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Authors: Mahdi Mohammadi, Shabnam Banisharif, Fatemeh Moradi, Maryam Zamanian, Ghazal Tanzifi, Sadegh Ghaderi

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Mahdi Mohammadi[1], Shabnam Banisharif[2], Fatemeh Moradi[3], Maryam Zamanian[2], Ghazal Tanzifi[4], Sadegh Ghaderi [5]

[1]*Department of Medical Physics and Biomedical Engineering, School of Medicine, Tehran University of Medical Sciences, Tehran, Iran*

[2]*Department of Medical Physics, School of Medicine, Isfahan University of Medical Science, Isfahan, Iran*

[3]*Department of Energy Engineering & Physics, Amirkabir University of Technology (Tehran Polytechnic), Tehran, Iran*

[4]*Department of Nuclear Engineering, Islamic Azad University, Central Tehran Branch, Tehran, Iran*

[5]*Department of Neuroscience and Addiction Studies, School of Advanced Technologies in Medicine, Tehran University of Medical Sciences, Tehran, Iran*

Addres for correspondence: Sadegh Ghaderi, Tehran University of Medical Sciences, Department of Neuroscience and Addiction Studies, Tehran, Iran; e-mail: S_ghaderi@razi.tums.ac.ir

Abstract

In addition to providing a measurement of the tumor’s size and dimensions, magnetic resonance imaging (MRI) provides excellent noninvasive radiographic detection of tumor location. The MRI technique is an important modality that has been shown to be useful in the prognosis, diagnosis, treatment planning, and evaluation of response and recurrence in solid cancers. Diffusion-weighted imaging (DWI) is an imaging technique that quantifies water mobility. This imaging approach is good for identifying sub-voxel microstructure of tissues, correlates with tumor cellularity, and has been proven to be valuable in the early assessment of cytotoxic treatment for a variety of malignancies. Diffusion tensor imaging (DTI) is an MRI method that assesses the preferred amount of water transport inside tissues. This enables precise measurements of water diffusion, which changes according to the direction of white matter fibers, their density, and myelination. This measurement corresponds to some related variables: fractional anisotropy (FA), mean diffusivity (MD), radial diffusivity (RD), axial diffusivity (AD), and others. DTI biomarkers can detect subtle changes in white matter microstructure and integrity following radiation therapy (RT) or chemoradiotherapy, which may have implications for cognitive function and quality of life. In our study, these indices were evaluated after brain chemoradiotherapy.
Key words: diffusion MRI; brain; chemoradiotherapy; imaging biomarkers; neuroimaging

Introduction

Diffusion-weighted imaging (DWI) quantifies an estimate of water mobility obtained by magnetic resonance imaging (MRI), is useful for assessing sub-voxel microstructure in tissues, correlates with tumor cellularity, and has been shown to be useful in the early evaluation of cytotoxic therapy in a variety of cancers [1–5].

Diffusion tensor imaging (DTI) is a non-invasive MRI-based approach that detects white matter structure more accurately than conventional MRI. Water diffusion in tissues is measured using DTI, an MRI method that analyzes the preferred direction and amount of the water's movement. Water diffusion in white matter tracts is often directionally dependent or anisotropic because of the ordered structure of axons and myelin sheaths. Radiation-induced white matter damage may be evaluated noninvasively using DTI, which has a long history of supporting evidence as an imaging biomarker [6–10].

DTI assesses water molecule diffusion in the brain, which changes with white matter fiber direction, density, and myelination. Mean diffusivity (MD), radial diffusivity (RD), and axial diffusivity (AD) are three related values of this measurement. These indices are related to the magnitudes of diffusion that are perpendicular and parallel to white matter fibers, respectively. The fractional anisotropy (FA) index is another kind of diffusion index that is often employed. It is a normalized value that may vary from zero (which indicates equal diffusion in all directions) to one (diffusion along a single axis only). FA is a measure of the overall density and integrity of the brain's white matter; a reduction in FA has been linked to a wide variety of brain disorders [7, 11–17].

Radiation therapy (RT) for primary brain tumors and brain metastases from extracranial tumors is performed annually on hundreds of thousands of patients around the world [18–23]. There are two types of brain radiotherapy: whole brain (WBRT) and partial brain (PBRT). WBRT involves irradiating the whole brain and brainstem, whereas PBRT involves irradiating the tumor or tumor bed and surrounding margin and some healthy brain tissue [21, 24, 25]. Stereotactic radiosurgery (SRS) uses accurate 3D imaging and localization to deliver ablative doses of radiation to the tumor while exposing healthy brain tissue to a minimum [23, 25].

RT may cause post-treatment neurocognitive deterioration, with verbal and visuospatial memory being the most commonly reported. Neurocognitive decline has been an independently associated predictor of survival in individuals with brain malignancies, and the long-term consequences of RT are usually permanent and gradual [12, 26]. Damage to white matter (WM) pathways, vascular injury, and neuroinflammation are all factors that contribute to radiation-induced brain damage. Axonal degeneration and demyelination of WM have been shown in histopathological investigations following radiation exposure, and diffusion tensor imaging (DTI) biomarkers are related to these alterations [12, 27, 28].

Based on our research, the aim of the study is to collect and classify brain diffusion MRI biomarkers after chemoradiotherapy.

Materials and methods

Search strategy

On November 12th, 2021, the search for articles was started, and on July 3rd, 2022, it was completed. Diffusion MRI, Brain, Chemoradiotherapy, Imaging Biomarker, and Neuroimaging

were among the keywords used in the search, which were entered into the following template in the PubMed electronic database and the Google Scholar search engine.

Inclusion criteria (refer to DWI biomarkers) were as follows:

- English-language original articles;
- original and review studies looked at DWI biomarkers after brain chemoradiotherapy and used MRI data;
- original research that looked at long-term cognitive and behavioral disorders.

Exclusion criteria were as follows:

- all of the articles are written in languages other than English;
- case studies and short reports;
- the studies did not employ an MRI or any other imaging modality (particularly in cases of neurological manifestations).

Literature screening

Approximately 100 publications were discovered during the first search, which comprised original studies, review articles, case reports, and short reports. As a result, case studies and short reports were excluded, but the references in the literature review were examined. After the final evaluation, 32 original papers and 6 review articles remained based on the inclusion and exclusion criteria. Biomarkers and long-term cognitive-behavioral disorders were comprehensively retrieved from all of the papers in the reference list.

The following parameters were considered throughout the search:

- first author;
- the date of publication;
- using MRI.

Finally, after doing database searches and collecting publications, they were divided into three categories: white matter changes, radiation necrosis, and neurocognitive damages.

MRI

Devices

Various investigations have employed devices of varying field strengths and commercial models to study changes in diffusion parameters in brain tissue in relation to necrotic and neurocognitive damage. The types of these devices include a 3.0T system (Philips Medical Systems, Best, the Netherlands), a 3.0T system (Achieva, Philips, Eindhoven, The Netherlands), a 3.0T 750, and 1.5 T and Signa Excite HDx scanner (General Electric Healthcare, Milwaukee, Wisconsin, United States), a Signa 1.5T and 3.0T scanner (General Electric Healthcare, Chicago, IL, United States), a Sonata 1.5T scanner (Siemens Healthcare, Erlangen, Germany), a TimeTrio 3.0T scanner (Siemens Medical Solutions, Malvern, PA, USA), and a 3.0T scanner (Trio MAGNETOM; Siemens Healthcare, Erlangen, Germany) cases. It is important to note that in some experiments, just one or even three types of a device were employed.

Diffusion-weighted techniques

DWI

DWI is a potential MRI technique for characterizing the response to RT and the damage to normal tissue. Changes in the mobility of water molecules in tissue are reflected in the MR signal in DWI. Brownian motion, as it is often referred to, is the result of heat agitation and is strongly impacted by the water's cellular structure. Neurosurgical evaluations of brain tumors may greatly benefit from DWI. One of the most commonly used parameters derived from DWI is the apparent diffusion coefficient (ADC), which quantifies the magnitude of water diffusion in tissue. ADC can provide valuable information about tumor cellularity, necrosis, edema, and perfusion, which can help in diagnosis, prognosis, treatment planning, and monitoring of brain tumors. ADC can also detect early changes in tissue microstructure after RT, which can indicate the efficacy of treatment and the risk of complications. Therefore, ADC is an important biomarker for assessing brain tumors and their response to RT [28, 29].

DTI

The advanced DTI technique is a helpful tool for measuring the damage to white matter that is caused by radiation. It is able to detect abnormalities much earlier than conventional imaging approaches. It is feasible to use the DTI's capacity to identify white matter degradation in order to determine whether or not RT has varied detrimental effects on various parts of the brain [29, 30].

We selected MD, RD, AD, and FA as biomarkers because they capture different aspects of white matter microstructure and integrity that can be altered by brain disorders. MD reflects the average diffusion of water molecules in the brain tissue, which can be affected by factors such as cell density, membrane permeability, and extracellular space. RD reflects the diffusion of water molecules orthogonal to the main fiber direction, which can be indicative of demyelination or axonal loss. AD reflects the diffusion of water molecules along the main fiber direction, which can be suggestive of axonal damage or degeneration. FA reflects the degree of anisotropy or directionality of water diffusion in the brain tissue, which can be associated with fiber coherence, organization, and alignment. These parameters have been widely used and validated in previous studies of various brain disorders, and they provide complementary information about the structural changes in white matter that may underlie the pathophysiology of these disorders. We did not use other parameters, such as mode of anisotropy or trace of the diffusion tensor, because they are less commonly used and less informative than the ones we selected [12, 27, 28].

Chemoradiation therapy techniques

Chemotherapy

Chemotherapy medications may be used after surgery, in conjunction with radiotherapy, in cases of recurrence of the disease, or even as a substitute for radiation treatment in children, depending on the patient's health. Brain tumors cannot be effectively treated with chemotherapy alone because of the blood-brain barrier (BBB) [31, 32].

External radiotherapy

Based on the type and location of the lesion, different radiotherapy techniques are used to treat brain tumors. For the most precise RT treatment, stereotactic radiosurgery (SRS) makes use of three-dimensional (3D) imaging to locate and treat brain malignancies in a single session. Some SRS techniques include the X-ray knife and the Gamma-knife [33–35].

Other methods of external radiotherapy include delivering the tumor from the outside in numerous doses. Three-dimensional conformal radiation therapy (3D-CRT) reliably identifies the planning target volume (PTV) and adjacent organs at risk (OARs) using 3D imaging [36]. In order to optimize the radiation flux profile, novel modulation systems, named intensity modulated radiation therapy (IMRT), computer-controlled multi-leaf dynamic collimators, and

methodologies such as inverse planning are required to apply this strategy [37, 38] .The most recent versions include rotating cone beams as therapy with multiple arcs at a consistent dose rate in each different sub-field of radiation or volumetric modulated arc therapies (VMAT) as treatment with rotating cone beam radiation with varying shapes and radiation intensities [39, 40].

Results and Discussion

Brain diffusion MRI biomarkers

White matter changes

Neuron myelinated fibers, also known as tracts, are found in white matter (WM), the deepest component of the brain tissue in the central nervous system. The white matter tracts of the corpus callosum and the internal capsules are crucial [41]. RT for various types of brain tumors, such as gliomas, medulloblastomas, and meningiomas, will always lead to alterations in the tumor's volume and the ratio of intracellular to extracellular volumes [42–44]. DTI and DWI, by using intrinsic tissue properties, offer a helpful quantitative evaluation of tissue structure, particularly myelinated fiber bundles in WM [45, 46].

Radiation necrosis

Focal neurological impairments are often associated with radiation necrosis, which affects mostly the white matter and is generally permanent and progressive [47]. According to the structure of the nerve fiber axons and the myelin sheath, the flow of water molecules along the length of the nerve fiber is greater than in other directions. Due to the existence of numerous membranes, restricted space, and high viscosity, the quantity of movement of water molecules in the intracellular space is smaller than that in the extracellular environment. As a result, since radiation affects the ratio of intracellular to extracellular volumes, diffusion imaging biomarkers are very useful to assess radiation damage. Utilizing these biomarkers, like other MR imaging procedures, is non-invasive and does not require any further interventions. White matter is particularly vulnerable to radiation damage because of the way water molecules move through the tissue [48]. White matter axial and radial diffusivity changes are often interpreted as

indicators of axonal injury or demyelination [49]. After beginning RT, an imaging biomarker might be used to determine the radiation sensitivity of an individual's brain normal tissue [50].

Neurocognitive damages

Neurocognitive abnormalities are clearly linked to radiation treatment and are an important adverse effect of life-saving interventions in youngsters [51]. After irradiation, cognitive loss may begin to show up months or years later and worsen with time [52]. IMRT, stereotactic radiosurgery, intracranial brachytherapy, and restricted fraction size may minimize normal tissue damage [53]. Some neuropsychological deficiencies (such as a lack of ability to recall information or spatially interpret information) still persist [54, 55].

Table 1 provides the findings that relate to alterations in diffusion biomarkers in WM changes, radiation necrosis, and neurocognitive damage. As well, Figure 1 is a representation of the common alterations that have occurred in the most significant MR diffusion biomarkers, including FA, MD, RD, AD, and ADC.

Table 1. Studies of diffusion biomarker assessment after radiation damage

First Author [year]	**Patient Numbers**	**Imaging Technique(s)**	**Max. Directions/b-values [s/mm^2]**	**Radiotherapy Technique(s)**	**Total dose/Fraction Size [Gy]**	**Chemotherapy**	**Imaging biomarker(s)**	**Brain tumor(s)**	**Changes in imaging Biomarker(s)**
White matter changes									

Chakhoyan (2018) [56]	23	DWI	NA/0, 50, 100, 250, 500, 750, 1000, 2500, 3500 and 5000	3D-CRT	60/2	Temozolomide	ADC	Glioblastoma	No difference in diffusion biomarkers change in NAWM between pre- and post-chemoradiation
Nagesh (2008) [6]	25	DTI	9/0 and 1000	3D-CRT	50–81/1.8–2.7	Temozolomide	FA MD AD RD	Cerebral tumors	FA decreased, and MD, RD, and AD increased in the genu

									and splenium
Hope (2015) [57]	18	DTI	15/0 and 800	3D-CRT	60/2	Temozolomide	FA MD AD RD	HGGs	In FA, no significant time evolution was observed, and there was increased MD, RD, and AD in NAWM
Haris (2008) [58]	5	DTI	10/0 and 1000	3D-CRT	54/1.8	Temozolomide	FA MD	LGGs	FA decreased and MD increa

									sed in NAWM
Tringale (2019) [59]	54	DTI	15/0, 500, 1500, and 4000	Proton or photons RT	50.4–60/1.8–2	NA	FA MD RD AD	Primary brain tumor	whereas FA decreased in the right caudal anterior cingulate, MD, RD increased bilaterally, whereas no significant changes in AD were found during

									this time-period
Chapman (2012) [60]	10	DTI	9/0 and 1000	3D-CRT	50.4 – 59.4/1.8	NA	FA AD RD	Benign tumors	While FA was used for volume adjustment, it was not included in the analysis. Following RT, AD decreased and RD increased

Connor (2016) [61]	32	DTI	15/0, 500, 1500, and 4000	EBRT	60/2	Chemotherapy	FA MD AD RD	HGGs	MD, AD, and RD increased significantly with time and dose, and a corresponding decrease in FA
Chang (2014) [62]	15	DWI DTI	6/0 and 1000	Partial brain irradiation or SRS	18–25	NA	ADC FA	Malignant gliomas	ADC increased (receiving more than 5 Gy) and decreased

									(more than 12 Gy) after 7 days and 2 months. FA decreased more after 2 months
Tibbs (2020) [63]	44	DTI	15/0, 500, 1500, and 4000	Proton therapy and IMRT or VMAT	50.4–70/1.8–2	NA	FA MD	Primary brain tumor	There was decreased FA in the left arcuate fasciculus, ILF, and IFOF. Increased MD in

									all of the left-sided white matter tracts, left arcuate fasciculus, ILF, IFOF
Qiu (2007) [64]	22	DTI	25/0 and 1200	3D-CRT	23.4–40/1.8–2	Chemotherapy	FA	Medulloblastoma	Decreased FA in the frontal lobe and parietal lobe white matter, and the frontal lobe having

									a significantly larger difference in FA compared with the parietal lobe
Connor (2017) [48]	49	DTI	15/0, 500, 1500, and 4000	3D-CRT	60/2	NA	FA MD AD RD	Primary brain tumors	Decreases in FA connote white matter disruption. For MD, the column and body of fornix,

									cingulum bundle, tapetum, and genu and body of the corpus callosum were among the ROIs to show the most dose sensitivity
Zhu (2016) [65]	33	DTI	20/0, 800, and 1000	EBRT	50.4–70/2	NA	ADRD	Low-grade or benign brain tumors	There was a dose-dependent progre

									ssive decrease in AD over time after RT. RD was significantly related to maximum doses received
Ding (2017) [66]	87	DTI	NA/0 and 1000	2D-CRT or IMRT	50–76/2	Chemotherapy	FA	Nasopharyngeal carcinoma patients with normal-appearing	Within an FA mask in the putative white matter, there was a signifi

								brains	cant reduction in the FA value. Specifically, after 12 months of follow ups from the completion of RT, the FA in the bilateral splenium of the corpus callosum was reduced

									compared to the pre-RT level
Hua (2012) [10]	109 DTI studies (from 20 brain tumor patients)	DTI	12/0 and 1000	3D-CRT	23.4 Gy or 36–39.6 Gy/1.8	Chemotherapy	FA	Medulloblastomas, supratentorial primitive neuroectodermal tumors, atypical teratoid rhabdoid tumors, and HGGs	Decreased FA

Raschke (2019) [67]	22	DTI	32/0 and 1000	Proton or photon therapy	13.6	Chemotherapy	MD RD AD FA	HGGs	Significant reductions in MD, RD, and AD and an increase in FA
Chapman (2013) [30]	14	DTI	15/0 and 1000	3D-CRT	30 and 37.5/3 and 2.5	Chemotherapy	FA RD AD	Brain white matter structures	Significant FA decreases and RD increases. There were no significant changes in AD betwe

									en pre-RT and end-RT
Huynh-Le (2021) [68]	44	DTI	15/0, 500, 1500, and 4000	Proton therapy, IMRT, and VMAT	50.4–70/1.8–2	NA	MD FA	Primary brain tumors	Reduction in FA and an increase in MD
Sahin (2021) [69]	17	DTI	7/0 and 1000	EBRT	60/2	Chemotherapy	FA	Glioblastoma	FA decrease
Cho (2020) [70]	40	DWI	NA/0 and 1000	EBRT	NA	Chemotherapy	ADC	Glioblastoma	The ipsilesional SVZ had lower ADC values compared to

									the contralesional SVZ before treatment, as ADC values of the ipsilesional SVZ increased
Khong (2003) [71]	9	DTI	25/0 and 1200	3D-CRT	30.6–40 and 50.4–54/1.8–2	NA	FA	Medulloblastoma	Significant reduction of FA was seen in all anatomic sites in the patient group compa

									red with FA in control subjects, except in the frontal periventricular WM.
Mabbott (2006) [72]	8	DWI DTI	25/0 and 1000	3D-CRT	36–36.6 and 23.4/NA	Either etoposide/cisplatin/cyclophosphamide/vincristine or CCNU/vincristine/cisplatin	ADC FA	Medulloblastoma	Overall, mean FA was lower and ADC was higher in the radiated group relative to

									controls
Ravn (2013) [29]	19	DWI	32/0 and 1300	3D-CRT	45–59.4/1.8	NA	ADC	Astrocytoma, pituitary adenoma, meningioma, and craniopharyngioma	ADC increase
Khong (2006) [73]	20	DTI	25/0 and 1250	3D-CRT	50–55.8/NA	Chemotherapy	FA	Childhood MED and ALL	FA increase
Makola (2017) [74]	22	DTI	25/0 and 1000	EBRT	45–59.4/NA	With or without chemotherapy	FA RD	A pediatric brain tumor	The FA and RD did not change

									signifi cantly
Prust (2015) [75]	14	DWI	NA	3D-CRT	60/2	Chemotherapy	ADC	Gliobl astoma	ADC increa sed within the subve ntricul ar zone
Radiation necrosis									
Nazem-Zadeh (2014) [76]	29	DTI	9/0 and 100 0	3D-CRT	60 and 66–81/2 and 2.5–2.6	Temozolomide	RD	Gliobl astoma	RD increa se
Liu (2018) [80]	43	DWI	NA/0 and 100 0	EBRT	40–50/NA	Chemotherapy	ADC	Brain metast ases from lung cancer	ADC values signifi cantly increa sed after both

									one and two treatment cycles. In effective group, the ADC values were significantly increased after one and two treatment cycles. While, there are no difference in invalid

									group after one treatment cycle but decreased after two treatment cycles
Feng (2022) [81]	46	DWI	20/0 and 1000	EBRT	NA	Surgical intervention followed by chemoradiotherapy	ADC	Glioblastoma	Significant differences between the tumor recurrence from radiation necrosis groups in

									terms of ADC
Neurocognitive damages									
Tringale (2019) [59]	54	DTI	15/0, 500, 1500, and 4000	Proton or photons RT	50.4–60/1.8–2	Chemotherapy	FA MD RD AD	Glioma and non-glioma	There were decreases in FA and increases in MD in the CAC at 3-months post-RT. CAC changes were characterized by increa

									sed RD bilaterally. AD did not change significantly
Chapman (2012) [60]	10	DTI	9/0 and 1000	3D-CRT	50.4 – 59.4/1.8	NA	AD RD	Low-grade or benign tumors	Following RT, AD decreased and RD increased
Chapman (2016) [77]	27	DTI	20/0 and 1000	3D-CRT and IMRT	50.4 – 70/2	15% had concurrent chemotherapy with temozolomide	RD AD	Benign or low-grade tumors	Decreasing AD and increasing RD during RT

Bian (2018) [78]	23	DTI	32/0 and 1000	IMRT	54 and 60/1.8 and 2	Temozolomid	FA	HGGs	FA in the contralateral hippocampus decreased at 6 and 9 months after radiotherapy. FA in the ipsilateral hippocampus before radiochemotherapy decreased compared with 6 months after

									radiotherapy
Tringale (2019) [12]	27	DTI	15/0, 500, 1500, and 4000	IMRT and proton therapy	50.4–60/1.8-2	Chemotherapy	FA MD	Primary brain tumor	Decreasing FA and increasing MD
Law (2011) [79]	67	DTI	31/0 and 1000	3D-CRT	23.4–36/NA	Chemotherapy	FA RD MD	Posterior fossa tumor	All imaging biomarkers have not changed significantly

DWI — diffusion-weighted imaging; NA — non available; 3D-CRT — three-dimensional conformal radiation therapy; ADC — apparent diffusion coefficient; NAWM — normal-appearing white matter; DTI — diffusion tensor imagin; FA — fractional anisotropy; MD — mean diffusivity; AD — axial diffusivity; RD — radial diffusivity; HGGs — high-grade gliomas; LGGs — low-grade gliomas; RT — radiation therapy; EBRT — external beam radiation radiation therapy; SRS — stereotactic radiosurger; IMRT — intensity modulated radiation therapy; VMAT — volumetric modulated arc therapy; ILF — inferior longitudinal

fasciculus; IFOF — inferior fronto-occipital fasciculus; ROIs — regions of interest; 2D-CRT — 2-dimensional conformal radiation therapy; SVZ — subventricular zone; CCNU — lomustine; MED — medulloblastoma; ALL — acute lymphoblastic leukemia; CAC — caudal anterior cingulate

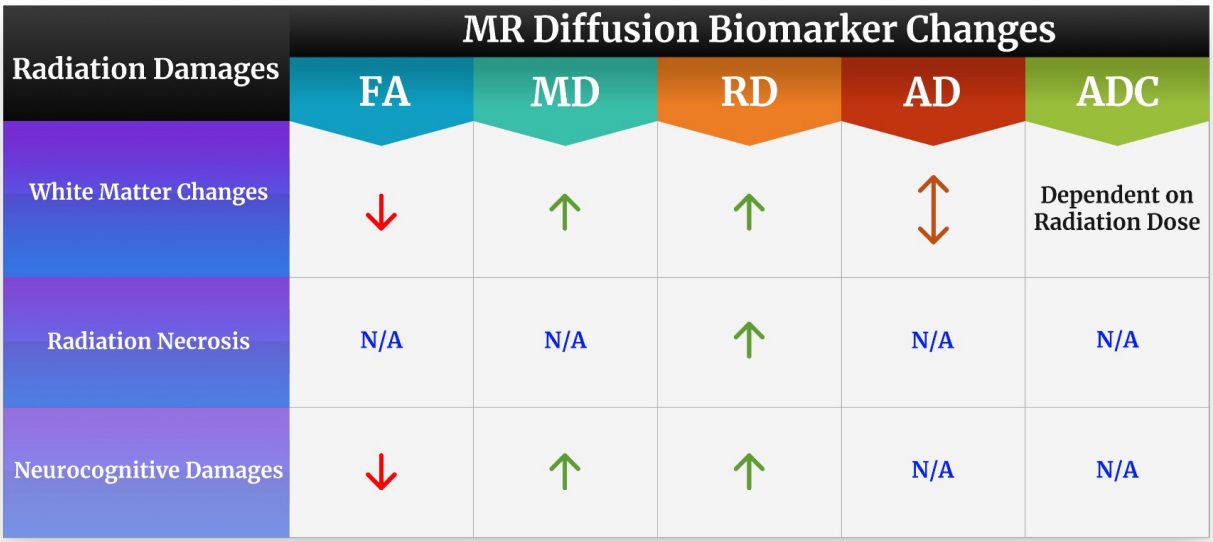

Figure 1. Magnetic resonance (MR) diffusion biomarkers changes. N/A — non available FA — fractional anisotropy; MD — mean diffusivity; RD — radial diffusivity; AD — axial diffusivity; ADC — apparent diffusion coefficient

Conclusion

Neuroimaging biomarkers after chemoradiotherapy were evaluated using diffusion imaging methods (DWI and DTI). We found that biomarkers change depending on the degree of tissue damage. Some studies demonstrate that biomarker alterations are increasing, while others show that they are decreasing. As a consequence, there is disagreement over the general pattern of change. Even so, FA changes are predicted to decrease, whereas MD and RD changes are

expected to increase. It is proposed that further longitudinal studies be conducted to determine the effectiveness of diffusion imaging biomarkers.

Conflict of interest

The authors declare no financial or other conflicts of interest.

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Author's Contributions

S.G. and M.M. contributed to the conception and design of the study; Sh.B., F.M., M.Z., and Gh.T. contributed to the data collection. S.G. and M.M. contributed to drafting the text and preparing the Figure 1.

Ethical statement

No human or animal subjects were used in the research.

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