of adjacent white-matter fibres. Future improvements in spatial resolution may increase the diagnostic capability of FA maps in this regard.

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