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Analysis of fractional anisotropy facilitates differentiation of glioblastoma and brain metastases in a clinical setting

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ABSTRACT

Purpose: Differentiating glioblastoma from brain metastases is important for therapy planning. Diffusion tensor imaging (DTI) was described as a promising tool, however with conflicting results.
Aim: of this study was to analyze the clinical utility of DTI for the differentiation of brain metastases and glioblastoma.
Methods: 294 patients (165 glioblastoma, 129 brain metastases) with preoperative DTI were included in this retrospective study. Fractional anisotropy (FA) was measured via regions of interest (ROIs) in the contrast-enhancing tumor, the necrosis and the FLAIR-hyperintense non-enhancing peritumoral region (NEPTR). Two neuroradiologists classified patient cases as glioblastoma or brain metastases without and with knowledge of FA values.
Results: Glioblastoma showed significantly higher $FA_{contrast}$ (median glioblastoma = 0.33, metastases = 0.23; $P < 0.001$) whereas no significant difference was observed for FA_{NEPTR} (0.21 vs. 0.22; $P = 0.28$) and for $FA_{necrosis}$ (0.17 vs. 0.18, P = 0.37). FA improved diagnostic accuracy of the neuroradiologists significantly from an AUC of 0.84/0.85 (Reader1/Reader2) to 0.89/0.92.
Conclusions: Glioblastoma show significantly higher FA values in the contrast enhancing tumor part than brain metastases. Implementation of a ROI-based measurement of FA values and FA color maps in clinical routine helps to differentiate between glioblastoma and brain metastases.

1. Introduction

Differentiation of intracerebral lesions is important for therapy planning, as treatment strategies (surgery, radio-/chemotherapy) differ between brain metastases and high grade glioma [1,2]. Despite advances in MR imaging, differentiation between high grade glioma and brain metastases remains still challenging. Both present with contrast enhancing and sometimes necrotic areas. In some cases clinical history might be helpful. However differentiation using morphologic criteria only is limited [3].

Many studies assessed the value of diffusion tensor imaging (DTI) for the differentiation between brain metastases and glioblastoma with conflicting results [4–11].

Recent studies showed that fractional anisotropy (FA) is significantly higher in the contrast enhancing tumor region whereas there were no differences in the non-enhancing peritumoral region [10,11]. In other studies lower FA was observed in the contrast enhancing region [12,13]. No differences were observed for mean diffusivity (MD) [11] whereas other studies reported that MD might be helpful in differentiation [14–16]. These conflicting results might be explained by different analysis of DTI parameters or small cohort size.

However, DTI seems to be a promising tool for differentiation between brain metastases and glioblastoma. A recent study showed that diagnostic accuracy of neuroradiologists was improved using FA and MD values of DTI [11].

The aim of this study was to analyze the additional value of FA for the differentiation between glioblastoma and brain metastases in clinical routine in a large patient cohort.

Abbreviations: GB, glioblastoma; ROC, receiver operating characteristics; FA, fractional anisotropy; DTI, diffusion tensor imaging; FLAIR, fluid attenuated inversion recovery; MPRage, magnetization prepared rapid gradient echo; ADC, apparent diffusion coefficient; ROI, region of interest; MD, mean diffusivity; NEPTR, non-enhancing peritumoral region; CI, confidence interval; AUC, area under curve.

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Table 1
Characteristics of MRI sequences.

[MRI]	[Sequence]	[Acquisition time]	[TR/TE]	[Spatial resolution]
Philips Achieva	2D FLAIR	3:00 min	12000/140 ms	0.45×0.45×4 mm
	3D FLAIR	4:52 min	4800/278 ms	1.04 × 1.04 × 1.12 mm
	DTI (15 dir.)	6:26 min	10728/55 ms	2 × 2 × 2 mm
	DTI (6 dir.)	2:09 min	7665/55 ms	2 × 2 × 2 mm
	T1w FFE	2:53 min	530/10 ms	0.45 × 0.45 × 4 mm
	MPRage	5:55 min	9/4 ms	1 × 1 × 1 mm
Siemens Verio	2D FLAIR	3:44 min	8560/136 ms	0.8 × 0.7 × 4 mm
	3D FLAIR	5:52 min	5000/395 ms	1 × 1 × 1 mm
	DTI (6 dir.)	1:28 min	3600/95 ms	1.8 × 1.8 × 4 mm
	T1w FFE	4:02 min	2000/9 ms	0.9 × 0.7 × 4 mm
	MPRage	4:18 min	1900/2.45 ms	1.1 × 1.1 × 1 mm
Philips Ingenia	2D FLAIR	3:00 min	12000/140 ms	0.9 × 0.95 × 4 mm
	3D FLAIR	4:34 min	4800/302 ms	1.12 × 1.12 × 1.12 mm
	T1 w SE	3:16 min	590/10 ms	0.9 × 1.12 × 4 mm
	DTI (15 dir.)	4:58 min	16119/61 ms	2 × 2.04 × 2 mm
	DTI (6 dir.)	3:46 min	8124/66.5 ms	2 × 2.03 × 2 mm
	MPRage	5:59 min	9/4 ms	0.99 × 1.05 × 1 mm

TR: Repetition time; TE: Echo time; TI: Time of inversion; IR: inversion recovery, SE: spin echo, w: weighted, dir.: directions.

Table 2
Morphologic criteria of glioblastoma and brain metastases.

		Glioblastoma	Brain metastases
Location	Supratentorial	164/165 (99.4%)	117/129 (90.7%)
	Infratentorial	1/165 (0.6%)	12/129 (9.3%)
	White matter	69/165 (41.8%)	28/129 (21.7%)
	Cortical	42/165 (25.5%)	81/129 (62.8%)
	Both	47/165 (28.5%)	13/129 (10.1%)
	Fiber tracts/basal ganglia	7/165 (4.2%)	3/129 (2.3%)
	Ventricle	0/165 (0%)	4/129 (3.1%)
Number	Solitary	110/165 (66.7%)	76/129 (58.9%)
	Multiple (>/=2)	55/165 (33.3%)	53/129 (41.1%)
	Multiple/FLAIR-connected	47/55 (85.5%)	9/53 (17.0%)
	Multiple/not FLAIR-connected	8/55 (14.5%)	44/53 (83.0%)
Hemorrhage		7/165 (4.2%)	8/129 (6.2%)
Contact to dura		85/165 (51.5%)	68/129 (52.7%)
Median diameter		40.2 mm [27.8–52.7]	28.0 mm [19.2–37.4]

Non-normally distributed data is shown as median [interquartile range].

2. Methods

The local institutional review board approved this retrospective, non-interventional single-center study (5625-12, 5626-12). The study was in accordance with the ethical standards of the 1964 Declaration of Helsinki and its later amendments [17].

2.1. Patient population

165 consecutive patients with a newly diagnosed (n = 136) or recurrent (n = 29) glioblastoma (WHO IV) and 129 consecutive patients with newly diagnosed (n = 128) or recurrent (n = 1) brain metastases were included in this retrospective study. Patients were included if preoperative DTI was available.

Histopathological analysis of the resected specimens was performed at the local Department of Neuropathology according to the WHO classification for CNS tumors of 2007. Diagnosis was proven histologically for all glioblastoma patients, for patients with brain metastases either by biopsy/surgery of the brain lesion (n = 127) or histopathologically proven primary tumor (n = 2).

2.2. Magnetic resonance imaging

MRI scans were performed at a 3 Tesla (T) MRI scanner, either Philips Achieva or Philips Ingenia (Philips Medical Systems, The Netherlands B.V.) or Siemens Verio (Siemens Healthcare, Erlangen, Germany).

All patients had preoperative T2-weighted fluid attenuated inversion recovery (FLAIR) images (2D or 3D), T1 weighted (w) images prior and after contrast agent (T1 w fast-field echo (FFE) or 3D Magnetization Prepared Rapid Gradient Echo (MPRage)) and diffusion tensor imaging (15 or 6 directions) (DTI)- (Table 1). The contrast agent Magnograf® or Magnevist® was administered intravenously using a standardized protocol (0.2 ml/kg, 0.5–1 ml/s), using a MR compatible contrast medium injection system (Spectris Solaris EP, Siemens Medical, Erlangen, Germany). 224 patients had MRI at Philips Achieva, 64 patients at Siemens Verio and 6 patients at Philips Ingenia.

2.3. Image analysis

Image analysis was done by a neuroradiologist (SB; 6 years of experience). FA was measured using Regions of Interest (ROIs) in the contrast enhancing tumor part ($FA_{contrast}$), the necrosis ($FA_{necrosis}$) and the FLAIR-hyperintense non-enhancing peritumoral region (FA_{NEPTR}) in the preoperative MRI. Four ROIs (5–10 mm) were measured in each region. Next, the mean value was calculated and divided by FA values in the crus posterior of the contralateral internal capsule as it was described before [18] to avoid bias to due measurement at different MRIs. To avoid bias due to hemorrhage,