Review Article

Evaluation of the potential of diffusion tensor imaging biomarkers in prediction of white matter changes after brain radiation therapy: A systematic review

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Background: The objective of this study was to systematically review the use of diffusion tensor imaging (DTI) biomarkers in the early detection of radiation-induced white matter (WM) changes. **Materials and Methods:** The PubMed and Scopus databases were searched for peer-reviewed articles published in English up to November 28, 2022, according to the PRISMA guidelines to identify studies that related to changes in DTI parameters after radiotherapy. **Results:** After reviewing the literature, eight studies met the inclusion criteria. The results indicated that changes in the late delay phase were completely related to changes in the acute phase. There was a difference in the sensitivity of the biomarkers between studies. Still, there was substantial evidence for the early detection of changes by axial diffusivity (AD), radial diffusivity (RD), and fractional anisotropy (FA). However, further research is still necessary on the potential of mean diffusivity (MD) sensitivity for detecting early changes. The majority of the included studies demonstrated progressive changes in DTI parameters over time and with dose. **Conclusion:** There is significant potential for DTI biomarkers to predict WM changes caused by radiation after brain radiation therapy by having significant predictive power.

Key words: Diffusion tensor imaging, MRI biomarkers, radiotherapy, white matter

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INTRODUCTION

Radiation therapy (RT) is one of the common methods in the treatment of primary and metastatic brain tumors. Unfortunately, due to the undesired dose that reaches healthy tissue, this method can lead to complications and limitations.[1] One such complication is microstructural changes in white matter (WM).[2] It is important to note that the pathogenesis of these changes is multifactorial, but vascular injury, demyelination or axonal injuries, and neuroinflammation play important roles.[3] An RT-induced brain injury generally manifests in three phases: acute (within a few days to a few weeks after RT), early delay (within 1–6 months after RT), and late delay (within 6 months–several years after RT). The acute and early delay phases are usually transient. Late delay phases are usually permanent and are characterized by necrosis and histopathological abnormalities. In the late delay phase, severe effects usually manifest after 6 months and at doses exceeding 60 Gy.[4] However, WM is not completely safe from microstructural changes, even for fraction doses that are traditionally considered safe (≤2 Gy).[5] To improve therapeutic indices in radiotherapy, there is a strong need to measure and understand the response of different parts of the brain to radiation during and after treatment.[6] As a noninvasive imaging modality, diffusion tensor imaging (DTI) provides an opportunity to characterize subtle changes to the microstructure of the WM.[7] DTI uses a tensor model to determine the overall motion of water. DTI provides quantitative metrics for tissue structures, especially fiber bundles in WM. DTI metrics most commonly used include fractional

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anisotropy (FA), mean diffusivity (MD), radial diffusivity (RD), and axial diffusivity (AD).[8] Radiation effects on WM have been studied using DTI in several studies. The results were different for the sensitivity of the metrics to the radiation dose; many studies have also considered time as a key factor in determining parameter changes.[9,10] In addition, some studies have examined the different responses of different regions to radiation also, they suggest that DTI metrics can act as a biomarker for early detection of radiation damage to the WM.[11] Therefore, the amount of change in DTI metrics due to factors such as radiation dose, time, and region can be different. Consequently, it is essential to have a study that can examine the relationship between all of these factors.

Principle of diffusion tensor imaging

Diffusion-weighted imaging (DWI) imaging is based on the Brownian motions of water molecules. Water molecules diffuse equally in all directions in a liquid-filled space, which is known as isotropic diffusion. *In vivo*, water diffusion is restricted by cell membranes and macromolecules. These structures increase anisotropy and reduce isotropy.[12] There is a direct correlation between the degree of anisotropy and the integrity and density of oriented structures in the tissue. The anisotropy in WM is high as a result of the fast diffusivity along the fibers and the slow diffusivity perpendicular to them. Thus, if there is a change in axonal microstructure or myelination, anisotropy can be measured.[10,13] DWI can estimate the magnitude of diffusion with a special metric called apparent diffusion coefficient. However, because diffusion-weighted sequences depend on a field gradient, they are sensitive to diffusion only in a single direction.[14] DTI is an extension of DWI that requires the application of diffusion gradients in at least six noncollinear directions for estimating the degree of diffusion anisotropy.[15] In general, DTI utilizes a tensor model, which is typically composed of a 3 × 3 symmetric matrix to calculate four main metrics. This model requires eigenvalues (λ) and eigenvectors (ε) to characterize the signal of water displacement within a voxel.[8] Eigenvectors represent an axis of dominant diffusion, and corresponding eigenvalues represent the magnitude of diffusion. As shown in Figure 1, if all eigenvalues are approximately equal (λ1≈ λ2≈ λ3), the diffusion is isotropic. Alternatively, when there is a special orientation of the diffusion, the first eigenvalue is larger than the second and third eigenvalues (λ1>> λ2, λ3), and the diffusion is anisotropic.

Based on the (1–4) formulas, four main metrics are derived from DTI: FA, MD, RD, and AD:[16]

$$FA = (3/2)^{1/2} \frac{\left[(\lambda_1 - \lambda)^2 + (\lambda_2 - \lambda)^2 + (\lambda_3 - \lambda)^2\right]^{-}}{(3\ )^{1/2}} \quad (1)$$

$$MD = \frac{(\lambda_1 + \lambda_2 + \lambda_3)}{3} \quad (2)$$

$$RD = \frac{(\lambda_2 + \lambda_3)}{2} \quad (3)$$

$$AD = \lambda_1 \quad (4)$$

Where (λ1> λ2> λ3) and λ is the mean of all eigenvalues.

The FA reflects the degree of anisotropy and is scaled from 0 to 1. When the FA value is 0, the diffusion is isotropic. Typically, the largest value is found at the center of the tracts.[17] In general, FA is considered to be a quantitative biomarker of WM integrity, some studies have demonstrated a correlation between reduced FA levels and neurodegenerative disease.[18]

MD Measures overall diffusivity and describes the magnitude of diffusion. In areas of the body with the greatest freedom of diffusion, it is highest, and in areas with the greatest complexity of tissues, it is lowest. In the ventricles, for example, MD is high because water molecules move freely within the ventricles.[19]

AD and RD are other important parameters in DTI. AD is the first eigenvalue (λ1) representing diffusion along the dominant direction, and RD represents the average diffusivity perpendicular to the principal direction of diffusion.[20] Research has suggested that RD is associated with axonal density, myelin integrity, axonal diameter, and fiber coherence, while AD has been linked with axonal damage and fragmentation in particular.[21]

Objectives

In the current review, studies that used DTI to determine the potential of DTI biomarkers to predict WM changes caused by radiation were considered. The purpose of this study was to systematically review the evidence to assess the potential of DTI biomarkers to predict WM changes after brain RT and to find a relationship between the factors of dose, time, and region, resulting in the change of DTI metrics.

METHODS

The searches were conducted on PubMed and Scopus for articles published in English language journals up to November 28, 2022. The research strategy and study screening were based on Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[22] We conducted the search using the following search terms (including synonyms and related words): (["diffusion tensor imaging" OR "DTI" OR "diffusion tractography" OR "Diffusion Tensor Magnetic Resonance Imaging" OR "Diffusion Tensor Magnetic Resonance Imaging" OR "Diffusion Tensor

MRI"] AND ["radiotherapy" OR "radiation therapy" OR "radiosurgery" OR "radiation" OR "radiation injury"]) AND ("white matter"). The related literature was evaluated by two reviewers. The following criteria were used to identify articles that met our inclusion criteria:

(1) Patients who underwent DTI
(2) The number of patients treated with radiotherapy and chemotherapy was more than half of the total number of patients
(3) The WM was selected as the region of interest
(4) Before–After (Pre–Post) studies with no control group

Several criteria were used to exclude articles:

(1) Changes in DTI parameters were not accurately reported
(2) The literature was a review article, conference abstract, case report, chapter, book, editorial, letter, or commentary
(3) The full text was not available
(4) Radiation dose, biomarker changes, and follow-up times were not reported exactly.

We selected the relevant papers using the PRISMA flowchart [Figure 2]. After removing duplicates, the literature search yielded 1415 papers. According to the titles and abstracts, 1323 articles were excluded from the study because they were not relevant to the research question. After reviewing the full text of 92 papers, 84 studies were excluded. Figure 2 summarizes the reasons for exclusion. In the end, eight studies were included. All retrieved articles were

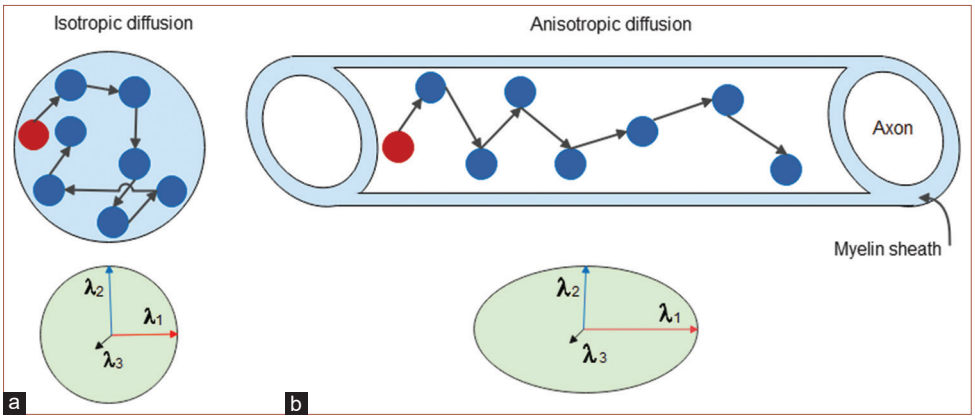

Figure 1: Isotropic diffusion (a) by a sphere versus anisotropic (b) by an ellipsoid

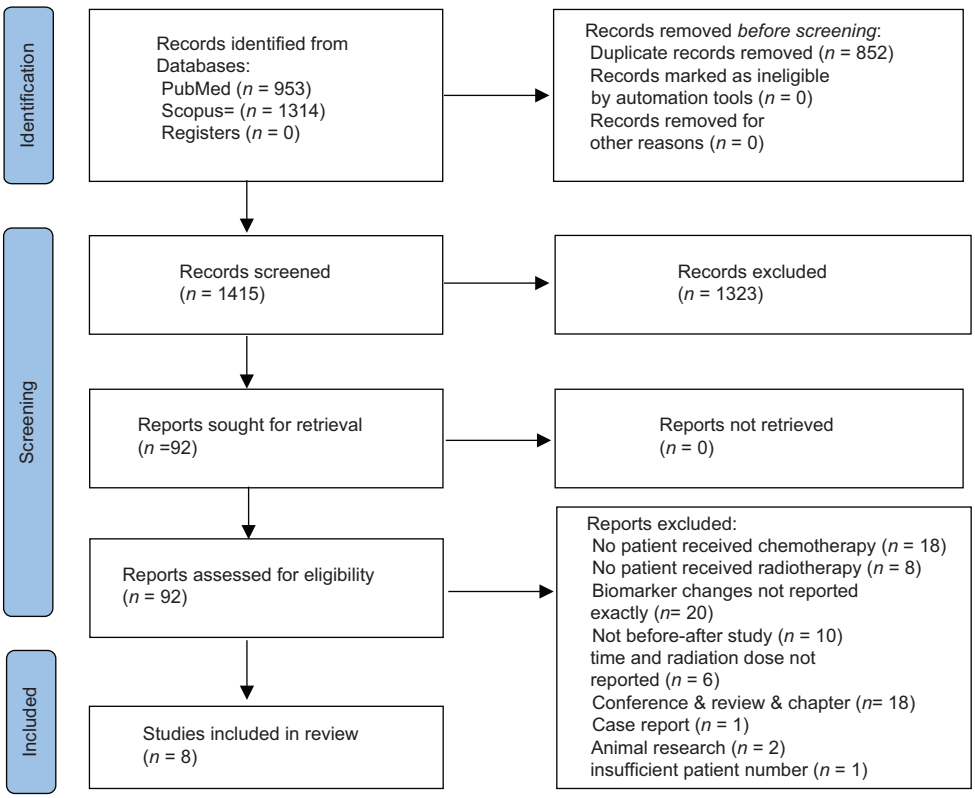

Figure 2: PRISMA Flow diagram of the search and inclusion process

independently assessed for methodological quality using the National Institutes of Health (NIH) quality assessment tool for before–after studies[23] [Table 1]. The NIH tool assists researchers in evaluating the potential for bias and the general quality of studies, thereby ensuring the reliability and validity of the findings. The NIH tool does not yield a numerical score; rather, it directs reviewers to classify the study as "Good," "Fair," or "Poor" according to the evaluation of the specified domains. We conducted a review of the studies, utilized the NIH tool's checklist to assess each domain, and subsequently assigned a quality rating. Based on the comprehensive evaluation, included studies were ultimately classified as either "Good" or "Fair."

RESULTS

Following our literature search, 8 studies, published between 2013 and 2022, with a total of 189 patients, were included in our study [Table 2]. According to Table 2, the FA, MD, RD, and AD parameters were evaluated by seven, five, eight, and eight studies, respectively. The classification was made according to the time of DTI scans for included studies, and acute, early delay, and late delay phases were assessed in these studies. DTI parameters change with time, dose, or region was evaluated in each of the three phases. An overview of included studies and used imaging parameters are represented in Tables 3 and 4, respectively.

Acute phase (during RT to 1 month after RT)

Four studies evaluated DTI parameters in the acute phase. Nazem-Zadeh *et al*.[24] reported that during RT, the mean RD and AD in the splenium (corpus callosum) of patients with necrosis increased significantly. Furthermore, they reported a significant correlation between RD and AD changes in the splenium 1 month after radiotherapy and those 3 months later, regardless of necrosis outcome. In a

Table 1: Quality assessment

	Nazem-Zadeh *et al*., 2014[24]	Tringale *et al*., 2019[29]	Chapman *et al*., 2013[25]	Connor *et al*., 2016[28]	Hope *et al*., 2015[26]	Rydelius *et al*., 2022[27]	Jinsoo *et al*., 2013[31]	Raschke *et al*., 2019[30]
1. Was the study question or objective clearly stated?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
2. Were eligibility/selection criteria for the study population prespecified and clearly described?	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes
3. Were the participants in the study representative of those who would be eligible for the test/service/intervention in the general or clinical population of interest?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No
4. Were all eligible participants that met the prespecified entry criteria enrolled?	Yes	No	Yes	Yes	No	No	Yes	No
5. Was the sample size sufficiently large to provide confidence in the findings?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
6. Was the test/service/intervention clearly described and delivered consistently across the study population?	Yes	Yes	No	No	No	Yes	Yes	Yes
7. Were the outcome measures prespecified, clearly defined, valid, reliable, and assessed consistently across all study participants?	No	Yes	Yes	Yes	Yes	No	Yes	No
8. Were the people assessing the outcomes blinded to the participant's exposures/ interventions?	No	No	No	No	No	No	No	No
9. Was the loss to follow-up after baseline 20% or less? Were those lost to follow-up accounted for in the analysis?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
10. Did the statistical methods examine changes in outcome measures from before to after the intervention? Were statistical tests done that provided *P* values for the pre- to post-changes?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
11. Were outcome measures of interest taken multiple times before the intervention and multiple times after the intervention (i.e., did they use an interrupted time-series design)?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
12. If the intervention was conducted at a group level (e.g., a whole hospital, a community, etc.) did the statistical analysis take into account the use of individual-level data to determine effects at the group level?	NA	NA	NA	NA	NA	NA	NA	NA

NA: Not available

Table 2: Study characteristics

Study	Number of patients	Gender	Mean age/ range (years)	Origin	Imaging times	Evaluated phases	Radiation dose	Anatomical structures examined	Chemotherapy	Studied Parameters	Tumor type
Nazem-Zadeh *et al.*, 2014[24]	29	14 males 15 females	Range: 22–78 (Necrosis: No) 31–75 (Necrosis: yes)	USA	Before treatment, at 3 weeks during RT, and 1, 3, and 6 months after RT	Acute and early delay	66–81 Gy to PTV/30 daily fractions	Corpus callosum and its substructures (genu, body, splenium)	Concurrent daily TMZ, followed by six cycles of adjuvant TMZ	RD and AD	Glioblastoma
Tringale *et al.*, 2019[29]	22	11 males 11 females	47.5±14.8	USA	Before RT, 3 and 6 months after RT	Early delay	50.4–60 Gy/1.8–2.0 Gy per fraction	SWM of the AC and dorsolateral prefrontal cortex	Protocol not reported	AD, RD, FA, and MD	Different brain tumors
Chapman *et al.*, 2013[25]	14	7 males 7 females	54.28	USA	Before RT, after completion of RT to 1 month later	Acute	30 Gy/3 Gy fractions or 37.5 Gy/2.5 Gy fractions	Fourteen WM structures	9 patients received bortezomib, 2 patients not received chemotherapy, 1 patient received cetuximab, 1 patient received paclitaxel and carboplatin, and 1 patient received gemcitabine	FA, RD, and AD	Metastatic brain tumors
Connor *et al.*, 2016[28]	15	9 males 6 females	Mean not reported Range (40–84)	USA	Before RT, 1, 4, 5, 9, and 19 months after RT	Early and late delay	13 patients: 60 Gy in 30 fractions One patient: 59.4 Gy in 33 fractions One patient: 40.05 Gy in 15 fractions	WM excluding tumor, tumor bed, surgical cavity, and surgical scars	Concurrent and adjuvant chemotherapy with different protocols	FA, MD, RD, and AD	High-grade glioma
Hope *et al.*, 2015[26]	18	14 males 4 females	54	Norway	Before RT, during RT, 3 and 6 months after the completion of RT	Acute, early, and late delay	30 fractions of 2.0 Gy	Whole WM	Concomitant TMZ	FA, MD, RD, and AD	High-grade glioma
Rydelius *et al.*, 2022[27]	27	17 males 10 females	Mean not reported Range (34–71)	Sweden	The start of RT and at 3, 6, 15, and 26 weeks after the onset of RT; 14 patients at week 52 after RT	Acute, early, and late delay	60 Gy in 30 fractions, 5 days per week (except for 1 patient: 34 Gy in 10 fractions)	The corpus callosum, the centrum semiovale, the hippocampus, and the amygdala	Concomitant chemotherapy with TMZ during RT, followed by adjuvant TMZ	FA, MD, AD, and RD	Glioblastoma

Contd...

Table 2: Contd...

Study	Number of patients	Gender	Mean age/ range (years)	Origin	Imaging times	Evaluated phases	Radiation dose	Anatomical structures examined	Chemotherapy	Studied Parameters	Tumor type
Jinsoo *et al*., 2013[31]	42	25 males 17 females	Mean not reported Range (6–20)	USA	Before RT and 48–72-month follow-up	Late delay	54 Gy	CST, ML, TPF, MCP, vTPF and dTPF	4 cycles of high-dose cyclophosphamide, cisplatin, and vincristine	FA, RD, and AD	Medulloblastoma
Raschke *et al*., 2019[30]	22	9 males 13 females	47.8± 13.9	Germany	Before RT and 3, 6, 9, 12, 15, and 18 months after RT	Early and late delay		Whole brain WM	Protocol not reported	FA, MD, RD, and AD	Glioma

RT=Radiotherapy; FA=Fractional anisotropy; MD=Mean diffusivity; RD=Radial diffusivity; AD=Axial diffusivity; WM=White matter; CST=Corticospinal tract; ML=Medial lemniscus; TPF=Transverse pontine fiber; MCP=Middle cerebellar peduncle; vTPF=Ventral TPF; dTPF=Dorsal TPF; TMZ: Temozolomide; AC=Anterior cingulate; SWM=Superficial white matter; PTV= Planning target volume

study Chapman *et al*.[25] demonstrated that in 87.8% of WM skeleton voxels, FA decreased significantly between pre-RT and end-RT, while in 64.6%, RD increased significantly. Furthermore, they reported that there were no significant changes in AD at end-RT in comparison to pre-RT. On the other hand, there was a significant decrease in AD in 12.9% of WM skeleton voxels between pre-RT and 1 month post-RT. In addition, there was a significant decrease in FA and a significant increase in RD in most of the WM skeleton voxels from pre-RT to 1 month after RT. Hope *et al*.[26] found different results and reported a significant increase in mean MD, AD, and RD over time within the different dose regions. The response was greater for high-dose regions than low-dose regions, but this was not significant until the last day of RT or later. After RT, or during the 6th week, significant changes were observed. In another study, Rydelius *et al*.[27] reported significant reductions in FA and increases in RD and MD following RT in the body of the corpus callosum at week 3.

Early delay phase (1–6 months after RT)

Six studies evaluated the early delay phase. Four studies found a significant progressive increase in RD with time and dose,[24,26,28,29] and one study found a significant progressive decrease in RD with time and dose.[30] AD decreased with time and dose in one study, and in three others, it increased;[24,26,28] however, in one study, AD did not show a significant change.[29] In two studies, FA decreased with time and dose, while in another, FA increased.[30] Two studies reported an increase in MD value with time and dose, whereas two studies reported a decrease in MD value.[29,30] Connor *et al*.[28] observed that all changes in the early delay phase occurred at doses >30 Gy. In addition, Rydelius *et al*.[27] showed that the changes in all parameters were irregular.

Late delay phase (more than 6 months after RT)

The late delay phase was evaluated by five studies. Compared with the early delay phase, the results of the Connor *et al*.[28] study in this phase was similar, with the exception that in this phase, there were significant changes in doses above 10 Gy. There was an increase in FA at this phase as well as at the early delay phase;[30] however, in two studies, the FA trend remained decreased with time and dose.[28,31] In three studies,[26,28,31] the RD parameter showed an increasing trend, while one study[30] showed a decreasing trend. Two studies reported a decreasing trend in AD,[30,31] and two other studies reported an increasing trend in AD with time and dose.[26,28] In three studies, MD trends in late delay phases were evaluated; two of the studies showed an increasing trend,[26,28] whereas one study showed a decreasing trend.[30] A study by Jinsoo *et al*.,[31] which evaluated the response of brainstem fiber tracts to radiation, reported that changes in different fiber tracts were

Table 3: Overview of reviewed articles

	Aim	Main results	Parameters trend (with time)	Parameters trend (with dose)	Conclusions
Nazem-Zadeh *et al*., 2014[24]	A response model for radiation necrosis prediction was developed using (DTI) to identify early individual response biomarkers	The results of the study indicated that patients with necrosis had a progressive increase in RD between 3 weeks after radiotherapy and 6 months following the procedure, while patients without necrosis did not show a significant change. In the splenium (corpus callosum) of patients with necrosis, the mean RD increased 3 weeks after radiotherapy, and 6 months after radiotherapy. From pre-RT to 6 months after RT, AD of the splenium in patients with necrosis presents a progressive increase, but in those without necrosis, the increasing trend was slight. there was a significant correlation between the RD and AD changes in the splenium 1 month after RT and those 3 months after RT, regardless of necrosis outcome	RD↑≈time↑AD↑≈time↑	RD↑≈dose↑ AD↑≈dose↑	The results of this study demonstrate that longitudinal changes in DTI parameters may be able to improve the accuracy of a radiation necrosis prediction model even before the total radiation dose is delivered
Tringale *et al*., 2019[29]	Analyses of longitudinal changes in the white matter microstructure in the frontal lobe of the brain following RT	The FA level in the left CAC decreased between pre-RT and 3 months post-RT, while MD increased in both the left and right CACs. A significant increase in MD was associated with an increase in RD in the right and left CAC, while there was no significant change in AD during this period. During the pre-RT and 3 months post-RT period, no changes were observed in the right or left RAC or the DLPFC	RD↑≈time↑MD↑≈time↑ AD↑≈time↑FA↓≈time↑	RD↑≈dose↑AD↑≈dose↑FA↓≈dose↑MD≈not defined	Radiation effects may be particularly damaging to the white matter underlying the AC. Microstructural changes in AC SWM represent an important biomarker of EF decline, and it may be possible to preserve cognitive function by reducing the dose in this region during radiotherapy
Chapman *et al*., 2013[25]	An analysis of white matter changes following chemoradiotherapy was conducted using DTI	There was a statistically significant decrease in FA in 87.8% of WM skeleton voxels from before and after RT. 82.9% of WM skeleton voxels showed significant reductions in FA and 12.9% of WM skeleton voxels displayed significant decreases in AD following RT	FA↓≈time↑AD↓≈ time↑RD↑≈time↑	Not reported	The WM structures of the brain responded differently to chemoradiotherapy. Also, reduction in FA and RD associated with the demyelination of the WM was prominent in the cingula and fornix
Connor *et al*., 2016[28]	To model the dose-dependent and time-dependent effects of radiation on white matter, DTI with multiple b-values was utilized in this study	In this study, it was found that the reduction trend in FA value and increasing trend in MD value are related to increasing radiation dose. Areas receiving low doses of 10–20 Gy showed significant changes after 9–11 months, whereas areas receiving doses of more than 30 Gy required 4–6 months. In addition, FA changes were significant even at the lowest dose (10 Gy), They also found that AD and RD increased dose and time-dependently (RD showed greater changes than AD)	RD↑≈time↑MD↑≈time↑ AD↑≈time↑FA↓≈time↑	RD↑≈dose↑AD↑≈dose↑FA↓≈dose↑MD↑≈dose↑	According to this study, treatment-related changes in MD, FA, AD, and MD occur up to 9–11 months following RT

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Table 3: Contd...

	Aim	Main results	Parameters trend (with time)	Parameters trend (with dose)	Conclusions
Hope *et al*., 2015[26]	In order to determine whether DTI can be used as a biomarker during RT treatment for radiation-induced brain injury	According to this study, mean MD, AD, and RD increased significantly in areas of>41 Gy dose in comparison to areas of 12 Gy dose. Across all dose regions, the MD, RD, and MD increased significantly with time. After 6 weeks of RT, or immediately following the treatment, significant changes were observed. However, none of the estimates of FA or skewness showed a significant time evolution	RD↑≈time↑MD↑≈time↑AD↑≈time↑	RD↑≈dose↑MD↑≈dose↑AD↑≈dose↑	DTI was not responsive to acute changes in NAWM during treatment of HGG but was responsive to early changes after treatment
Rydelius *et al*., 2022[27]	Using DTI to examine the longitudinal changes in normal-appearing brain tissue following volumetric modulated arc RT or helical tomotherapy for glioblastoma patients	In this study, significant DTI changes were limited to the corpus callosum, and in the other structures, only transient and sparse changes were seen. The data indicated that RD and MD were increased in the corpus callosum body while FA was decreased. Also, genu almost shows a similar pattern	RD≈irregular MD≈irregular FA≈irregular AD≈irregular	Not any relation	Only a limited number of brain structures showed longitudinal changes in MD, FA, and RD, and the changes were smaller than expected
Jinsoo *et al*., 2013[31]	To examine whether the white matter tracts within the brainstem are uniformly affected by radiation	There was a significant decline in FA in the pons, dTPF, vTPF, and MCP in the patient group, though the decline was more pronounced in the pons. During 18 and 45 months from baseline, the TPF demonstrated more changes (FA reductions were evident at the pons level) consistent with WM injury than did the CST, ML, and MCP, regardless of dorsal or ventral compartments. Also, the dTPF showed significantly lower AD, higher RD, and lower MD than the CST, ML, and MCP. As a result of these changes in regional and temporal patterns, the dose distribution was unable to explain them. There was no significant dose dependence observed in this study between changes in DTI parameters between different regions	RD↑≈time↑AD↓≈time↑FA↓≈time↑	Not any relation	White matter tract's structural integrity was not uniformly altered after radiation therapy, as assessed by DTI. Based on these findings, it appears that tract-based assessments play an important role in radiation treatment planning and brainstem tolerance assessment
Raschke *et al*., 2019[30]	This longitudinal study used DTI to quantify changes in the white and gray matter following RT as a function of dose and time after treatment	In the WM regions with normal appearance, significant reductions were found in MD, RD, AD, and T2*. The radiation dose received in these regions throughout the 18-month observation period ranged from 10 Gy to 20 Gy. According to their study, these changes increased in magnitude with increasing radiation dose and progressed with time after RT. Additionally, their study demonstrated that FA increased significantly at high doses	RD↓≈time↑MD↓≈time↑AD↓≈time↑FA↑≈time↑	RD↓≈dose↑MD↓≈dose↑AD↓≈dose↑FA↑≈not any relation	Diffusion tensor imaging revealed normal-appearing white matter changes following radiation treatment. The changes were dose-dependent and progressed over time

↑=Increasing trend; ↓=Declining trend. RT=Radiotherapy; FA=Fractional anisotropy; MD=Mean diffusivity; RD=Radial diffusivity; AD=Axial diffusivity; WM=White matter; CST=Corticospinal tract; ML=Medial lemniscus; TPF=Transverse pontine fiber; MCP=Middle cerebellar peduncle; vTPF=Ventral TPF; dTPF=Dorsal TPF; DLPFC=Dorsolateral prefrontal cortex; CAC=Caudal anterior cingulate; RAC=Rostral anterior cingulate; EF=Executive function; SWM=Superficial white matter; AC=Anterior cingulate; HGG=High grade glioma; NAWM=Normal appearing white matter; DTI=Diffusion tensor imaging, T2*=Relaxation time

not dose dependent. However, they found that parameters changed over time. Similar to the early delay phase, the results of Rydelius *et al*.[27] demonstrated an irregular trend in all parameters during the late delay phase.

Table 4: Imaging parameters

Author	Scanner	Field strength (T)	Sequence	Voxel size (mm^3)	Matrix size	FOV (mm)	TE (ms)	TR (ms)	DTI directions	b (s/mm^2)	Slice thickness (mm)
Nazem-Zadeh *et al*., 2014[24]	Signa GE Achieva Philips	1.5 3	NA	1.72×1.72×3.75 1.75×1.75×2	128×128	NA	NA	NA	9 And 15	1000 and 0	NA
Tringale *et al*., 2019[29]	GE	3	Single-shot pulsed-field gradient spin EPI	NA	128×128×48	NA	96	17	1 6 6 15	0 500 1500 4000	2.5
Chapman *et al*., 2013[25]	Achieva Philips	3	Spin-echo echo-planar imaging	1.75×1.75×2.0	NA	224×224×120	60	7032	15	1000 and 0	NA
Connor *et al*. 2016[28]	Signa GE	3	Single-shot pulsed-field gradient spin-echo-planar imaging	NA	NA	NA	96	17	1 6 6 15	0 500 1500 4000	NA
Hope *et al*., 2015[26]	Achieva Philips	3	Stejskal-Tanner spin-echo EPI	2.5×2.5×2.5	96×96	240×240	60	4369	1 15	0 800	NA
Rydelius *et al*., 2022[27]	Magnetom siemens	3	NA	NA	NA	NA	NA	NA	30	1000	NA
Jinsoo *et al*., 2013[31]	Siemens	1.5	Double spin-echo pulse sequence	NA	128×128	230×230		100	12	1000 and 0	3
Raschke *et al*., 2019[30]	Philips	3	NA	NA	112×112	224×224	66	6500	32 2	1000 0	2

EPI=Echo-planar-imaging; NA=Not available; T=Tesla; DTI=Diffusion tensor imaging; FOV: Field of view; TR: Repetition time; TE: Echo time

DISCUSSION

Over the past few years, DTI has become recognized as a valuable tool for studying WM. Through the analysis of FA, MD, RD, and AD values, DTI could provide insight into the changes in WM following brain RT.[32] Various studies have examined the role of DTI biomarkers in the prediction of WM changes after brain RT. However, evaluating the accuracy and efficiency of these biomarkers requires a comprehensive study.[33,34] To the best of our knowledge, this systematic review is the first to determine the potential of DTI biomarkers to predict WM changes caused by radiation.

Radiation-induced injury develops in three phases: acute phase, early delay phase, and late delay phase. It is important to note that the effects of acute and early delay reactions are usually reversible, even if severe reactions can occur such as transient demyelination along nerve fibers. As opposed to early delayed reaction injuries, late delay reaction injuries are characterized by damage to the endothelial cells in the vascular system, demyelination, necrosis in WM, and severe functional impairment, which is usually permanent and irreversible.[3,35]

According to clinical research, early changes can predict more severe late-delay changes, which means that, with further clinical investigations, they can be used for early screening and intervention, such as RT.[36] There are different types of neuroglia, compact axons, and other small cell populations in the WM tracts of the CNS. In an axon, water diffusion perpendicular to fiber orientation is restricted by the axonal membrane and well-aligned protein fibers. Water diffusion in the WM may also be anisotropic due to myelin sheaths around the axons.[37,38] It is possible to detect the quantitative description of this anisotropy through DTI images that are weighted with the microstructural characteristics of water diffusion in a particular region of the tissues. For the evaluation of radiation-induced WM changes, we classified the studies into three phases.

Acute phase

Studies that assessed the acute phase revealed that the RD parameter changed significantly during RT. There were progressive dose and time-dependent changes in RD in these studies;[24-26] in addition, Rydelius *et al*.[27] demonstrated a significant AD change in the corpus callosum compared to other regions. The changes in RD were also accompanied by an increase in AD and a decrease in FA at this phase. Nazem-Zadeh *et al*.[24] found that AD and RD can predict necrosis in WM even before the completion of RT. These findings are in agreement with those of Hope *et al*.[26] who showed the potential of DTI biomarkers in the prediction of radiation-induced WM changes.

Early delay phase

Almost all studies that analyzed early delay phase FA showed a significant reduction compared to pre-RT.[27-29] During this phase, the FA trend was dose dependent and time dependent. In addition, AD and RD showed an increasing trend over time, and the dose in this phase was the same as in the acute phase.[24,26,28,29] It can be said that AD and RD changes in the acute phase are related to the early delay phase. RD changes are associated with myelin damage in preclinical models, and AD changes are associated with pathologies that damage axons.[39,40]

Furthermore, an increasing trend in MD at this phase was concurrent with the changes in other DTI parameters. Although Raschke *et al*.[30] reported reverse trends in all the biomarkers.

Late delay phase

Parameters change at the late delay phase almost were similar to the early delay phase.[26,28,31] Connor *et al*.[28] demonstrated that dose and time-dependent progressive changes can be seen at 9–11 months after RT. They found significant changes at this time, even in 10–20 Gy dose levels. These results can demonstrate progressive WM changes over time.

Nevertheless, all the included studies in this systematic review did not analyze biomarker changes at all three phases, but the results show that the changes at the late delay phase are completely related to acute phase changes. The sensitivity of the biomarkers was different between studies, but there was strong evidence for the early detection of changes by AD, RD, and FA. However, further research is needed on the potential of MD sensitivity for the detection of early changes. Although most studies reported progressive time- and dose-dependent changes in DTI parameters, Rydelius *et al*.[27] reported that observed transient and sparse changes may be because of using volumetric-modulated arc RT or helical tomotherapy. It is important to note that at the acute phase, changes in biomarkers were not significant in <30 Gy dose bins.[24,26,28] Variations in FA rate have also been observed in different WM structures and fiber bundles. According to Liu *et al*.,[41] the fiber bundles of the right hemisphere are more sensitive to radiation dose than those of the left hemisphere. Therefore, it can be said that the anatomical region is one of the other reasons that impress biomarker changes. In addition, there was no observed exact time for the recovery of posttreatment parameter values to pretreatment values. It can be seen in almost all the studies examined in this review that WM changes can occur even at low doses. Consequently, WM dose limitations in RT should receive more attention. As a result, the implementation of advanced imaging techniques such as DTI may facilitate a more effective treatment planning process and reduce secondary brain damage following brain radiotherapy.

Between the investigated studies, there was a high level of heterogeneity and variability in evaluation metrics. As a result, we were unable to conduct a meta-analysis. In this study, there were some limitations, such as the fact that the areas examined in the included studies were different. Moreover, the rate of changes in WM caused by chemotherapy may also affect the results.[42] Moreover, it is necessary to investigate the effects of factors such as the RT method, the type of cancer, and concurrent treatments. It should be noted that many brain WM changes occur in the delay phase, so it is recommended that future research follow up on the patients for several years.

CONCLUSION

The studies included in this systematic review provide some indication that DTI biomarkers may have significant potential for predicting WM changes induced by radiation after brain RT. Despite the need for additional research on MD's sensitivity, the parameters of AD, RD, and FA could be able to detect microstructural changes in the acute phase; as well, changes detected in the early and delayed phases are associated with changes detected in the acute phase. The changes in all parameters were dose and time dependent; additionally, they occurred at different rates depending on the brain structure.

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Conflicts of interest

There are no conflicts of interest.

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