







## Diffusion tensor imaging in brain tumors: The role of fractional anisotropy values

Beyin tümörlerinde difüzyon tensör görüntüleme: Fraksiyonel anizotropi değerlerinin rolü

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### Abstract

**Aim:** To evaluate the role of Fractional anisotropy (FA) values obtained from diffusion tensor magnetic resonance imaging (DTI) in the differentiation and grading of brain tumors.

**Materials and Methods:** This study examined the conventional and diffusion tensor MR imaging findings of twenty-seven patients diagnosed with brain tumors between 2008 and 2010. Patients were divided into four groups based on tumor types; meningiomas, low-grade gliomas, high-grade gliomas, and metastases. Fractional anisotropy (FA) values were then obtained from the solid components and (if present) peritumoral vasogenic edema of the tumors for each patient by using the region of interest (ROI) method. Finally, the patient groups were analyzed in terms of any statistically significant differences.

**Results:** The FA values obtained from the solid portions and peritumoral edema of meningiomas were found to be higher than those of all other groups ( $p < 0.015$ ). Moreover, the FA values of high-grade gliomas were found to be higher than those of low-grade gliomas ( $p = 0.042$ ). Finally, no statistically significant difference was observed between high-grade gliomas and metastases in terms of the FA values of solid components and peritumoral edema.

**Conclusion:** The determination of FA values among DTI results can be a useful method for differentiating brain tumors such as meningioma, low-grade glioma, high-grade glioma, and metastasis, as the treatment protocols and prognoses of each may differ. Moreover, FA values may contribute preoperatively to the differentiation of brain tumors in multimodal brain tumor imaging. It would be useful to use diffusion tensor imaging in conjunction with conventional MRI in the imaging of brain tumors.

**Keywords:** Brain tumors, diffusion tensor magnetic resonance imaging, fractional anisotropy.

### Öz

**Amaç:** Beyin tümörlerinin evrenmesi ve ayrımında difüzyon tensör manyetik rezonans görüntüleme ile elde edilen fraksiyonel anizotropi değerlerinin katkısını araştırmak.

**Gereç ve Yöntem:** 2008 ve 2010 yılları arasında beyin tümörü tanısı almış ve bölümümüzde konvansiyonel MRG ve difüzyon tensör görüntüleme yapılmış 27 olgu retrospektif olarak tarandı. Olgular menenjiom, düşük dereceli ve yüksek dereceli gliomlar ile metastazlar olmak üzere 4 gruba ayrıldı. Her olguda tümörün solid komponentinden ve peritümöral ödem barındıranlarda vazojenik ödem sahasından ROI (region of interest) yöntemi kullanılarak FA değerleri ölçüldü. Gruplar arasında anlamlı farklılık olup olmadığı istatistiksel yöntemlerle analiz edildi.

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**Bulgular:** Tüm tümör grupları karşılaştırıldığında; menenjiomların solid komponentinin ve peritümöral ödeminin FA değeri diğer gruplara oranla istatistiksel anlamlı olarak yüksek bulundu ( $p<0.015$ ). Düşük ve yüksek dereceli gliomlar kıyaslandığında ise yüksek derecelilerin FA değeri düşük derecelilere göre anlamlı yüksek bulundu ( $p=0.042$ ). Yüksek dereceli gliom grubu ile metastazların karşılaştırılmasında ise gerek solid kısımlar arasında gerekse peritümöral ödem sahasında FA değerlerinde anlamlı farklılık saptanmadı.

**Sonuç:** Difüzyon tensör manyetik rezonans görüntüleme ve kantitatif FA ölçümü tedavi ve prognozu farklılıklar gösteren menenjiom, metastaz, düşük ve yüksek dereceli glial tümörlerin ayırımında faydalı bir yöntem olabilir. Beyin tümörlerinin görüntülenmesinde konvansiyonel MR görüntüleri ile birlikte difüzyon tensor görüntülemenin kullanılması faydalı olacaktır.

**Anahtar Sözcükler:** Beyin tümörleri, difüzyon tensör manyetik rezonans görüntüleme, fraksiyonel anizotropi.

## Introduction

The most common group of tumors after leukemia and lymphoma in children, brain tumors affect 3.8% to 5.1% of every 100.000 individuals (1). In addition, 2.7% of cancer-related deaths are caused by brain tumors. Due to their prevalence and morbidity rate, it is important for researchers to recognize tumor type as well as grade during the preoperative period, which involves the planning of treatment and determination of prognoses. It is also important in the staging of heterogeneous tumors to choose the site where the biopsy should be performed (2). As conventional MRI techniques are unable to produce sufficient information regarding these matters, some researchers have sought different methods of examination. One such method is perfusion MRI, which provides information about tissue blood flow; and the others are the imaging of microscopic water movement (diffusion-weighted MRI, and diffusion tensor imaging with directional information); and the direct imaging of biochemical processes in tissue (MR spectroscopy) (3). Moreover, ongoing technological developments in neuroradiology have enabled a non-invasive understanding of the biological characterization and behavior of brain tumors.

One such development is diffusion tensor imaging (DTI), a non-invasive technique that involves the *in vivo* detection of tissue structure by measuring the rate and direction of the diffusion of water molecules (4). This technique involves the measurement of fractional anisotropy (FA) values, which are utilized as markers of tissue damage in the white matter of many diseases such as multiple sclerosis, amyotrophic lateral sclerosis, and ischemia (5,6,7). Myelinated nerve fibers play one

of the most significant roles in the formation of anisotropic diffusion. For this reason, FA values in tissues with damaged myelin fibers are relatively low. In addition, anisotropy in brain tumors is almost always lower in comparison to normal brain parenchyma (8).

This study investigated the efficiency of DTI in the staging and characterization of primary brain tumors.

## Materials and Methods

In this study we retrospectively examined the cranial MRI and diffusion tensor MRI scans of the brain tumors which were obtained with a 1.5 Tesla MRI system (Siemens Vision-Symphony Upgrade, Erlangen, Germany) in our radiology department between 2008 and 2010. Participants included patients whose pathologic diagnoses had been evident after surgical resection.

In all cases, conventional, diffusion-weighted, diffusion tensor images and postcontrast conventional MRI sequences were obtained using a circular, polarized head-coil on a 1.5 Tesla superconductive system MRI device. First, conventional MRI sequences were acquired; three planar T1-weighted localized images were obtained. Next, axial T2-weighted images (TR 4450 ms, TR 114 ms, slice thickness 5 mm, interslice gap 2 mm, NEX 2 and matrix 214x384 ) were obtained followed by the acquisition of three orthogonal plan T1-weighted images (TR 470 ms, TE 12 ms, slice thickness 5 mm, interslice gap 2 mm, NEX 1 and matrix 173 x 320) and coronal plane FLAIR (TR 8700 TE 128, slice thickness 5 mm, interslice gap 1.5 mm, NEX 1 and matrix 209x256). DTI sequence (involving spin-echo single-shot echo planar sequences, voxel sizes of 2x2x2.2 mm, FOV 256x256, Matrix 128x 128,

TR/TE 10070/103 msn, b: 0 and 700 s/mm<sup>2</sup>, and 60 numbers of direction) was utilized, as well.

In the present study, conventional MR images were analyzed in terms of the presence of mass; localization; presence or absence of edema, necrosis, and/or cyst; and contrast enhancement ratio and pattern by reviewing all images with and without a contrast medium. The diffusion tensor images were then transferred to the workstation (Leonardo Workstation) and analyzed by means of the DTI Task Card software (MGH, Boston, USA). FA and ADC maps were created automatically with this software from source diffusion tensor images. FA Measurements were obtained by manually scanning the area as broadly as possible using the region of interest (ROI) method over b = 0 images, as the anatomical details of maps are more clear with this images than with others. For each patient, FA Measurements were obtained separately from peritumoral edema and solid components of the tumors. At the same time, the necrotic and hemorrhagic components of the tumors were avoided in examination.

SPSS Version 13 software was employed for statistically analyzing the data. Moreover, a one-way analysis of variance (ANOVA) test was conducted to determine whether a statistically significant difference existed among the tumor types. Finally, a post-hoc test was applied to determine the nature of the differences among these types. When the p-value was less than 0.05, the differences were considered as statistically significant.

## Results

Seventeen of the twenty-seven patients with brain tumors were female and ten were male, and their ages ranged from 8 to 74 years (with a mean age of 47.07). They were divided into four groups according to tumor type and grade to ease the interpretation of statistical analysis results and differentiate the tumors as benign or malign. The groups were arranged as follows:

Group 1: Meningiomas

Group 2: Grade 1 and 2 brain tumors

Group 3: Grade 3 and 4 brain tumors

Group 4: Metastases

Group 1 consisted of four patients with one atypical meningioma (Grade 2), while Group 2 involved a

total of seven patients, one of which possessed ganglioglioma (Grade 1), one of which possessed oligoastrocytoma (Grade 2), two of which had oligodendroglioma (Grade 2), and three of which had diffuse astrocytoma. Group 3 included nine patients, one with anaplastic astrocytoma (Grade 3), one with PNET (Grade 4), and seven with glioblastoma (GBM). Finally, Group 4 was comprised of seven patients, one with breast, one with endometrial, and five with lung adenocarcinoma metastases.

Peritumoral edema was observed within three groups among a total of twelve patients, including two (meningioma) in Group 1, four (GBM) in Group 3, and six (metastasis) in Group 4. On the other hand, it was not present in Group 2 (Grade 1-2 tumors). Moreover, no contrast enhancement was observed in the images of six patients. Of these patients, three had diffuse astrocytoma (Grade 2), one had ganglioglioma (Grade 1), one had oligodendroglioma (Grade 2), and one had anaplastic astrocytoma (Grade 3). Among Group 4 (metastasis) patients, sufficient peritumoral edema was not observed to measure in the one with breast cancer.

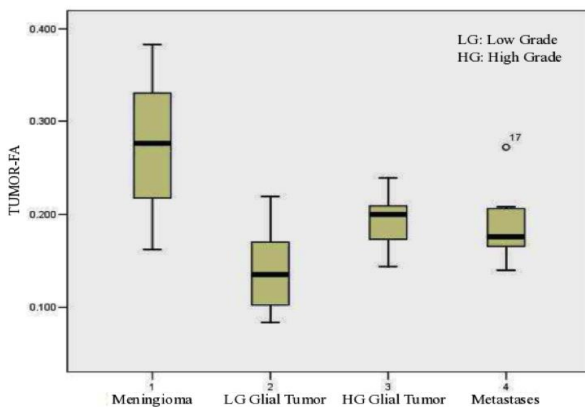
**Table-1.** Maximum, Minimum and Mean FA Values in Brain Tumors.

Groups	Case count	FA (mean±SD)	FA min/ FA max
<b>Solid component</b>			
Group 1	4	0.274±0.09	0.162–0.389
Group 2	7	0.140±0.05	0.084–0.219
Group 3	9	0.195±0.02	0.144–0.239
Group 4	7	0.190±0.04	0.140–0.272
<b>Peritumoral edema</b>			
Group 1	2	0.208±0.03	0.183–0.234
Group 2	0		
Group 3	4	0.135±0.03	0.111–0.183
Group 4	6	0.144±0.01	0.123–0.174

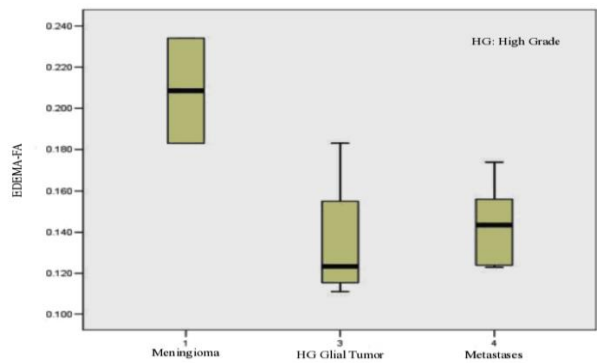
p<0.05 is significant.

There was dense, homogeneous contrast enhancement in all cases of meningioma. Moreover, peripheral and heterogeneous contrast enhancement patterns were observed in all cases of GBM. In the metastases group, some displayed peripheral, rim-like patterns; others homogenous patterns; and still others heterogeneous enhancement patterns. The measured values are summarized in Table-1 below.

A one-way ANOVA test indicated a statistically significant difference among FA values in terms of all measurement parameters ( $p < 0.05$ ). Following a post-hoc test, the mean FA value of the tumor and peritumoral edema in Group 1 patients ( $0.274 \pm 0.09$ ,  $0.208 \pm 0.03$ , respectively) was found to be higher than in other groups ( $p < 0.015$ ). In the meningioma group, the mean FA value in a patient diagnosed with atypical meningioma (Grade 2) was 0.162, while the mean FA value in a patient with transitional meningioma (Grade 1) was 0.383. The mean FA value for high-grade glioma patients ( $0.195 \pm 0.02$ ) was significantly higher at borderline than that of low-grade glioma patients ( $0.140 \pm 0.05$ ) ( $p = 0.042$ ). Similarly, in the metastases group ( $0.190 \pm 0.04$ ), the mean FA value was higher than that of the low-grade glioma group ( $0.140 \pm 0.05$ ), but this difference was not statistically significant. In the present study, FA values obtained from the solid portion of the tumor and peritumoral edema displayed similar characteristics in high-grade glioma (Group 3;  $0.195 \pm 0.02$  and  $0.135 \pm 0.03$ ) and metastases (Group 4;  $0.190 \pm 0.04$  and  $0.144 \pm 0.01$ ) patients. Thus, no statistically significant difference was observed between the two groups. The measured values are summarized in Figure-1 and 2. Case examples have shown in Figure-3,4 and 5.



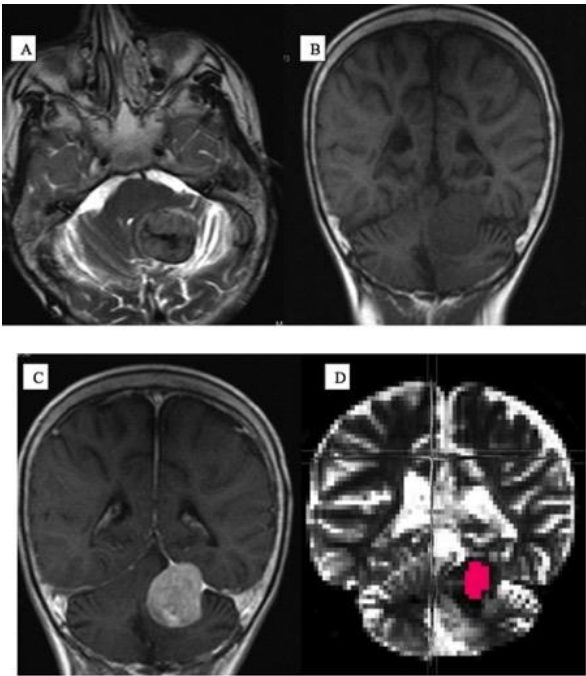
**Figure-1.** Tumor groups and FA values obtained from solid parts of the tumor.



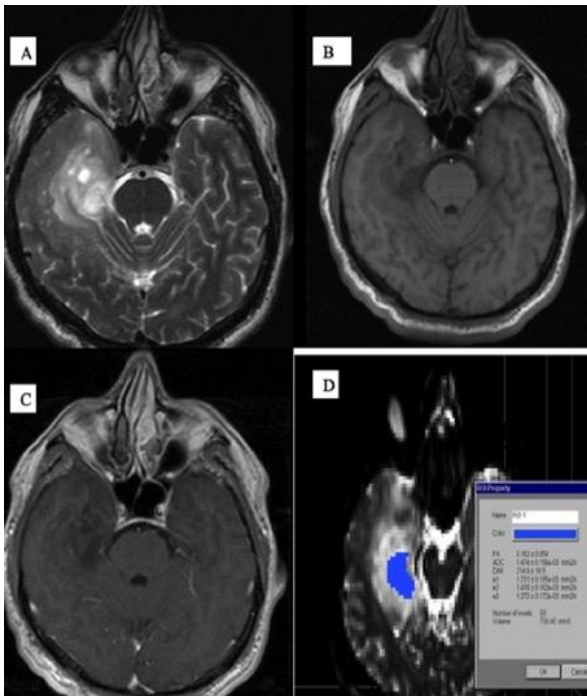
**Figure-2.** Tumor groups and FA values obtained from peritumoral edema.

## Discussion

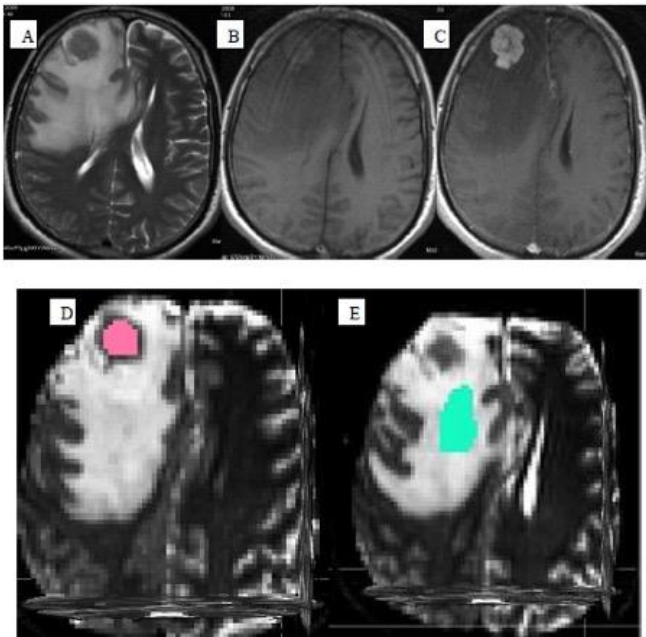
Toh et al. (9) investigated the difference between FA values among twenty-four patients with twelve classical (Grade 1) and twelve atypical (Grade 2) meningiomas. They observed that the FA value ( $0.230 \pm 0.08$ ) of classic meningiomas was significantly lower than that of atypical ones ( $0.336 \pm 0.105$ ) ( $p < 0.012$ ). Moreover, cellular growth in classical meningiomas was more irregular, as intracellular fascicles, protein wands, and nodules caused more isotropic diffusion. At the same time, cellular growth in atypical meningiomas was reported as being continuous and stratified while diffusion was more pronounced in one direction. However, in the present study, only four patients possessed meningioma, and this number was not significant enough for discriminating between meningioma types. For this reason, we focused more on the FA values of the meningiomas and the edema in their environments. The FA values of Group 1, the meningioma group, were significantly higher than in all other groups ( $p < 0.015$ ). This might indicate that the solid component of the tumors in meningiomas display more organized and uninterrupted growth patterns. Also, the mean FA value measured for meningiomas was 0.274 (for Groups 2, 3, and 4, 0.140, 0.195 and 0.190, respectively). Therefore, it may be concluded that it is possible to distinguish meningiomas from other tumor groups according to the FA values measured from the solid parts of tumors.



**Figure-3.** Left tentorial transitional meningioma which is extending to the supratentorial region. T2 weighted images show left tentorial mass lesion which is hypointense (due to calcification) in the center (A) and isointense in the periphery and does not produce significant peritumoral edema. The lesion caused mass effect over the 4th ventricle and pons. It is slightly hypointense on T1 weighted images (B) and shows intense and homogeneous enhancement after Gd injection (C). In the lower right, FA Measurement is demonstrated using the ROI method on (D) coronal plane b=0 images.



**Figure-4.** Right temporal Grade 2 oligoastrocytoma with heterogeneous T2 signal. A mass lesion is seen in the right temporal lobe, heterogeneous hyperintense on T2 weighted images (A), hypointense on T1 weighted images (B). After Gd injection, the tumor does not show any contrast enhancement (C). At the bottom right is shown how the measurement with the ROI method was performed on the b=0 images (D).



**Figure-5.** Right frontal lobe metastases (due to lung adenocarcinoma). Right frontal lobe mass isointense to gray matter on T2 - and T1 weighted images (A-B). On T2 weighted images mass has significant peritumoral edema (A). After Gd injection (C), the mass lesion shows intense enhancement (C). FA Measurements with ROI were shown from the solid portion of the tumor at the bottom left (D) and from the area of peritumoral edema at the lower right (E) on the b=0 images.

In another study among forty-one patients, Inoue et al. (10). found that FA values were significantly lower in Grade 1 and 2 glioma patients than in Grade 3 and 4 gliomas ( $p < 0.0001$ ). However, when low- and high-grade gliomas were internally assessed (i.e. between Grade 1 and Grade 2 or between Grade 2 and Grade 3), no statistically significant difference was observed. The high FA values observed in high-grade gliomas may be attributed to the fact that diffusion becomes more prominent in one direction due to more symmetrical histological arrangement and vascular proliferation. In addition, Ferda et al. (11) have suggested that FA values are not enough for discriminating between low- and high-grade gliomas alone and that the sensitivity as well as specificity of discrimination is increased when contrast-enhanced images are added to FA maps. In contrast the current study observed a statistically significant difference between the FA values of low- and high-grade gliomas ( $p=0.042$ ). Moreover, it is thought that this significance may become more evident with an increasing number of cases. The FA values were measured as  $0.140 \pm 0.05$  and  $0.195 \pm 0.02$  in low- and high-grade gliomas, respectively.

In a study conducted by Tsuchiya et al. (12), FA Measurements were obtained from both the solid, enhancing and non-enhancing areas of tumors in a total of fourteen patients, seven of whom

possessed high-grade glial tumors and the other seven of whom possessed solitary metastasis. The researchers did not observe any statistically significant difference between these two groups. However, only five of the metastatic patients and one of the glioma patients exhibited a mass effect on the white-matter pathways. For this reason, metastasis should be considered first, if the white matter pathways are displaced due to mass effect instead infiltrated by the lesion. Similarly, the current study found no statistically significant difference among the FA values obtained from both high-grade glial tumors and the solid components of metastases. For this reason, it has been concluded that measuring FA values is not a reliable method of distinguishing between these two pathologies.

High-grade gliomas and metastases contain heterogeneous signal features due to existing necrosis areas and susceptibility artifacts. For this reason, the diffusion tensor parameters obtained from the tumor may not accurately reflect this. Peritumoral assessments increase the accuracy of the tumor compared to measurement obtained from the tumor itself. Some investigators have suggested that high-grade glial tumors can be distinguished from metastases in terms of their FA and ADC values by assessing the cellular density of peritumoral edema tissue and varying water content. This suggestion is premised on the idea

that gliomas contain predominantly infiltrating tumoral cells, whereas vasogenic edema in metastases is predominantly composed of water molecules. Deng et al. (13) quantitatively analyzed glial cell infiltration in which tumor invasion decreased as FA values obtained from peritumoral edema increased (13). Moreover, in their study of twelve high-grade gliomas (three anaplastic astrocytomas and nine GBM) and twelve metastases, Lu et al. (14) observed that no statistically significant difference existed between the vasogenic edema FA values of both groups (FA values of 0.248 and 0.181, respectively). However, the ADC values of vasogenic edema observed in metastases ( $0.798 \times 10^{-3} \text{ mm}^2 / \text{sec}$ ) was found to be significantly higher ( $p < 0.05$ ) compared to those of high-grade gliomas ( $0.622 \times 10^{-3} \text{ mm}^2/\text{s}$ ). (14) The current study similarly observed that no statistically significant difference existed between the FA values of four high-grade gliomas and six metastatic cases with vasogenic edema ( $0.135 \pm 0.03$  and  $0.144 \pm 0.01$ ). Therefore, it can be concluded that the FA measurement of peritumoral vasogenic edema alone are insufficient for distinguishing between high-grade gliomas and metastases.

In such cases especially with primary malignancy, it is difficult to distinguish between two pathologies such as meningioma and metastasis, both showing homogeneous enhancement and are close to dura mater but have different prognosis and treatment approaches. In a study conducted by Toh et al. (9)

comparing the FA values of peritumoral edema in twenty-six patients (fifteen meningiomas and eleven metastases), low values (0.146 for metastases and 0.199 for meningiomas) were found to be in favor of the metastasis group (15). The findings of the current study support these findings, as the FA values obtained from the peritumoral edema of patients with meningioma were higher than those of high-grade glial tumor patients and metastases patients. Therefore, DTI may prove beneficial in distinguishing between these two pathologies. Moreover, we consider that these tumors which are benign in nature do not cause extreme occlusion in white-matter pathways due to extra-axial placement and cause less damage to axonal fibers than do other tumor groups.

Patients groups' heterogeneity, the subjectivity of the ROI method, low geometrical resolution of the FA maps and absence of the lymphoma case which may interfere with metastasis and glioblastoma multiforme are the limitations of the study.

### Conclusion

Overall, this study has shown that DTI could be a useful method for distinguishing between meningioma, metastasis, and low- as well as high-grade glial tumors, all of which exhibit significant differences in terms of treatment and prognosis. Finally, the benefits of DTI will be better understood over time with more extensive studies.

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