Diffusion tensor imaging derived metrics in high grade glioma and brain metastasis differentiation

Alma Brakus[1], Jelena Ostojić[2], Miloš Lučić[2, 3]

SUMMARY

Background: *Pretreatment differentiation between glioblastoma and metastasis is a frequently encountered dilemma in neurosurgical practice. Distinction is required for precise planning of resection or radiotherapy, and also for defining further diagnostic procedures. Morphology and spectroscopy imaging features are not specific and frequently overlap. This limitation of magnetic resonance imaging and magnetic resonance spectroscopy was the reason to initiate this study. The aim of the present study was to determine whether the dataset of diffusion tensor imaging metrics contains information which may be used for the distinction between primary and secondary intra-axial neoplasms.* **Methods:** *Two diffusion tensor imaging parameters were measured in 81 patients with an expansive, ring-enhancing, intra-axial lesion on standard magnetic resonance imaging (1.5 T system). All tumors were histologically verified glioblastoma or secondary deposit. For qualitative analysis, two regions of interest were defined: intratumoral and immediate peritumoral region (locations 1 and 2, respectively). Fractional anisotropy and mean difusivity values of both groups were compared. Additional test was performed to determine if there was a significant difference in mean values between two locations.* **Results:** *A statistically significant difference was found in fractional anisotropy values among two locations, with decreasing values in the direction of neoplastic infiltration, although such difference was not observed in fractional anisotropy values in the group with secondary tumors. Mean difusivity values did not appear helpful in differentiation between these two entities. In both groups there was no significant difference in mean difusivity values, neither in intratumoral nor in peritumoral location.* **Conclusion:** *The results of our study justify associating the diffusion tensor imaging technique to conventional morphologic magnetic resonance imaging as an additional diagnostic tool for the distinction between primary and secondary intra-axial lesions. Quantitative analysis of diffusion tensor imaging metric, in particular measurement of fractional anisotropy in peritumoral edema facilitates accurate diagnosis.*

Keywords: primary neoplasms, malignant neoplasms, brain, metastases, diffusion tensor imaging

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[1] Center for radiology, Clinical Center of Vojvodina, Hajduk Veljkova 1, 21000 Novi Sad

[2] Faculty of Medicine, University Novi Sad, Hajduk Veljkova 3, 21000 Novi Sad

[3] Oncology Institute of Vojvodina, Put dr Goldmana 4, 21204 Sramska Kamenica

Correspondence to:
Alma Brakus
alma.brakus@kcv.rs
alma.brakus@gmail.com

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INTRODUCTION

Pretreatment distinction between a high-grade glioma (HGG) such as glioblastoma (GBM) and intracranial secondary deposits (ISD) is frequently encountered dilemma in neurosurgical practice (1, 2). But, precise distinction is needed in order to define further diagnostic algorithm and to plan surgical resection or radiotherapy. A solitary brain metastasis may be the first manifestation of disease in a patient without a known primary malignancy.I In this case, dedicated diagnostic algorithm is required (2). Precise plan for surgical resection or radiotherapy permits minimizing injury of healthy tissue (3–6). In case of glioblastoma, due to its tendency to infiltrate the adjacent white matter (WM),a greater extent of resection is needed. Besides that, patients with metastatic disease are at increased risk of perioperative complications, or surgery could be even precluded (4).

Despite their different histological structure, the distinction between primary and secondary tumors based on conventional morphologic magnetic resonance imaging (MRI) may present a challenge. Imaging features are not specific and frequently overlap: both tumors present as a solitary or multiple space-occupying lesion(s), inhomogeneous due to areas of cystic degeneration or necrosis. Both neoplasms induce the neoangiogenesis - proliferation of the blood vessels without a blood-brain barrier resulting in irregular, peripheral contrast enhancement (2-7).

This limitation of morphological MRI was the initial point for this study. With the development of stronger diffusion gradients, recent applications of diffusion-weighted imaging in whole-body imaging have attracted considerable attention. DTI is a noninvasive imaging technique which reveals microstructural tissue properties by measuring water molecule movement. Within one voxel, DTI quantifies the magnitude and the preferential direction of the diffusion (8-9). A variety of difusion-derived feature maps, such as fractional anisotropy (FA) and mean difusivity (MD) can be extracted from DTI images.

FA and MD values have been indicated as an alternative discriminator between HGG and ISD in several studies and meta-analyses (10-33). FA values are negatively correlated with the extent of tumor infiltration (11, 12). This finding indicates that the reduced FA within the peritumoral tissue can be attributed to increased extracellular water but also to axonal disorientation caused by infiltration of the tumor beyond the margin detectable on T2w sequences. Conversely, ADC values are increased in the peritumoral edematous region and negatively correlated with the degree of gliomatous infiltration (13- 15).

Systematic review with meta-analysis conducted by Sternberg *et al.* (10) found that DTI is more sensitive for neoplastic infiltration of peritumoral WM compared to other imaging modalities: MR perfusion, MR spectroscopy or conventional MRI. In addition, this research demonstrated that decreased fractional anisotropy in peritumoral tissue, compared with the corresponding contralateral brain region is an indicator of neoplastic invasion beyond the tumor borders on T2w images (10). The other analysis of the DTI maps assessed a significant increase of FA and a significant decrease of MD in the region surrounding glioma in comparison with brain metastases (11,12).

Histologic diagnosis	N (%)
ISD	38 (46.91)
GBM	43 (53.09)

ISD- intracranial secondary deposit, GBM - glioblastoma

Table 1: The frequency of pathological diagnoses

Gender	ISD	GBM	Total
		N (%)	
Male	1.2	2.3	1.9
Female	1.4	1.1	0.9
Age	**ISD**	**GBM**	**Total**
		Years	
Range	41-85	37-75	37-85
Mean ±SD	62.6 ± 11.5	59.4 ± 10.97	60.8 ± 11.02

ISD- intracranial secondary deposit, GBM - glioblastoma

Table 2: Frequency of pathological diagnoses concerning gender and age

However, some other researches (16-33) used DTI with varying results. In the present study, we collected the data from the patients examined in our institution and analyzed it. Lastly, we compared our results with findings of other similar studies.

Different types of interaction between neoplasm and its environment result in distinct diffusion properties: a metastasis induces vasogenic edema and increased water content reduces density but preserves fiber orientation. Glioblastomas also induce vasogenic edema, In addition, another factor that contributes to the reduction of anisotropy is distortion of surrounding axons caused by glioma infiltration (34, 35).

Fractional anisotropy (FA) is a DTI derived parameter that quantifies the fraction of diffusion that is anisotropic. Thus, FA value is a scalar, unitless metric scaled between 0 and 1. Value zero is assigned to random, isotropic diffusion with equal diffusion coefficients in all directions - as in cerebrospinal fluid or gray matter (GM). Higher FA value indicates there is a preferential direction of water molecule motion, as it is within axonal bundles. Value 1 describes a theoretical case where all molecules diffuse along the same axis (5, 17, 28, 33).

Mean diffusivity (MD) is a calculated averaged diffusion. Therefore, MD is a non-specific parameter sensitive to the diffusion magnitude. MD can be affected by increased extracellular water, but also by any process that affects water motion barriers within the intra- and extracellular space such as increased tissue cellularity, demyelination or rarefaction of neuropil (20, 21, 28, 34–37).

The purpose of this study was to determine whether the dataset of DTI metrics contains information that may be used for the distinction between primary and secondary intra-axial neoplasms. FA and MD values were measured and compared. We also tested differences of means between intratumoral and peritumoral locations.

METHODS

In this prospective study, standard contrast MRI and diffusion tensor imaging (DTI) examinations were performed in 84 adult patients with expansive, ring-enhancing, intra-axial lesion. At the time of the initial presentation, all patients were untreated. The study protocol and data collection were approved by the Ethics Committee for Medical Research of the Medical Faculty in Novi Sad. Moreover, written informed consent was obtained from all examinees, in accordance with the Declaration of Helsinki for the use of MR images for research purposes.

MRI exams were carried out on a 1.5-T MRI system (GE Healthcare Signa HDxt scanner 1.5T), with a head coil, included axial and sagittal T2-weighted (W) sequences, and axial fluid-attenuated inversion recovery (FLAIR) DWI, SWI and T1 sequences. After standard protocol including contrast-enhanced T1-weighted (W) spin-echo (SE) imaging (TR/TE, 600/12; 256 × 256 matrix size; 3 mm slice thickness) and DTI Single Shot Echo Planar sequence DTI acquisitions were applied with b-values 1000 s/mm^2 in 25 gradient directions (TR/TE 6.200/103; 256 × 256 matrix size; 3 mm slice thickness).

All examinations were reviewed and analysed by a neuroradiologist. The DTI datasets were transferred to a workstation and processed using Functool LX software. Diffusion parameter maps were generated, including the mean diffusivity (MD) map, fractional anisotropy (FA) map, and color-coded FA-derived map. ADC maps were co-registered with FA, to properly place the region of interest (ROI). The size of ROI ranged from 20 to 30 mm^2.

Each lesion was subdivided into two regions for quantitative analysis: enhancing region and immediate peritumoral region in the white matter (IPR) (location 1 and 2, respectively). ROI of location 1 was placed in the enhancing portion of tumor, excluding areas of colliquative necrosis and hemorrhagic parts. IPR (location 2) was defined as the area that was not enhancing on contrast-enhanced T1-weighted images, within 1 cm of the enhancing portion of the tumor, that correlates to a zone of hyperintensity on T2-weighted and FLAIR images (Figures 1 and 2).

In the first part of the study, FA and MD values were measured and the mean values of each parameter were compared. In the second part of the study, differences of the mean values of fractional anisotropy (FA) and MD values between locations 1 and 2 were tested, in each group of patients.

STATISTICAL ANALYSIS

Statistical analysis of the data was performed with software package SPSS version 20. Variables were presented as mean ± standard deviation (±SD), median, range, number of cases (n), frequencies, and percentage (%). Shapiro-Wilk test was used to check whether data were normally distributed. Data that violated the normality assumptions were compared using Mann-Whitney test. The null hypothesis significance test was used to determine if there was a significant difference in DTI parameters between two tumor groups. Independent sample t-test was used for comparison of mean values, at a significance level of $p < 0.05$ (within the 95% confidence interval). Histograms and boxplots were used for graphic assessment.

After the exam, specimens were obtained by CT-assisted stereotactic biopsy. According to the pathohistological findings, patients were divided into two groups: GBM or ISD.

RESULTS

Our study included 85 patients with ring-enhancing tumefactive lesions on MRI imaging. Four patients were excluded out from the analyses due to

inconclusive or inappropriate patohistology findings. Patohistology proved diagnosis of high grade glioma in 43 (64.4%) patients; metastatic lesion was verified in 38 (44.6%) patients (Table 1). The majority of patients were in the 6th decade (32/81, 39.5%). GBM patients were of mean age 59.4± 13.89 (median ± SD). Patients with secondary deposits were of average age (62.6 ± 11.5 years). Distribution concerning gender and age is represented in Table 2.

Assesing normality of the measured data with Shapiro-Wilk test observed normal distribution in all datasets except for a small deviation of the MD values in location 2, which violated the normal or Gaussian distribution. For this reason, the distribution of this variable was additionally tested with Mann -Whitney U- test, that confirmed variable was normally distributed. The range and mean values of each measured parameter with its standard deviation were shown in Table 3.

In the first part of the study, means between two groups of neoplasms were compared. Statistically significant difference between FA means was found on location 2. FA values were higher in the peritumoral region of glioblastomas in comparison with peritumoral region of brain metastases ($t = 2.476$, $p = 0.016$). Conversely, in other cases the null hypothesis was not rejected: there was no statistically significant difference in peritumoral MD values between groups on location 2 ($t = 1.627$, $p = 0.108$). On intratumoral location, difference between FA and MD values was negligible in both groups ($t = 1.284$, $p = 0.203$ and $t = 0.9$, $p = 0.371$, respectively) (Table 3).

In the second part of the study, inter-location differences were tested: mean values of both parameters in location 1 and location 2 were compared.

Inter-location difference between MD means exceeded the level of statistical significance in both groups ($t = 2.042$, $p = 0.045$ and $t = 4.1$, $p < 0.01$). A significant reduction of FA value in the intratumoral location, in comparison to peritumoral location was observed in the group with a primary tumor ($t = 2.869$, $p = 0.005$).

Contrary to the above mentioned, no significant difference was found for FA values within secondary deposits in tumoral and peritumoral region ($t = 0.369$, $p = 0.714$).

		FA (10^{-3} mm^2/s)		MD (10^{-3} mm^2/s)	
		ISD	GBM	ISD	GBM
Location 1	Range	0.57- 2.34	0.54 -2.92	0.72-2.99	0.68 -1.98
	means±SD	1.29 ±0.39	1.45± 0.61	1.26 ±.0.44	1.128± 0.34
Location 2	Range	0.83 -2.35	0.84 -3.06	0.5-1.41	0.56 - 1.49
	means±SD	1.25± 0.46	1.59 ± 0.56	0.92± 0.20	1.00 ±0.27

SD- standard deviation

Table 3: Values of fractional anisotropy (FA) and mean diffusivity (MD) in intracranial secondary deposit (ISD) and glioblastoma (GBM) cases, in intratumoral (location 1) and peritumoral (location 2) locations

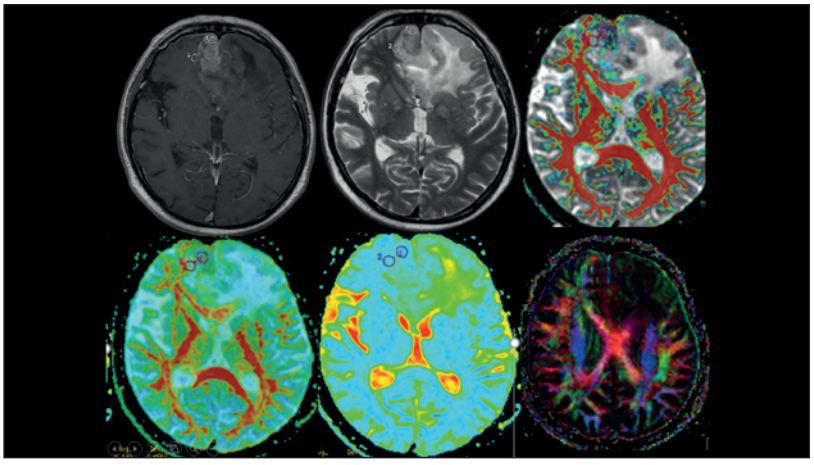

Figure 1. Technique of ROIs placements. Upper row: axial T2w FLAIR, postcontrast T1w image, ADC map co-registered with FA map, respectively. Lower row: FA, MD and color-coded map ROI of location 1 (respectivey) were placed in the enhancing portion of tumor (circle 1), excluding areas of necrosis and hemorrhage. Location 2 was positioned in immediate peritumoral region (circle 2). IPR (location 2) was defined as the area that is not enhancing on contrast-enhanced T1-weighted images, within 1 cm adjacent to the enhancing portion. Within two selected locations, mean values of fractional anisotropy (blue circles) and mean diffusivity (white circles) were measured

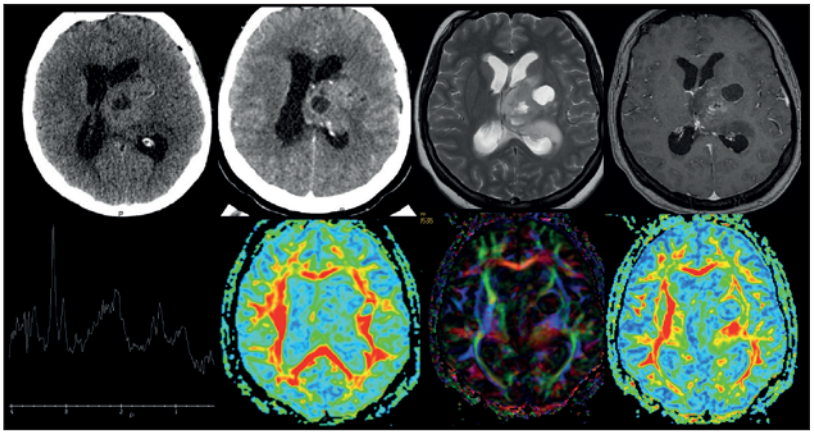

Figure 2. Upper row: CT without and with contrast (T2w and T1w images), respectively. Lower row: magnetic resonance spectroscopy, ASL, FA color coded, and FA map, respectively. The intra-axial lesion with a peritumoral cyst, elevated choline/creatine ratio, and reduced N-acetylaspartate and elevated lactate levels. Peritumoral edematous region in ASL map was characterized by moderate to low signal indicating its hypovascularisation. FA color-coded and FA map demarcated central zone with reduced anisotropy, surrounded by an incomplete ring of elevated FA values (ASL – arterial spin labeling; FA – fractional anisotropy)

DISCUSSION

There has been growing interest in MR techniques that bring quantified data related to structural tissue properties. Signal intensity is relatively quantified and image analysis is based on the interpretation of signal changes. For this reason, many studies analyzed the sensitivity of DTI, but there was a diversity of survey results (7, 10-46).

Our findings are concordant with the majority of the published studies: alterations of diffusion tensor metrics reflect changes in fiber integrity or in water content, thus indicating neoplastic micro-infiltration or edema (5-13,16-25). Changes in FA values, compared to a mirrored region in the contralateral normal-appearing white matter, were noticed within six days after the implementation of glioma cells in rats (39).

Concluding remark of the meta-analysis that summarized data from nine studies confirmed an increased MD and a decreased FA value in peritumoral tissue, compared to corresponding contralateral region (10). In addition, this analysis pointed out inconsistency in the selection of the peritumoral region. Undoubtedly, standardized methods both for acquisition as well as post-processing are required.

In our study, a statistically significant increase of FA values was noticed in the region surrounding high-grade gliomas, compared to brain metastases. Results collected from our patients were consistent with

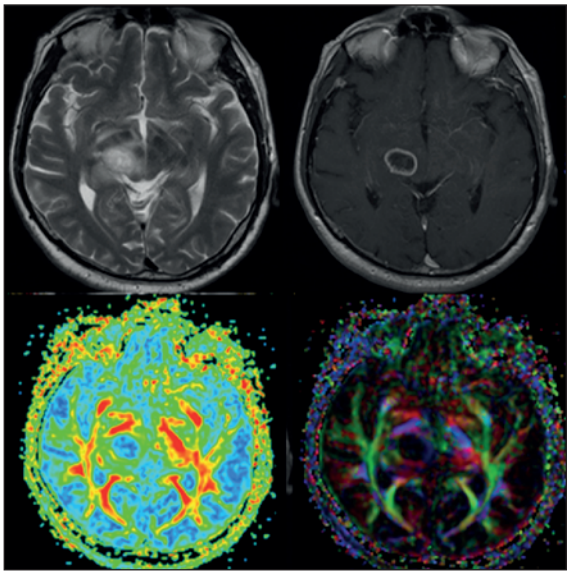

Figure 3. Upper row: T2w and T1w postcontrast series delineate expansive cystic lesion in the right cerebral crus. Lower row: Fractional anisotropy map. Color-coded FA map showing a central zone of reduced anisotropy values, embedded within a circle of displaced fibers

meta-analysis of Sternberg and Lipton (10) and several other studies (7, 13-16, 25, 27, 43-45). On the contrary, El-Serougy *et al.* included broad peritumoral area, observing higher FA values around metastatic brain tumors (37, 38).

However, some studies did not find significant differences in the peritumoral edematous region, questioning the discriminative ability of these metrics (42, 46).

In our study, no significant difference was found between MD means both in the peri-tumoral and intratumoral area- indicating the limited usage of this parameter for discerning gliomas from brain metastases. This was consistent with several previous researches (15, 22, 42). The discriminative power of this parameter would possibly be stronger if 3T MRI device was used.

Inter-location differences of both parameters were present in both types of neoplasms, with one exception: in patients with a secondary deposit the difference in FA values was not observed in the (peripheral?) enhancing part of the tumor and non-enhancing peritumoral region. These results were concordant with research that registered centripetally growing gradient of ADC values– from tumoral lesion to peritumoral region (13). Region of tissue immediately surrounding the tumor exhibited lower rates of diffusivity (ADC) (7, 13, 18, 19, 32). Also, some studies confirmed a difference in ADC values or MD values of vasogenic and interstitial edema (13, 15, 23).

In the intra-tumoral area, no significant change in FA or MD was detected between gliomas and metastases, that was consistent with previous studes (36-43). This observation may be related to the presence of microcystic degeneration within the glioblastomas and varying degrees of necrosis or hemorrhage in the two tumor types. On the other hand, Bette *et al.* found that glioblastoma shows significantly higher FA values in the contrast-enhancing tumor part than brain metastases (29).

These diferences in published results reflect a diversity of factors that determine the values of DTI parameters. Alteration of metrics can be attributed not only to increased extracellular water and infiltration of WM tracts, but also to myelination, axon diameter, and intravoxel axonal coherence of fiber orientation. Secondly, a considerable heterogeneity of FA was observed even between specific WM tracts (43).

Measurement error can occur within the voxel containingof two tracts directed in perpendicular planes. This is the case when displacement probability is incorrectly calculated as - equal for all directions (44).

There are some properties of primary neoplasms that increase anisotropy *i.e.* high cellularity correlate inversely with ADC and reduced diffusion rate reflects with decreased MD values. In the solid part of the tumor, high-grade gliomas may present higher cellular density in comparison with metastases. This cellularity originates from neoplastic cell proliferation or reactive gliosis induced by gliomas (9, 18, 25).

Unlike metastasis, glioblastoma cells produce tumor-specific products that change the content of the extracellular matrix. Serving as substrates for adhesion and subsequent migration of cells through the extracellular space, these molecules are accumulated in a directed way, leading to a high anisotropy of extracellular matrix (34).

The rapid growth of the tumor exerts pressure over the region that changes the average shape of cells from spherical to oblate spheroidal, effectively increasing anisotropy (20, 25).

In metastatic lesions, surrounding brain parenchyma shows reactive astrocytosis, proliferation of microglia and vascular proliferation, all of which might be the source of broad range of measured values (45, 46).

Metastasis express more vascular endothelial growth factor that contributes to vascular permeability (34, 42). Vasogenic edema involves an increased water component and reduces axonal density, therefore diffusivity is enhanced and MD increased.

Ischemia also decreases the rate of diffusion. Furthermore, two effects related to MR equipment (eddy currents and non-linear gradients) can affect the measured diffusion coefficients within that voxel (44).

We believe that significant variabilities in published studies can be atributed to the plurality of factors mentioned above.

Our study has some limitations. The first one was related to reproducibility in the selection of ROIs, due to its manual placement. To overcome this potential bias, ROIs were selected on FA and MD maps that have been superimposed on T1w contrast series (Figures 1 and 2). Several studies suggested advantage of a larger, more inclusive, ROI (8, 21, 36, 37, 39). However, we feel that variations in the ROI drawing schemes were small. The second limitation related to the potential spatial mismatch between the ROI determined for measurements, and the location of the specimen taken at biopsy. This issue could be relevant in heterogeneous lesions with zones of different histologic tumor grade. The third limitation was heterogeneity among metastases, but analysis with a subdivided sample did not find the significant difference, hence justifying collecting metastasis in one group (28, 43). Despite the above-mentioned shortcomings, significant reproducibility was reached.

CONCLUSION

The results of our study justify the use of the DTI technique as an additional diagnostic tool for the purpose of distinction between primary and secondary intraaxial lesions. Quantitative analysis of DTI metric, measurement of FA in peritumoral edema in particular improves interpretation of

conventional morphologic MRI and further extraction of valuable informations from DTI dataset is possible.

Declaration of Interests

Authors declare no conflicts of interest.

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