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Diagnostic utility of fractional anisotropy in differentiating glioma grades

Zeynep FIRAT[1], Cumhur Kaan YALTIRIK[2], Gazanfer EKINCI[1]

[1] Department of Radiology, School of Medicine, Yeditepe University, Istanbul, Turkiye
[2] Department of Neurosurgery, School of Medicine, Maltepe University, Istanbul, Turkiye
Corresponding Author: Zeynep FIRAT
E-mail: zeyfirat@yahoo.com

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ABSTRACT

Objective: This study investigates the diagnostic potential of fractional anisotropy (FA), derived from diffusion tensor imaging (DTI), for distinguishing low-grade (grade 1–2) from high-grade (grade 3–4) gliomas by evaluating the tumor core, tumor margin, and peritumoral region.

Patients and Methods: Sixty patients with histopathologically confirmed gliomas (grade 1–2, n=30; grade 3–4, n=30) underwent preoperative 3T Magnetic Resonance Imaging (MRI) including DTI. FA was measured in the tumor core (solid component), tumor margin, peritumoral region, and contralateral normal-appearing white matter (NAWM). NAWM-normalized FA ratios were also evaluated. Groups were compared using independent-samples t tests, and diagnostic performance was evaluated with receiver operating characteristic (ROC) analysis including AUC, optimal cut-off, sensitivity, and specificity.

Results: Fractional anisotropy in tumor-related regions was lower than contralateral NAWM in both groups. Grade 3–4 gliomas showed significantly lower raw FA in the tumor core, tumor margin, and peritumoral region, whereas NAWM FA did not differ between groups. NAWM-normalized FA ratios were also significantly reduced in grade 3–4 gliomas (all $p < 0.05$). Tumor core raw FA showed the highest discrimination (AUC = 0.842, 95% CI: 0.734–0.932, cut-off = 0.150, sensitivity = 0.80, specificity = 0.73).

Conclusion: Raw and NAWM-normalized FA metrics, particularly in the tumor core and peritumoral region, differentiated grade 1–2 from grade 3–4 gliomas and may serve as supportive noninvasive markers for preoperative grading.

Keywords: Diffusion tensor imaging, Fractional anisotropy, Glioma, Tumor grading

1. INTRODUCTION

Gliomas are the most common primary brain tumors in adults and show substantial heterogeneity in clinical course and histopathological features [1, 2]. According to the World Health Organization (WHO) classification of central nervous system tumors (2021), glioma grading (grade 1–4) is based on key histologic criteria, including cellularity, mitotic activity, necrosis, and microvascular proliferation [3]. High-grade gliomas (grade 3–4), particularly glioblastoma (grade 4), are typically aggressive and associated with a poor prognosis, whereas low-grade gliomas (grade 1–2) generally progress more slowly and have more favorable outcomes [1, 2]. Therefore, accurate preoperative grading is critical for treatment planning, prognostication, and patient counseling [4].

Magnetic Resonance Imaging (MRI) remains the cornerstone of glioma evaluation by providing detailed anatomic characterization [5]. Conventional MRI sequences, including contrast-enhanced T1-weighted imaging and T2/FLAIR, are routinely used to assess features such as enhancement and edema. However, these findings may overlap between low – and high-grade gliomas, limiting the specificity of conventional MRI for reliable tumor grading [6, 7]. Accordingly, advanced techniques such as diffusion tensor imaging (DTI) have

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attracted increasing interest for probing tissue microstructure beyond gross morphology [8].

Diffusion tensor imaging enables quantitative assessment of water diffusion anisotropy within white matter, generating metrics such as fractional anisotropy (FA) [9, 10]. FA reflects the degree of directional diffusion, with higher values indicating preserved and coherent fiber organization. In contrast, decreased FA may reflect microstructural disruption due to tumor infiltration, vasogenic edema, or necrosis [11, 12]. Prior studies have consistently reported reduced FA in gliomas, and lower FA has been associated with higher tumor grade and greater microstructural disorganization [13-17].

Beyond the tumor core, the tumor margin and peritumoral region may harbor infiltrative tumor cells and reactive changes that are relevant for surgical planning and margin definition [18, 19]. In addition, normalizing FA values to contralateral normal-appearing white matter (NAWM) may reduce inter-individual variability and better emphasize tumor-related alterations [20-22]. Despite this growing evidence, direct comparisons of FA across distinct tumor regions using both absolute and contralateral-normalized measurements, remain limited.

In this study, we evaluated whether FA measurements from the tumor core, tumor margin, and peritumoral region, obtained as raw values and normalized to contralateral NAWM, can differentiate low-grade (grade 1–2) from high-grade (grade 3–4) gliomas. We also assessed their diagnostic performance using receiver operating characteristic (ROC) analysis. We further hypothesized that normalization would enhance grade discrimination by reducing inter-subject variability.

2. PATIENTS and METHODS

Patients

This study included 60 patients with histopathologically confirmed gliomas (21 females and 39 males). In the low-grade group, there were 10 females and 20 males, whereas the high-grade group comprised 11 females and 19 males. Pathological evaluation identified 30 low-grade gliomas (grade 1–2), including 5 pilocytic astrocytomas, 9 astrocytomas, and 16 oligodendrogliomas. The remaining 30 patients had high-grade gliomas (grade 3–4), including 9 astrocytomas (grade 3) and 21 glioblastomas (grade 4). Tumor classification was based on histopathological grading; molecular data were not uniformly available for all cases.

Patients were excluded if DTI was unavailable, image quality was inadequate, or if there was a history of prior brain surgery, radiotherapy, or chemotherapy, or co-existing intracranial lesions. The study was approved by the Yeditepe University Institutional Ethics Committee (Approval No: 202507Y0884, 2025). All participants provided written informed consent in accordance with institutional and international ethical guidelines.

Magnetic Resonance Imaging (MRI)

All preoperative MRI examinations were performed on a 3T clinical scanner (Philips Healthcare, Best, the Netherlands) using a 32-channel head coil and a standard brain tumor protocol. In addition to routine non-contrast and contrast-enhanced MRI sequences, a DTI sequence was acquired in the axial plane covering the entire brain (TR = 6500 ms, TE = 77.3 ms, b-values = 0 and 800 s/mm^2, 32 diffusion-encoding directions, voxel size = 2.5 × 2.5 × 2.5 mm). FA maps were generated using Philips Extended MR WorkSpace (EWS) software (Philips Healthcare).

FA Measurement and ROI Placement

Four regions of interest (ROIs) were defined for FA analysis: (1) contralateral NAWM at the corresponding anatomic level and mirrored location of the lesion, used as the reference; (2) the solid component of the tumor core, placed within the most viable tumor portion; (3) the tumor margin, positioned along the interface between tumor and adjacent brain parenchyma; and (4) the peritumoral ROI, placed approximately 1 cm from the tumor boundary on T2-weighted/FLAIR images within the perilesional tissue, using the visible lesion margin as the reference. All ROIs were manually drawn with an area of 10–20 mm^2. Care was taken to avoid cystic, necrotic, hemorrhagic, vascular, and artifact-prone areas (Figure 1).

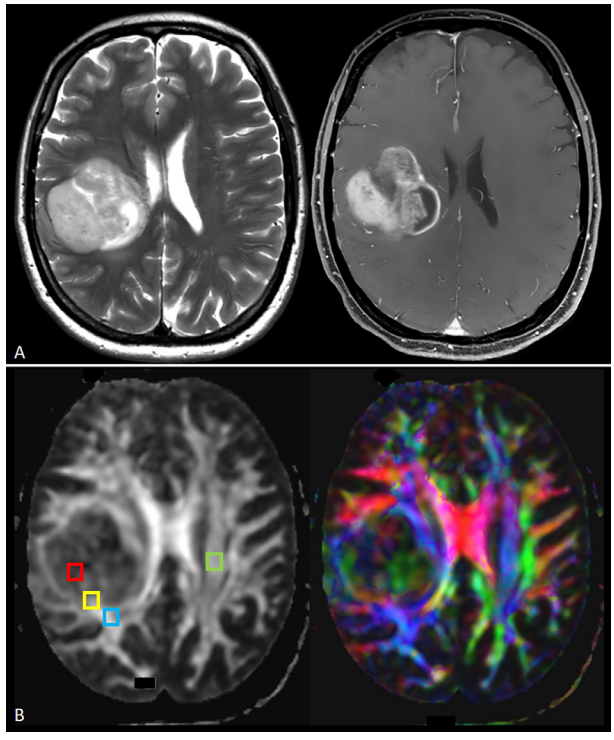


Figure 1: *A 47-year-old woman with a glioblastoma.* ***(A)*** *Axial T2-weighted and post-contrast T1-weighted MR images demonstrate tumor involvement of the right transverse parietal gyrus and insular region.* ***(B)*** *Corresponding FA map and color-coded FA map illustrating ROI placement for FA measurements:* ***red****, tumor core (solid component);* ***yellow****, tumor margin;* ***blue****, peritumoral region;* ***green****, contralateral normal-appearing white matter (NAWM) used as the reference.*

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ROI placement was adapted to grade-related imaging features. In grade 1–2 gliomas, where contrast enhancement is often absent or limited, T2-weighted and FLAIR images were primarily used to delineate tumor extent and guide placement of the tumor margin and peritumoral ROIs. In grade 3–4 gliomas, post-contrast T1-weighted images were additionally used with T2/FLAIR to define tumor boundaries; the tumor-core ROI was preferentially placed within the enhancing viable solid portion. T2/FLAIR sequences were also used to characterize peritumoral edema and to support peritumoral ROI placement by distinguishing edematous tissue from the enhancing tumor component (Figure 2). Because ROI placement was performed manually, observer-dependent variability should be considered.

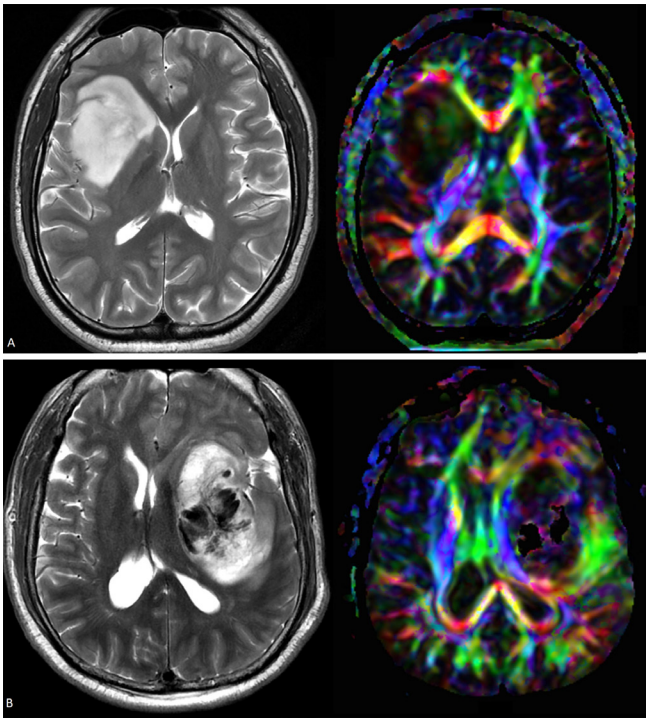


Figure 2: *Representative examples of low – and high-grade gliomas. (A) A 36-year-old man with a right frontal oligodendroglioma: axial T2-weighted image and corresponding color-coded FA map. (B) A 52-year-old man with a glioblastoma in the left insular region: axial T2-weighted image and corresponding color-coded FA map.*

Statistical Analysis

All analyses were performed using SPSS (version 27; IBM Corp., Armonk, NY, USA). Continuous variables were summarized as mean ± standard deviation (SD). Grade 1–2 and grade 3–4 groups were compared using independent-samples t tests. Regional FA values were normalized to contralateral NAWM by calculating FA(region)/FA(NAWM) for each patient. Effect sizes were reported as Cohen's d. ROC analysis was performed to assess diagnostic performance, reporting area under the ROC curve (AUC) with 95% confidence intervals, Youden index–based cut-offs, sensitivity, and specificity. A two-tailed $p < 0.05$ was considered statistically significant. Interobserver and intraobserver reproducibility analyses were not performed in the current study.

3. RESULTS

We evaluated whether FA measured in the tumor core (solid component), tumor margin, and peritumoral region, both as raw values and as ratios normalized to contralateral NAWM, could differentiate grade 1–2 from grade 3–4 gliomas.

The cohort included 60 patients (21 females, 39 males), evenly distributed between grade 1–2 (n=30) and grade 3–4 (n=30). The grade 3–4 group was older (48.60 ± 16.57 vs 39.47 ± 17.09 years; p=0.040), while sex distribution was similar between groups (p=0.787) (Table I).

Table 1. *Patient demographics and histopathological classification*

Variable	Grade 1–2 (n=30)	Grade 3–4 (n=30)	Total (n=60)	p
Sex (Female / Male), n	10/20	11/19	21/39	0.787
Age (years), Mean ± SD	39.47 ± 17.09	48.60 ± 16.57	44.03 ± 17.32	0.040
Histopathological diagnosis, n				
Low-grade glioma				
Pilocytic astrocytoma	5	0	5	
Astrocytoma	9	0	9	
Oligodendroglioma	16	0	16	
High-grade glioma				
Astrocytoma (grade 3)	0	9	9	
Glioblastoma (grade 4)	0	21	21	

p < 0.05 was considered statistically significant. SD: Standard deviation

In both groups, FA values in tumor-related regions were lower than contralateral NAWM. Grade 3–4 gliomas showed significantly lower raw FA than grade 1–2 gliomas in the tumor core (0.13 ± 0.04 vs 0.21 ± 0.07; $p < 0.001$), tumor margin (0.25 ± 0.07 vs 0.32 ± 0.10; $p = 0.002$), and peritumoral region (0.27 ± 0.07 vs 0.38 ± 0.10; $p < 0.001$), whereas contralateral NAWM FA did not differ between groups ($p = 0.265$). Effect size analysis indicated the largest between-group differences in the tumor core (Cohen's $d = 1.38$) and peritumoral region ($d = 1.23$). NAWM normalization preserved these differences, with significantly lower core/NAWM (0.362 ± 0.120 vs 0.533 ± 0.166; $p < 0.001$; $d = 1.18$), margin/NAWM (0.655 ± 0.165 vs 0.791 ± 0.196; $p = 0.005$; $d = 0.75$), and peritumoral/NAWM ratios (0.717 ± 0.191 vs 0.920 ± 0.147; $p < 0.001$; $d = 1.20$) in grade 3–4 gliomas (Table II).

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Table II. *Raw and NAWM-normalized FA values by glioma grade and between-group comparison*

Region / Metric	Grade 1–2 (n=30) Mean ± SD	Grade 3–4 (n=30) Mean ± SD	t	p	Cohen's d
Raw FA (non-normalized)					
Contralateral NAWM	0.41 ± 0.10	0.38 ± 0.08	1.126	0.265	0.29
Tumor core	0.21 ± 0.07	0.13 ± 0.04	5.363	<0.001*	1.38
Tumor margin	0.32 ± 0.10	0.25 ± 0.07	3.198	0.002*	0.83
Peritumoral area	0.38 ± 0.10	0.27 ± 0.07	4.767	<0.001*	1.23
NAWM-normalized FA ratio					
NAWM (reference)	1.000 ± 0.000	1.000 ± 0.000	—	—	—
Tumor core / NAWM	0.533 ± 0.166	0.362 ± 0.120	4.554	<0.001*	1.18
Tumor margin / NAWM	0.791 ± 0.196	0.655 ± 0.165	2.906	0.005*	0.75
Peritumoral region / NAWM	0.920 ± 0.147	0.717 ± 0.191	4.631	<0.001*	1.20

*NAWM: normal-appearing white matter, FA: fractional anisotropy, SD: Standard Deviation, *p < 0.05 was considered statistically significant.*

Table III. *Diagnostic performance of raw and NAWM-normalized FA metrics for differentiating glioma grades (ROC analysis)*

Metric	AUC (95% CI)	Optimal cut-off (grade 3–4 if ≤)	Sensitivity	Specificity
Raw FA				
Tumor core FA	0.842 (0.734–0.932)	0.150	0.80	0.73
Tumor margin FA	0.700 (0.549–0.833)	0.330	0.90	0.57
Peritumoral FA	0.801 (0.674–0.904)	0.350	0.93	0.67
NAWM-normalized FA ratio				
Tumor core/ NAWM ratio	0.783 (0.655–0.888)	0.477	0.87	0.60
Tumor margin/ NAWM ratio	0.724 (0.580–0.854)	0.755	0.80	0.67
Peritumoral/ NAWM ratio	0.808 (0.679–0.919)	0.810	0.80	0.83

ROC: receiver operating characteristic, AUC: area under the ROC curve, CI: confidence interval, NAWM: normal-appearing white mmatter, SD: Standard Deviation, CI: Confidance Interval

On ROC analysis (grade 3–4 if ≤ the optimal cut-off), tumor core FA provided the highest discrimination among raw metrics (AUC = 0.842, 95% CI: 0.734–0.932; cut-off = 0.150; sensitivity = 0.80; specificity = 0.73), and the peritumoral/NAWM ratio performed best among normalized metrics (AUC = 0.808, 95% CI: 0.679–0.919; cut-off = 0.810; sensitivity = 0.80; specificity = 0.83) (Table III).

4. DISCUSSION

This study evaluated whether DTI–derived FA measured in the tumor core, tumor margin, and peritumoral region can differentiate grade 1–2 from grade 3–4 gliomas. Across all lesion-related regions, grade 3–4 gliomas showed significantly lower FA values than grade 1–2 gliomas, while contralateral NAWM did not differ between groups. These results support prior work indicating that FA is sensitive to tumor-related microstructural disruption [12, 23] and varies with glioma grade [13, 16].

Reduced FA in higher-grade gliomas is biologically plausible and consistent with established diffusion findings, reflecting disorganization of white matter architecture driven by increased cellularity, and loss of structural coherence [11, 12, 23]. In our cohort, the most pronounced absolute FA reduction occurred within the tumor core, consistent with reports linking DTI metrics to tumor microstructure and grade [13, 16]. This aligns with DTI-based grading studies showing that diffusion characteristics of the tumor core can provide informative grading signals beyond conventional imaging [15, 16, 24].

Beyond the core, we observed significant FA reductions at the tumor margin and in the peritumoral region in grade 3–4 gliomas. This is clinically relevant because conventional MRI may underestimate microstructural alterations beyond areas of enhancement or overt signal abnormality, whereas DTI can detect subtle disruptions in tissue organization at and around the tumor boundary [18, 25]. Histopathologic and image-guided biopsy studies have demonstrated that DTI metrics can better delineate infiltrated white matter and tumor margins, supporting our finding of lower margin and peritumoral FA in higher-grade gliomas [25]. These observations are consistent with greater disruption in adjacent tissue compartments where invasion and reactive changes may co-exist in higher-grade tumors [18].

To reduce inter-individual variability, we normalized regional FA values to contralateral NAWM. Normalized ratios remained significantly lower in grade 3–4 gliomas across all evaluated regions, supporting the use of an internal reference to improve comparability across patients. Similar approaches have been proposed to increase robustness and comparability of diffusion-based assessments, particularly in multicenter settings [20, 22]. Importantly, the absence of a between-group difference in contralateral NAWM FA suggests that the observed diffusion alterations were localized to tumor-related regions rather than reflecting global white matter differences [12, 23].

From a diagnostic performance perspective, ROC analysis demonstrated good discrimination for tumor core FA and peritumoral FA, and among normalized metrics, the peritumoral/NAWM ratio showed strong performance with relatively high specificity. More specifically, tumor core FA yielded the highest discrimination among raw metrics (AUC = 0.842), whereas the peritumoral/NAWM ratio showed the best performance

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among normalized metrics (AUC = 0.808; specificity = 0.83). These findings complement the observed effect sizes (Cohen's d), which indicated the largest grade-related differences in the tumor core and peritumoral region, collectively supporting region-specific FA assessment for preoperative grading [13, 16, 24]. Incorporating such diffusion-derived markers may help refine preoperative risk stratification and could be integrated into multiparametric frameworks and predictive models for noninvasive tumor characterization [26, 27].

Several limitations should be noted. First, this was a single-center study with a modest sample size. Second, histopathologic sampling was not performed specifically from the margin or peritumoral ROIs, limiting direct biological correlation of FA changes in these compartments. Third, FA is sensitive but not specific to tumor infiltration and may be influenced by edema, inflammation, demyelination, and partial-volume effects, particularly in heterogeneous lesions. Fourth, FA measurements were manual and reproducibility was not assessed. Fifth, tumor classification was based on histopathological grading rather than full WHO 2021 molecular integration, which may limit generalizability. Future studies with larger cohorts, targeted tissue correlation, and external validation of cut-offs may further clarify the relative contributions of infiltration versus edema and strengthen the clinical utility of region-specific and normalized FA thresholds.

Conclusion

FA values in the tumor core, tumor margin, and peritumoral region were lower than contralateral NAWM in both grade groups, with significantly greater reductions in grade 3–4 gliomas. Both absolute and NAWM-normalized FA metrics differentiated grade 1–2 from grade 3–4 gliomas, with the strongest discriminatory information arising from the tumor core and peritumoral region. These findings support DTI-derived FA as a useful adjunct for preoperative glioma grading and surgical planning, although the results should be interpreted with consideration of manual ROI-based measurement and incomplete molecular classification.

Compliance with Ethical Standards

Ethical approval: The study was approved by the Yeditepe University Institutional Ethics Committee (Approval No: 202507Y0884, 2025). All participants provided written informed consent in accordance with institutional and international ethical guidelines.

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Conflict of interest: The authors declare no conflict of interest related to this article.

Authors' contributions: ZF: Study design, data analysis, literature review, and manuscript drafting, CKY: Manuscript editing and organization, GE: Study supervision and critical review. All authors have read and approved the final manuscript.

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