



HOKKAIDO UNIVERSITY

Title	Performance of MRI Indices in Evaluating Myelin and Brain Injury following Whole-Brain Radiotherapy
Author(s)	Oppong, Philip Kyeremeh Jnr
Degree Grantor	北海道大学
Degree Name	博士(医理工学)
Dissertation Number	甲第16556号
Issue Date	2025-06-30
DOI	https://doi.org/10.14943/doctoral.k16556
Doc URL	https://hdl.handle.net/2115/97876
Type	doctoral thesis
File Information	Oppong_Philip_Kyeremeh_Jnr.pdf



Thesis

**Performance of MRI Indices in Evaluating Myelin and Brain
Injury following Whole-Brain Radiotherapy**

(ミエリン及び全脳放射線治療後の脳損傷の評価における

MRI 指標の成績)

June 2025

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Presentation Paper List and Conference Presentation List

Part of this study was presented in the following paper:

Oppong, P.K.J., Hamaguchi, H., Kitagawa, M., Patzke, N., Wakeman, K.C., Tha, K.K. (2025). Comparative Sensitivity of MRI Indices for Myelin Assessment in Spinal Cord Regions. *Tomography*, 11(1), 8.

Part of this study was presented at the following academic conference:

Oppong, P.K.J., Wang, J., Tha, K.K. (2023). Radiomics Analysis in the Era of Quantitative MRI [Poster presentation]. 31st Annual Meeting & Exhibition of the International Society for Magnetic Resonance in Medicine (ISMRM), Toronto, Canada.

Abbreviation Table

2D	Two-dimensional
3D	Three-dimensional
AC	Anterior column
ACR-L	Left anterior corona radiata
ACR-R	Right anterior corona radiata
AD	Axial diffusivity
A _E	Signal amplitude for extra-axonal water
A _I	Signal amplitude for intra-axonal water
ALIC-L	Left anterior limb of internal capsule
ALIC-R	Right anterior limb of internal capsule
A _M	Signal amplitude for myelin water
ANOVA	Analysis of variance
b	Diffusion weighting factor
b ₀	Echo planar image with no diffusion weighting factor
BBB	Blood-brain barrier
BCC	Body of corpus callosum
BP	Brain parenchyma
CC	Corpus callosum
CE	Contrast enhanced
CNS	Central nervous system
cm	Centimeter
CPMG	Carr-Purcell-Meiboom-Gill
CSF	Cerebrospinal fluid

DKI	Diffusion kurtosis imaging
DTI	Diffusion tensor imaging
DWI	Diffusion-weighted imaging
EPT	Electric properties tomography
FO 10 th	First order 10 th percentile
FO 90 th	First order 90 th percentile
FO kurt	First order kurtosis
FA	Fractional anisotropy
FLAIR	Fluid-attenuated inversion recovery
FOV	Field of view
Gd-T1WI	Gadolinium contrast-enhanced T1-weighted image
GCC	Genu of corpus callosum
GLCM cS	Gray level co-occurrence matrix cluster shade
GLCM cT	Gray level co-occurrence matrix cluster tendency
GLCM J.av	Gray level co-occurrence matrix joint average
GLCM ImC1	Gray level co-occurrence matrix informational measure of coherence 1
GLCM Diff.v	Gray level co-occurrence matrix difference variance
GM	Gray matter
GRASE	Gradient and spin Echo
GRE	Gradient echo
Gy	Gray
$\hat{g}_k$	Diffusion direction
ICBM	International consortium of brain mapping
IQ	Intelligence quotient

IRB	Institutional Review Board
KPS	Karnofsky performance status
LC	Lateral column
LFB	Luxol fast blue
MBP	Myelin basic protein
MD	Mean diffusivity
MHz	Megahertz
MNI	Montreal Neurological Institute
MPRAGE	Magnetization prepared rapid gradient echo
MP2RAGE	Magnetization prepared 2 rapid gradient echoes
MRI	Magnetic resonance imaging
MTI	Magnetization transfer imaging
MTR	Magnetization transfer ratio
MWF	Myelin water fraction
MWI	Myelin water imaging
NCE	Non-contrast enhanced
NEX	Number of excitations
NITRC	Neuroimaging informatics tools and resources clearinghouse
NODDI	Neurite orientation dispersion and density imaging
OsO ₄	Osmium tetroxide
PB	Phosphate buffer
PLIC-R	Right posterior limb of internal capsule
PET	Positron emission tomography
QOL	Quality of life
PC	Posterior column

RANO	Response assessment in neuro-oncology
RBANS	Repeatable battery for the assessment of neuropsychological status
rFOV-DTI	Reduced field of view-diffusion tensor imaging
RD	Radial diffusivity
RFE	Recursive feature elimination
RF	Radiofrequency
ROI	Region of interest
RLIC-L	Retrolenticular part of left internal capsule
RLIC-R	Retrolenticular part of right internal capsule
RMSE	Root mean square error
SCC	Splenium of corpus callosum
SD	Standard deviation
SLF-L	Left superior longitudinal fasciculus
SLF-R	Right superior longitudinal fasciculus
SCR-L	Left superior corona radiata
SCR-R	Right superior corona radiata
S_0	Baseline signal intensity
S_k	Signal intensity after applying the diffusion-sensitizing gradient
SPACE	Sampling perfection with application-optimized contrast
SSFP	Steady-state free precession
T1	Longitudinal relaxation time
T2	Transverse relaxation time
T1 ρ	Spin-lattice relaxation time in the rotating frame

T1WI	T1-weighted image
T2 _m	Myelin transverse relaxation time
T2 _I	Intra-axonal transverse relaxation
T2 _E	Extra-axonal transverse relaxation time
T2WI	T2-weighted image
TA	Acquisition time
TE	Echo time
TEM	Transmission electron microscopy
TR	Repetition time
TSL	Time of spinlock
UCLA	University of California, Los Angeles
ROI	Region of interest
WBRT	Whole brain radiotherapy
WM	White matter
WT	Whole tumor
σ	Electrical conductivity
$\lambda_1, \lambda_2, \lambda_3$	Diffusion tensor eigenvalues
ω	Lamor frequency
MCP	Middle cerebellar peduncle
T	Tesla
μ_0	Magnetic vacuum permeability
φ	Transceive phase

Introduction

Magnetic resonance imaging (MRI) is a noninvasive modality conventionally used for assessing myelin in both normal and pathological states, offering insights into microstructural alterations caused by injury and pathology. The rapid and efficient transmission of motor and sensory signals within the central nervous system (CNS) is facilitated by myelin, which is a protective sheath that encases axons (Simons et al., 2015; Kister et al., 2023). Myelin consists primarily of lipids (about 70–80%), including cholesterol, phospholipids, and glycolipids, and proteins (20–30%), such as myelin basic protein (MBP) and proteolipid protein (PLP), which are essential for its function. The lipid content raises electrical resistance and enhances signal conduction speed, while the proteins maintain structural integrity by ensuring the compact arrangement of myelin layers. Damage or abnormalities in myelin disrupt signal transmission, leading to muscle weakness, sensory loss, and coordination deficits, which are hallmark features of demyelinating diseases such as multiple sclerosis (Love, 2006).

Evaluating myelin composition, necessary for diagnosing and monitoring demyelinating diseases and other myelin-related conditions, relies on invasive histological methods such as Luxol fast blue (LFB) staining, osmium tetroxide (OsO₄) staining, and transmission electron microscopy (TEM). Less invasive approaches, including cerebrospinal fluid (CSF) analysis and positron emission tomography (PET), have also been developed to detect myelin damage in patients (Whitaker et al., 1998; Wu et al., 2010). However, the ultimate goal remains to develop entirely noninvasive methods that are capable of quantifying and evaluating myelin integrity reliably, enhancing diagnostic precision and patient monitoring across clinical settings.

Various MRI techniques have been proposed for evaluating myelin noninvasively, each demonstrating potential as a biomarker when validated against histological and immunohistochemical data. T1 and T2 relaxation times, fundamental determinants of MRI signal, are influenced by the degree of myelination (Hagiwara et al., 2018). The ratio of T1-weighted (T1WI) to T2-weighted (T2WI) images can be used as a simplified metric for myelin content. T1WI and T2WI images generate contrast that highlight myelin by leveraging the direct proportionality of pixel intensity to myelin in T1WI and the inverse in

T2WI. This ratio has been investigated to evaluate myelin content in cortical gray matter (GM), assess neonatal brain myelination and related pathologies (Sui et al., 2022; Soun et al., 2017; Yasuno et al., 2016). Beyond conventional MRI, advanced techniques, such as myelin water imaging [MWI] (Prasloski et al., 2012), magnetization transfer imaging [MTI] (Schmierer et al., 2004), T1 ρ or spin-lattice relaxation in the rotation frame (Menon et al., 2018), diffusion tensor imaging (DTI) metrics, including fractional anisotropy [FA] and mean diffusivity [MD], have demonstrated sensitivity to myelin content (Chang et al., 2017). Another promising approach, electric properties tomography (EPT), which uses electrical conductivity (σ) as a potential indicator of tissue integrity, is hypothesized to reflect elevated σ in demyelinated areas due to increased ion mobility (Tha et al., 2018). Indices of these techniques provide quantitative insights into myelin integrity and pathology.

Despite the demonstrated sensitivities of these MRI techniques to myelin content and integrity, their relative sensitivities have not been directly evaluated. Therefore, Chapter 1 of this thesis aimed to compare these techniques to determine the most sensitive MRI index for characterizing myelin composition in CNS tissue. Identifying this index is expected to have important implications for the accurate, noninvasive evaluation of myelin in normal and pathological states, including injury caused by whole brain radiotherapy (WBRT).

In chapter two, DTI metrics—FA and MD, whose sensitivity to myelin was demonstrated in chapter 1, are further examined for their utility in assessing potential WM changes, including myelin and axons within the acute and early-delayed phases. In parallel, other DTI indices—axial diffusivity (AD) and radial diffusivity (RD) are incorporated to provide a comprehensive analysis of WM regional vulnerability to WBRT-associated changes.

WBRT, delivered alone or combined with chemotherapy, is conventional for treating brain metastases (Li et al., 2021; Minniti et al., 2014) but is often associated with brain microstructural changes, which contributes to neurocognitive impairments across multiple domains (Li et al., 2024; Zhang et al., 2016). Detrimental effects of such changes are progressive, including late-delayed declines in intelligence quotient (IQ), episodic memory, information processing speed, attention, and executive functions (Cavatorta et al., 2021;

Greene-Schloesser et al., 2012). Additionally, neuropsychological sequelae, including emotional and behavioral disorders, have been reported across diverse patient populations, contributing to social burdens and diminishing quality of life [QOL] (Slykerman et al., 2021; Butler et al., 1994; Cavatorta et al., 2021).

The pathophysiological mechanisms underlying WBRT-associated neurocognitive impairments include acute-phase blood-brain barrier (BBB) disruption, which manifests as headaches, drowsiness, and elevated intracranial pressure. In the early-delayed phase, transient demyelination may occur, presenting as somnolence, attention deficits, short-term memory loss, and leukoencephalopathy (Greene-Schloesser et al., 2012).

Conventional clinical MRI techniques are sensitive for detecting severe WBRT-associated brain injuries (Monje and Dietrich, 2012). However, acute, and early-delayed phase injuries linked to mild and moderate cognitive impairments often show inconsistent correlations with imaging findings. These impairments may occur even in patients whose neuroimaging appears normal under standard protocols (Dropcho, 1991; Turnquist et al., 2020). This diagnostic gap increases the risk of under-recognition, delaying timely interventions, and potentially leading to progressive, irreversible cognitive declines that compromise the patient's functional independence.

Regional variability in brain tissue vulnerability to WBRT-associated changes has been suggested (Calvo et al., 1988; Nagai et al., 2000; Nakaya et al., 2005; Connor et al., 2017), with WM regarded as more susceptible than GM (Steen et al., 2001). Acute-phase WBRT-associated BBB disruption permits infiltration of water and immune cells into the brain parenchyma (BP), leading to increased extracellular water content. This mechanism influences AD and RD, which characterize the directionality of water diffusion. AD quantifies diffusion along fibers, with elevated values suggesting structural disruption, such as axonal injury, degeneration, or loss. Conversely, reduced AD is associated with axonal swelling, which restricts water diffusion along fiber tracts (Song et al., 2003) while increased RD reflects myelin disruption, including demyelination (Song et al., 2005). Together with FA and MD, these metrics when applied in a longitudinal study, may facilitate the development of sensitive biomarkers for assessing acute and early-delayed WBRT-

associated WM injury. Such biomarkers may help elucidate regional variations in vulnerability to WBRT-associated injury, offering further insights into underlying injury mechanisms (Welzel et al., 2008). Additionally, identifying biomarkers of acute and early-delayed WBRT-associated injury may support timely neuroprotective interventions while advancing personalized brain radiotherapy.

In deriving more quantitative data from standard-of-care medical images for objective quantitative assessment of tissue microstructural alterations in pathological states, devoid of qualitative biases, radiomics—a rapidly expanding field of quantitative imaging analysis—has emerged as an extension of machine learning-driven pattern recognition. It involves the high-throughput extraction of extensive statistical features from medical images and correlating them with the underlying pathophysiology, to facilitate objective, observer-independent imaging interpretation (Abbasian et al., 2022).

Chapter 2, therefore, explores the value of DTI-radiomics for noninvasive assessment of WBRT-associated microstructural alterations in WM within the acute and early-delayed phases, aimed at determining whether DTI-radiomics could enhance the characterization of regional variations in vulnerability to WBRT-associated injury.

Chapter 1

Exploring the Sensitivity of MRI Indices in Myelin Characterization Across Spinal Cord Regions

1. Introduction

Myelin is a protective insulating sheath that encases axons, facilitating rapid and efficient saltatory conduction of nerve impulses (Kister et al., 2022; Nave and Werner, 2014). Myelin is relevant, as its disruption—known as demyelination—is a defining feature of neurological disorders such as multiple sclerosis (Höftberger and Lassmann, 2018). Given its central role in nerve signal transmission, *in vivo* myelin quantification is essential for diagnosing and monitoring demyelinating diseases and other myelin-related conditions (Mancini et al., 2020).

Multiple MRI techniques have demonstrated sensitivity in noninvasively assessing myelin. Quantitative indices of such techniques have been shown to exhibit promising correlations with histological data, which is standard for myelin evaluation *in vivo* (van der Weijden et al., 2021; Laule et al., 2008; Sui et al., 2022; Yasuno et al., 2016).

The extent of myelination influences T1(longitudinal) and T2 (transverse) relaxation times, which are fundamental determinants of MRI signals. Higher myelination is associated with shorter T1 and T2 relaxation times (Hagiwara et al., 2018). The ratio of T1-weighted image (T1WI) and T2-weighted image (T2WI) can serve as a simplified metric for myelin content. It has been suggested that myelin content in a cortical area covaries with both T1WI and T2WI intensities, but in opposite directions. Thus, the T1WI and T2WI (T1WI/T2WI) ratio enhances the contrast related to myelin content (Glasser et al., 2011). Previous studies have used this ratio to evaluate myelination in neonatal brains, quantify tissue damage associated with multiple sclerosis, and explore potential links to amyloid-beta accumulation (Sui et al., 2022; Soun et al., 2017; Yasuno et al., 2016). Next, the myelin water fraction (MWF), derived from an advanced 3D gradient and spin echo sequence (3D-GRASE), quantifies water trapped

within myelin bilayers by analyzing T2 relaxation time (Prasloski et al., 2012; Whittall et al., 1997). The short T2 component, relative to the total T2 distribution, has been established as an *in vivo* myelin biomarker, strongly correlating with histological measures considered standard for evaluating myelin's structure and composition. Additionally, the magnetization transfer ratio (MTR), obtained from magnetization transfer imaging (MTI), quantifies magnetization transfer between myelin macromolecules and free water (Schmierer et al., 2004). MTI employs off-resonance radiofrequency (RF) pulses to selectively saturate macromolecules, with the saturated protons transferring magnetization to free water. MTR has been shown to correlate significantly with myelin histological measures (Hagiwara et al., 2018). T1 ρ , or spin-lattice relaxation in the rotating frame, is sensitive to proton exchange between bound water in myelin and free water. This measure, typically obtained through spin-locking sequences, has been reported to have potential in quantifying myelin content (Menon et al., 2018).

Other advanced MRI techniques, such as DTI, offer insights into WM integrity through indices like FA and MD, which assess water molecule motion within the extracellular spaces of myelin sheaths (Chang et al., 2017). To minimize artifacts from surrounding osseous structures of the spine and suppress outer volume effects, a reduced field-of-view (rFOV) DTI variant has been optimized for spinal cord imaging (Wilm et al., 2007). Confining the field of view (FOV) to the region of interest (ROI) enables higher spatial resolution and enhances the visualization of fine anatomical details (Wilm et al., 2007; Wargo et al., 2103). Another promising technique, electric properties tomography (EPT), utilizes electrical conductivity (σ) as a potential marker of tissue integrity. Although the direct relationship between σ and myelin integrity has not been fully established, it is hypothesized that myelin disruption may elevate ion mobility, resulting in increased σ in demyelinated regions (Tha et al., 2018).

Notwithstanding the demonstrated sensitivities of multiple quantitative MRI indices for noninvasive assessment of myelin content and integrity, their relative sensitivities have not been extensively compared. This chapter focused on identifying the

most sensitive MRI index for characterizing myelin composition in GM and WM columns using a deer model. The findings of this study are expected to have important ramifications for the accurate, noninvasive evaluation of myelin and related pathologies.

2. Materials and Methods

2.1. Specimen Processing for MRI

Within 4 hours post-euthanasia, the head and neck of a 2–3-year-old Ezo Sika Deer (*Cervus nippon yesoensis*) were acquired from the Rakuno Gakuen University's Veterinary Medicine Department. To minimize tissue degradation and maintain structural integrity, the specimen was processed within 4 hours post-euthanasia. First, the specimen was perfused through the carotid arteries by rinsing with 1 L of 0.9% saline, followed by fixation with 3 L of 4% paraformaldehyde in a 0.1 M phosphate buffer (PB), following the protocol used by Manger et al. (2009). The cervical spinal cord was then extracted and post-fixed for 48 hours at 4 °C in 4% paraformaldehyde in 0.1 M PB with sodium azide. The specimen was subsequently transferred into a 11.60 × 2.65 cm² container, oriented with the rostral end superior and the caudal end inferior. To stabilize the specimen against movements and prevent compression, gauze was used to secure the specimen centrally within the container. Anatomical landmarks were referenced to ensure accurate orientation, with the dorsal surface facing upwards and the ventral surface facing downwards (Figure 1).

The specimen was obtained from an animal culled for pest control under the Hokkaido Ezo Deer Management Plan (Phase 5) and utilized opportunistically, as the deer was not sacrificed explicitly for research (Hokkaido Ezo Deer Management Plan, 2024). No special permissions were required for its use in this study.

2.2. MRI Acquisitions

The container holding the spinal cord was positioned inside the MRI scanner and allowed to thaw to 22 °C, ensuring the specimen's orientation was aligned within the scanner. Straps and pads were used to secure the container during scanning to prevent movement. Two 3T scanners (Achieva TX, Philips Healthcare, Best, the Netherlands, and Magnetom Prisma, Siemens Healthineers, Erlangen, Germany), each equipped with a standard 32ch or 64ch head coil, were used for imaging.

The imaging sequences included an axial 3D gradient and spin echo (3D-GRASE), sagittal 3D gradient echo magnetization transfer imaging (3D-GRE MTI), sagittal magnetization-prepared rapid gradient echo (MPRAGE), axial T2-sampling perfection with application-optimized contrast (T2-SPACE), axial rFOV DTI, sagittal 3D steady-state free precession electric properties tomography (3D-SSFP EPT), sagittal magnetization prepared 2 rapid gradient echoes (MP2RAGE), sagittal Carr-Purcell-Meiboom-Gill (CPMG), and axial 3D ultrafast gradient echoes T1 ρ imaging (3D-GRE T1 ρ). The scan parameters associated with each sequence are given in Table 1.

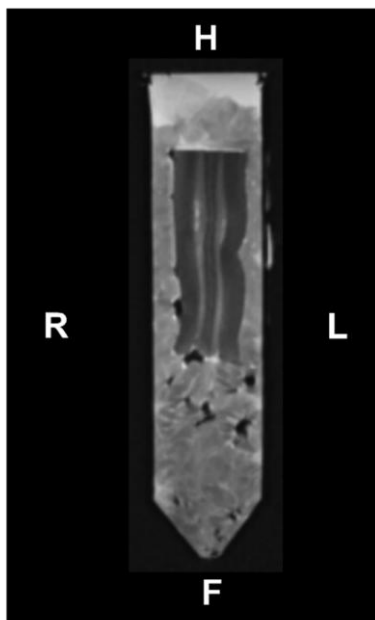


Figure 1. Set up of specimen for MRI.

Abbreviations: R, right; L, left; H, cranial; F, caudal

2.3. Generation of Index Maps

After MRI acquisitions, maps of nine quantitative MRI indices were reconstructed at the operator console or on a standalone workstation.

From 3D-GRASE image data, MWF maps were reconstructed voxel-wise based on the MRI signal model characterized by time-dependent multi-exponential decay. This model considers distinct WM water pools, i.e., myelin and axonal (intra- and extra-) (Faulkner et al., 2024). The measured signal at echo time (TE) is expressed as $S_{TE} = A_M e^{\frac{-TE}{T2_M}} + (A_I e^{\frac{-TE}{T2_I}} + A_E e^{\frac{-TE}{T2_E}})$, where A_M , A_I , and A_E represent signal amplitudes for myelin water, intra-axonal, and extra-axonal water, respectively, and $T2_M$, $T2_I$, and $T2_E$ are the associated transverse relaxation times. MWF maps were thus generated using the ratio of myelin water signal amplitude to the total water signal amplitude $MWF = \frac{A_M}{A_M + (A_I + A_E)}$. The reconstruction was performed using MatLab version R2014b at a standalone workstation.

MTR maps were calculated voxel-wise from 3D-GRE MTI data based on the theory of magnetization transfer between tissue macromolecular protons and free water protons, achieved by selective saturation of macromolecular protons with an off-resonance RF pulse. The saturation reduces the longitudinal magnetization of free water protons through continuous exchange with the saturated macromolecular pool, resulting in decreased signal intensity. MTR was then calculated using the equation $MTR = M_0 - M_{sat}/M_0$, where M_{sat} represents the signal intensity after RF pulse saturation, and M_0 is the baseline signal intensity without RF pulse saturation (Henkelman et al., 2001). The reconstruction was performed at the operator console.

T1WI and T2WI obtained from MPRAGE and T2-SPACE images, respectively, were used to reconstruct T1WI/T2WI maps. Mathematically, T1WI/T2WI was computed as a quotient using the formula $T1WI/T2WI = \text{signal intensity from T1WI} / \text{signal intensity from T2WI}$. (Hagiwara et al., 2018; Sui et al., 2022; Soun et al., 2017; Yasuno

et al., 2016). The reconstruction was implemented using Dr. ViewPro version 5.0 (AJS, Tokyo, Japan) on a dedicated workstation.

FA and MD maps were calculated from rFOV-DTI data based on similar principles as standard DTI. FA accounts for the degrees of water diffusion anisotropy within a voxel, calculated using the formula (Chang et al., 2017):

$$FA = \sqrt{\frac{3}{2} \frac{\sqrt{(\lambda_1 - MD)^2 + (\lambda_2 - MD)^2 + (\lambda_3 - MD)^2}}{\sqrt{\lambda_1^2 + \lambda_2^2 + \lambda_3^2}}}$$

The parameters λ_1 , λ_2 , and λ_3 are eigenvalues that represent the diffusivities of the diffusion tensor along the three orthogonal axes, with their mean reconstructed as mean diffusivity (MD), using the equation $MD = \frac{\lambda_1 + \lambda_2 + \lambda_3}{3}$. Reconstruction of both maps was performed at the main operator console of the MRI scanner.

From phase images acquired using a 3D-SSFP sequence, based on the truncated Helmholtz equation $\sigma = (\partial x^2 + \partial y^2 + \partial z^2)\varphi/2\mu_0\omega$, the σ maps were reconstructed. Here, φ denotes the transceive phase, μ_0 is the magnetic vacuum permeability, and ω is the Lamor frequency (128MHz for 3T). Applying partial derivatives along the x, y, and z coordinates facilitates volumetric imaging, enabling EPT on a 3D-SSFP (Tha et al., 2018; Katscher et al., 2013). σ maps were calculated voxel-wise using an in-house program on a standalone workstation.

T1 maps were reconstructed from MP2RAGE imaging data using a signal model describing the measured signal intensity at a given inversion time $T(I)$ $S_{TI} = S_0(1 - 2e^{\frac{-TI}{T_1}})$. S_0 describes the equilibrium magnetization signal, and T1 is the longitudinal relaxation time (Marques et al., 2010). Reconstruction was performed at the operator console.

From CPMG imaging data, T2 maps were generated using the MRI signal model described by a mono-exponential decay function of the transverse relaxation time, T2. At a given echo time TE , the signal intensity is given as $S_{TE} = S_0 e^{\frac{-TE}{T_2}}$, where S_0 describes

the equilibrium signal intensity, and T2, the transverse relaxation time. The kernel of the equation given by $e^{\frac{-TE}{T2}}$ describes the magnitude of signal decay after TE (Whittall and MacKay 1989). Reconstruction of T2 maps was performed at the operator console.

T1 ρ maps were reconstructed voxel-by-voxel from 3D-GRE T1 ρ imaging data by fitting the MRI signal across the entire FOV to a mono-exponential decay model, given by $S_{TSL} = S_0 e^{\frac{-TSL}{T1\rho}}$. Here, S_{TSL} represents the magnetization signal after T1 ρ spin-lock preparation for a given spin-lock duration (TSL), S_0 is the equilibrium magnetization signal, and $T1\rho$ is the $T1\rho$ relaxation time (Witschey et al., 2008). The reconstruction was performed using Jim8 software (Xinapse Systems Ltd., Essex, UK) on a standalone workstation.

Maps, including MTR, T1WI/T2WI, σ , T1, and T2, initially generated in sagittal sections, were resliced into 1 mm thick axial images to match other maps. This image processing step was conducted using Dr. ViewPro version 5.0. Subsequently, semiautomated image co-registration of all maps was performed with the default settings of SPM12 (Wellcome Trust Centre for Neuroimaging, University College of London, Oxford, UK), running on MatLab. The co-registered maps were reviewed for potential misregistration, and manual corrections were applied when necessary.

2.4. Mean Index Values: Measurements and Analysis

Myelin distributions across regions were evaluated by placing rectangular ROIs measuring 3.75 mm², 6 mm², 3 mm², and 2.25 mm² bilaterally in the anterior (AC), lateral (LC), posterior column (PC), and GM across eight consecutive slices (Figure 2). ROIs were drawn directly on the T1WI/T2WI maps and allowed to superimpose onto other co-registered maps. The dimensions of the ROIs were chosen to capture myelin distribution effectively and ensure robust measurements. Regions impacted by artifacts and partial volume effects were carefully excluded, and the mean values were subsequently extracted using Image J software (version 1.47, Wayne Rasband and contributors, National Institute of Health, Bethesda, MD, USA).

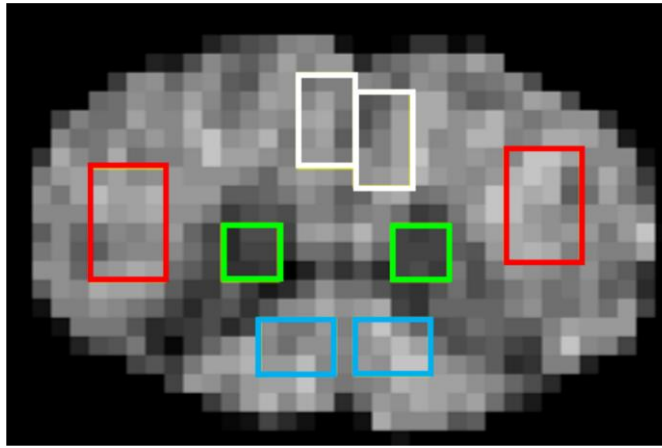


Figure 2. Set up of ROIs. ROIs for AC, LC, PC, and GM are shown in white, red, blue, and green, respectively. Abbreviations: ROI, regions of interest; AC, anterior column; LC, lateral column; PC, posterior column; GM, central gray matter

2.5. Specimen Preparation for Histological Analysis

Following MRI, the spinal cord tissue was quickly transferred into a solution of 30% sucrose in 0.1 M PB at 4 °C until it had equilibrated. Subsequently, it was transferred into an antifreeze solution comprising 30% glycerol, 30% ethylene glycol, 30% distilled water, and 10% 0.244 M PB. Again, it was allowed to equilibrate in the solution at 4 °C before being moved into storage at -20°C in a freezer.

A 3 cm segment was dissected from the spinal cord, allowed to equilibrate in 30% sucrose in a 0.1M PB, and then frozen in crushed dry ice. The tissue block was mounted onto a metal stage and sectioned into 50 µm thick transverse slices using a sliding microtome.

The 50 µm thick specimen was then re-fixed in 4% glutaraldehyde in 0.1 M PB for 48 hours at 4°C. Afterwards, it was equilibrated in 30% sucrose in 0.1 M PB. The specimen was transferred into an antifreeze solution containing 30% glycerol, 30% ethylene glycol, 30% distilled water, and 10% 0.244 M PB to equilibrate again at 4°C before moving into storage in a -20°C freezer.

Table 1. MRI sequences and corresponding scan parameters.

MRI Sequence	Section	TR/TE/flip angle (ms/ms/°)	Voxel size (mm ³)	Slice thickness (mm)	FOV (mm ²)	Number of slices	TA (m:s)	NEX	Other scan parameters
3D-GRASE	axial	500/10/90	1.25 × 1.25 × 1.25	1.25	160 × 160	96	35:40	1	32 multi-echoes, echo space = 32 ms
3D-GRE MTI	sagittal	26/2.65/12	0.5 × 0.5 × 0.5	0.5	96 × 128	120	29:57	3	MT pulse on and off
MPRAGE	sagittal	1900/2.42/9	0.5 × 0.5 × 0.5	0.5	96 × 128	120	24:18	4	TI = 900 ms
T2-SPACE	axial	4000/416/120	0.5 × 0.5 × 0.5	0.5	128 × 96	288	36:52	2	ETL = 174
rFOV DTI	axial	3000/53/90	0.47 × 0.47 × 5	5	70 × 52	40	21:09	14	b = 0, 1000 s mm ⁻² , Diffusion gradient directions = 6
3D-SSFP EPT	sagittal	3.6/1.79/25	1.02 × 1.02 × 1	1	179 × 179	199	10:16	3	Non-selective RF pulse
MP2RAGE	sagittal	5000/5.26/5	0.5 × 0.5 × 0.5	0.5	96 × 128	120	55:26	6	TI ₁ = 935 ms, TI ₂ = 2770 ms
CPMG	sagittal	3500/13.8/180	0.78 × 0.78 × 4	4	200 × 200	45	7:52	2	5 multi-echoes, echo space = 13.8 ms
3D-GRE T1ρ	axial	3.8/1.48/12	0.63 × 0.63 × 5	5	138 × 138	27	15:37	1	Spin lock time = 0, 20, 40, 80 ms

Abbreviations: GRASE, gradient and spin echo; GRE MTI, gradient echo magnetization transfer imaging; MPRAGE, magnetization prepared rapid gradient echo; T2-SPACE, T2-sampling perfection with application optimized contrast; rFOV-DTI, reduced field of view-diffusion tensor imaging; 3D-SSFP EPT, 3D state free precession electric properties tomography; MP2RAGE, magnetization prepared 2 rapid gradient echoes; CPMG, Carr-Purcell-Meiboom-Gill; FOV, field of view; TA, acquisition time; NEX, number of excitations; MT, magnetization transfer; TI, inversion time; ETL, echo train length; RF, radio frequency

2.6. Staining

The specimen was prepared for staining by first incubating in a 1% osmium tetroxide (OsO₄) solution in 0.1 M PB for 1–2 hours at room temperature. To remove OsO₄ residue, it was thoroughly rinsed with distilled water. The specimen was then processed for imaging by serial dehydration, resin embedding, and sectioning, based on a protocol outlined in Odle et al (Odle et al. 2024).

2.7. Histological Analysis

A light microscope (Olympus CX23, Olympus Corporation, Japan) with an attached camera was used to visualize and capture the GM and WM columns of the specimen. Subsequently, high-resolution transmission electron microscopy (TEM) images of WM columns were acquired with a Hitachi H-7650 TEM (Hitachi High-Tech Corporation, Tokyo, Japan). Two images were captured from each ROI, as used in the MRI analysis.

The myelin density measurement of each column was evaluated by converting the TEM images into a binary format, which isolates myelin from other tissue components. Myelin density is calculated as the ratio of myelinated fibers or myelin sheaths to the total volume of tissue. This measure provides a quantitative estimate of the overall myelin content in a given region (Huitema et al., 2021). This analysis was performed using Image J software.

2.8. Statistical Analysis

The sensitivities of the indices in differentiating GM and WM columns were assessed by analyzing their mean values across regions. Depending on the normality of data distribution, either repeated measures analysis of variance (ANOVA) with post hoc Bonferroni tests or Friedman with post hoc Wilcoxon tests were used. A corrected $p < 0.05$ was considered statistically significant for all comparisons.

Correlations among indices were analyzed using different techniques to assess potential associations between myelin characterization. The strength of these correlations was determined using Spearman's rank-order correlation analysis, which is appropriate for non-normally distributed or ordinal data. Statistical significance was set at a corrected value of $p < 0.05$. All statistical analyses were performed using Statistical Package for the Social Sciences (SPSS), version 26 (IBM, New York, NY, USA).

3. Results

3.1. Maps of Quantitative Indices

Figure 3 shows the co-registered maps of all nine quantitative MRI indices. These maps highlight the contrast between GM and WM columns, visualizing differences in tissue characteristics and myelin across the ROIs.

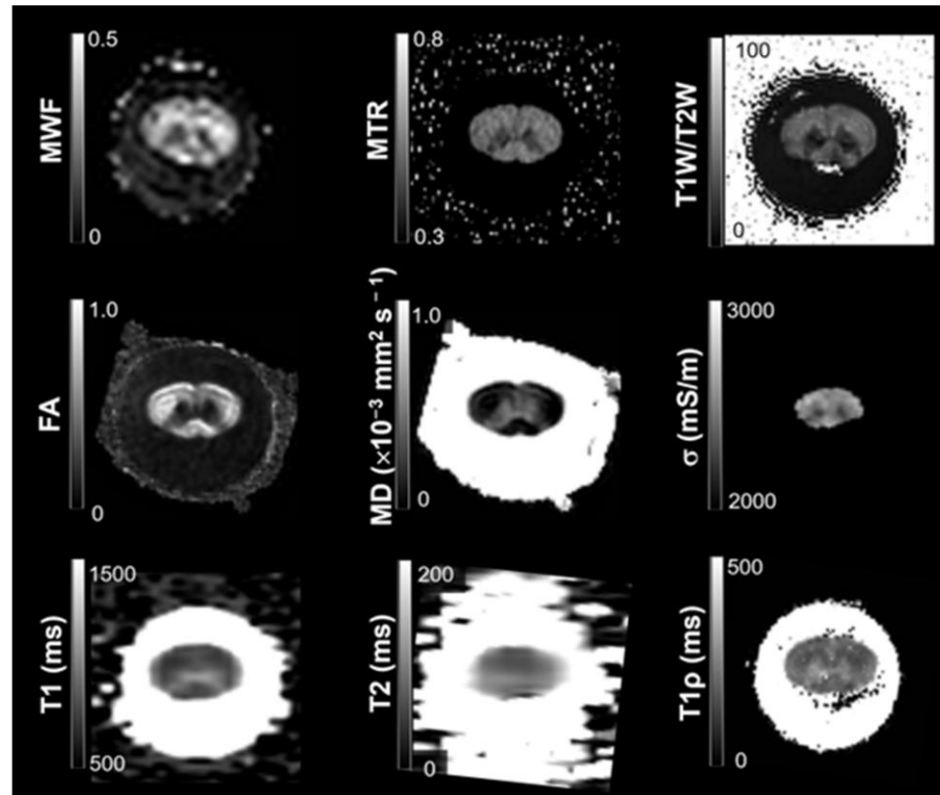


Figure 3. Representative co-registered maps of the quantitative MRI indices. The name of each index is given on the left side, along with look-up table.

3.2. Histological Data

Figure 4 presents a light microscope image of the GM and WM columns. The pale staining of the GM region distinctly distinguishes it from the surrounding WM columns. Within the WM columns, AC and LC appeared darker, while PC is notably lighter, reflecting variations in myelin density.

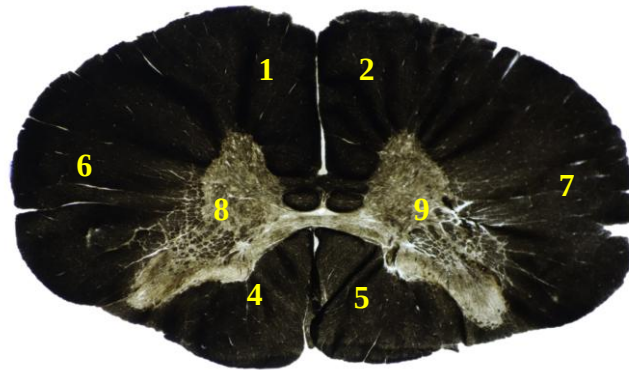


Figure 4. A light micrograph of the transverse section of cervical spinal cord of deer showing clear distinction of GM and WM columns. Labels: 1—2, AC; 3—4, PC; 5—6, LC; 8—9, GM. Abbreviations: GM, central gray matter; WM, white matter; AC, anterior column; LC, lateral column; PC, posterior column; GM, gray matter

Figure 5 shows TEM images obtained from the anterior, lateral, and posterior columns of the cervical WM locations.

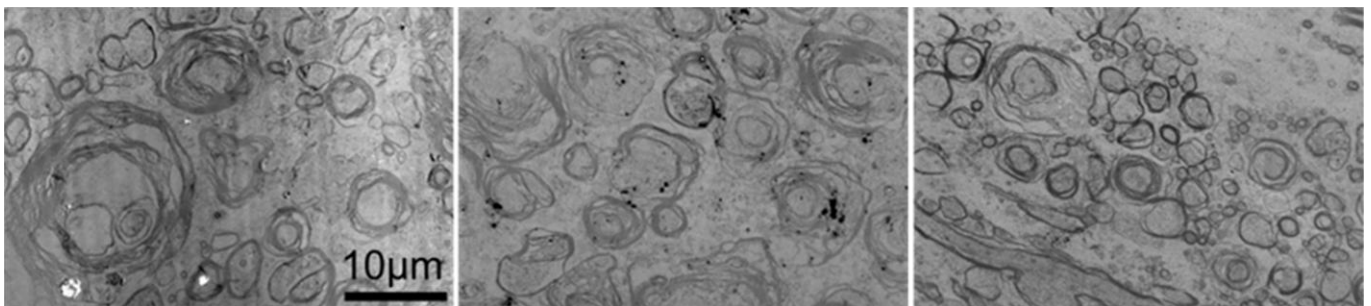


Figure 5. TEM of AC (**left**), LC (**middle**), and PC (**right**) of cervical spinal cord of deer. Abbreviation: TEM, Transmission electron micrograph, AC, anterior column; LC, lateral column; PC, posterior column

Figure 6 presents the binarized TEM image used to calculate the mean myelin densities and standard deviations for AC, LC, and PC, which were 0.35 ± 0.03 , 0.37 ± 0.07 , and 0.32 ± 0.00 , respectively.

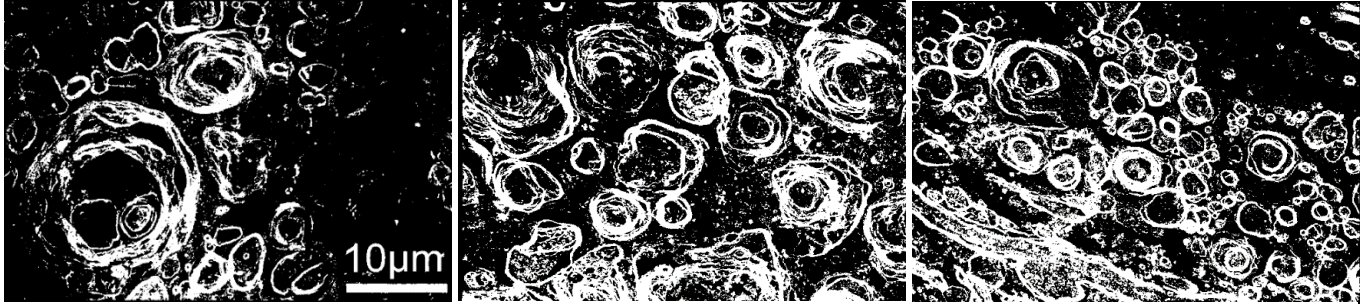


Figure 6. Binarized TEM of AC (**left**), LC (**middle**), and PC (**right**) of cervical spinal cord of deer. Abbreviation: TEM, Transmission electron micrograph, AC, anterior column; LC, lateral column; PC, posterior column

3.3. The Performances of Indices in Differentiating GM and WM columns

The performance of each MRI index in differentiating GM and WM columns, based on the measured mean quantitative values, is presented in Figure 6. All indices, except σ , distinguished GM from WM columns. GM recorded lower MWF, MTR, T1WI/T2WI, and FA, along with higher MD, T1, T2, and T1 ρ compared to the WM columns. The σ value of GM was similar to that of AC and LC. Within the WM columns, LC showed higher MWF, MTR, and FA than PC, as well as higher FA and T2, and lower MD than AC. AC, on the other hand, had higher MWF, σ , and MD and lower T1, T2, and T1 ρ than PC.

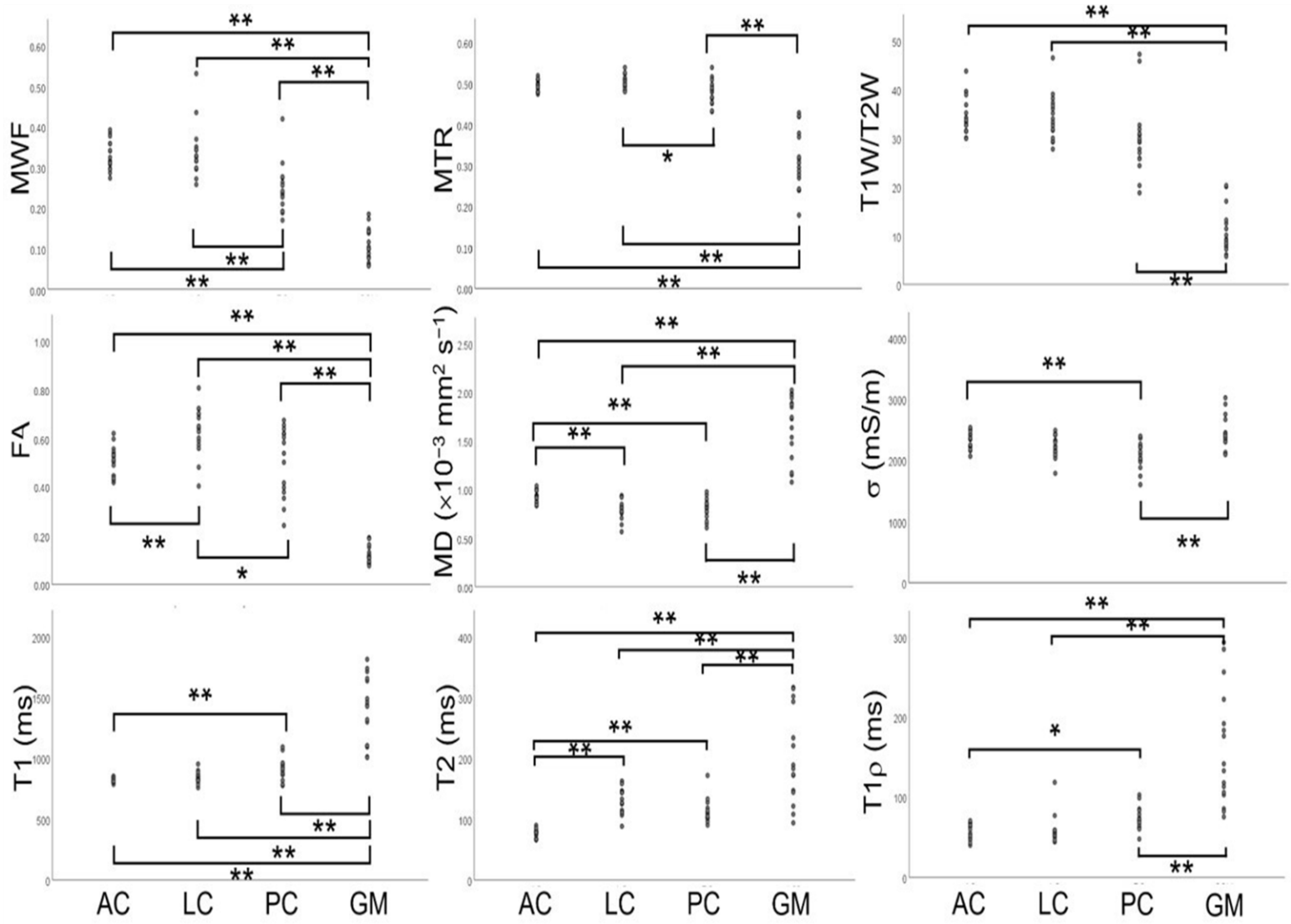


Figure 7. The quantitative values of MRI indices: MWF, MTR, T1W/T2W, FA, MD, σ , T1, T2, and T1 ρ of the GM and WM columns, i.e., the AC, LC, and PC. * and ** indicate corrected $p < 0.05$ and $p < 0.01$, respectively. Abbreviations: MWF, myelin water fraction; MTR, magnetization transfer ratio; T1W/T2W, ratio between T1-weighted and T2-weighted images; FA, fractional anisotropy; MD, mean diffusivity; σ , electrical conductivity; T1, longitudinal relaxation time; T2, transverse relaxation time, T1 ρ , spin-lattice relaxation in the rotating frame; GM, central gray matter, WM, white matter; AC, anterior column; LC, lateral column; PC, posterior column.

3.4. Correlation Among MRI Indices

Several pairs of significant moderate and strong correlations were found across regions, as summarized in Figure 8.

The relationships among MRI indices, particularly the correlation of each index with MWF, a validated myelin quantifier, within GM and WM columns, are shown in Figure 9 and Figure 10, respectively.

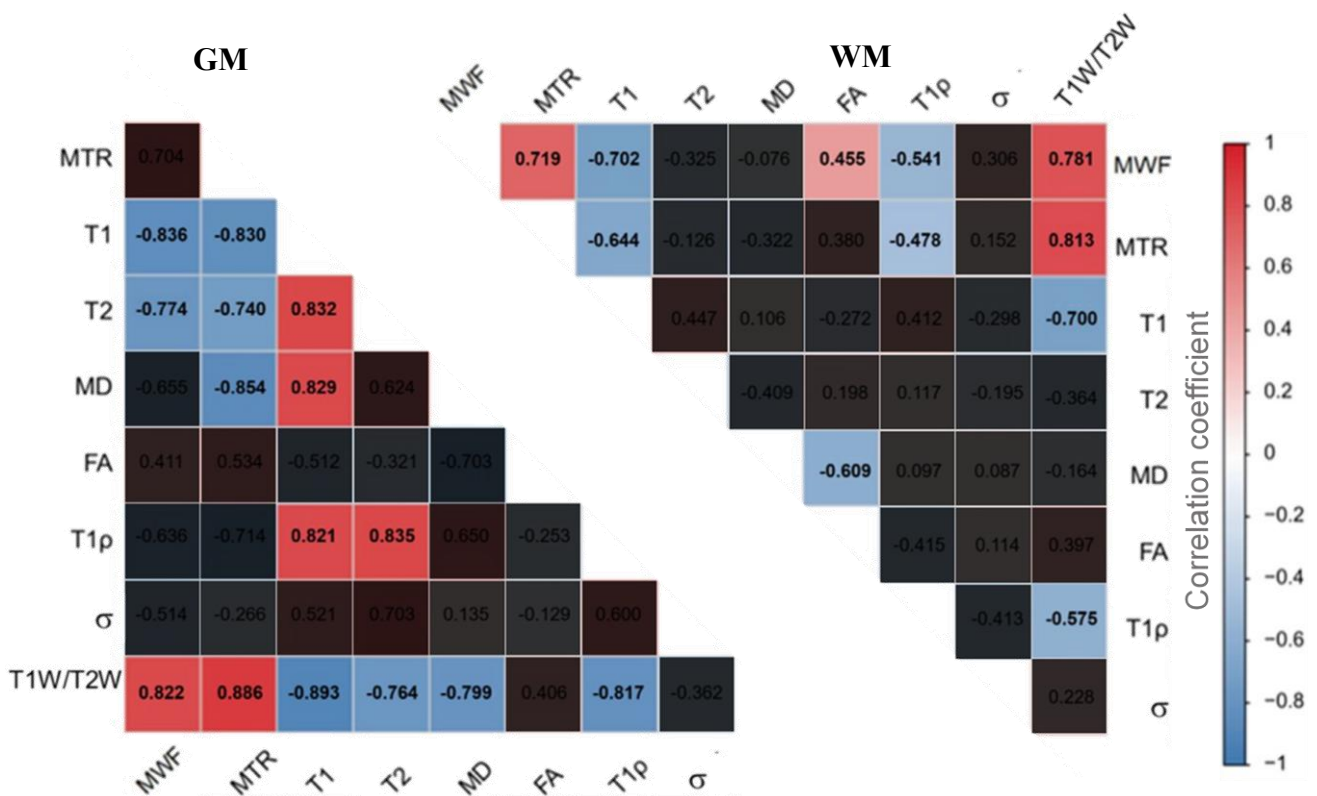


Figure 8. Correlation matrix showing correlation coefficients (ρ) among quantitative MRI indices with scale. The left triangle presents GM, and the right triangle presents WM. Colored values indicate statistical significance (corrected $p < 0.05$): Abbreviations: WM, white matter; GM, central gray matter.

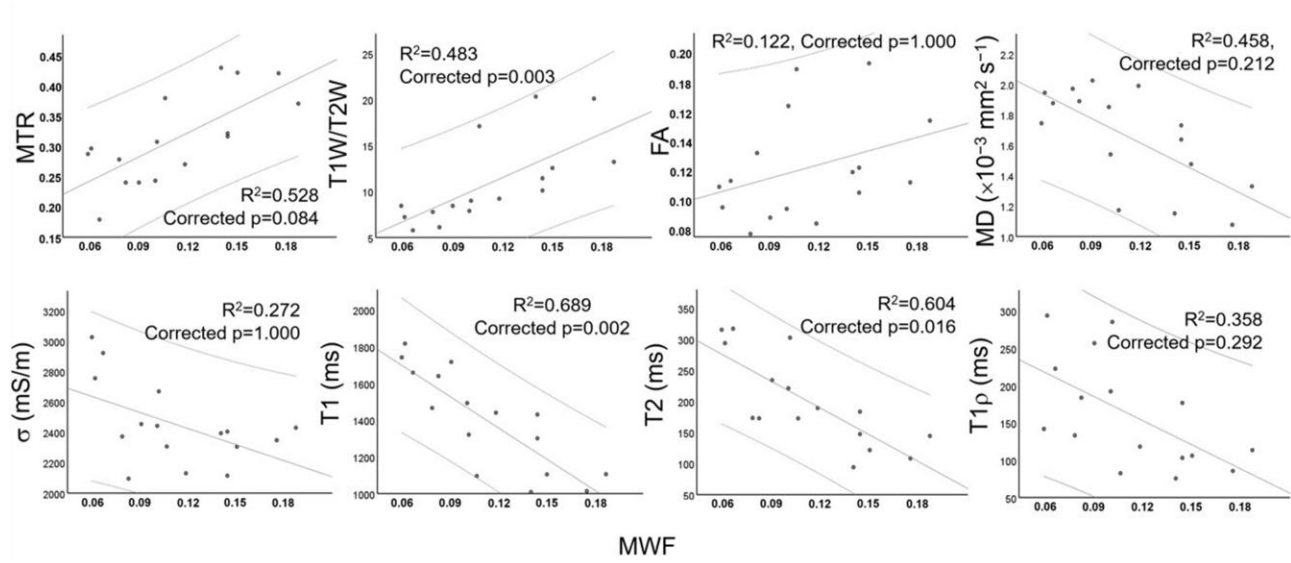


Figure 9. Scatterplots showing the relationships of quantitative MRI indices: the MTR T1W/T2W, FA, MD, σ , and T1, T2, and T1 ρ relaxation times of GM, with MWF. The mean and 95% confidence interval are given. Abbreviations: MTR, magnetization transfer ratio; T1W/T2W, ratio between T1-weighted and T2-weighted images; FA, fractional anisotropy; MD, mean diffusivity; σ , electrical conductivity, T1; longitudinal relaxation time; T2, transverse relaxation time; T1 ρ , spin-lattice relaxation in the rotating frame; GM, central gray matter; MWF, myelin water fraction.

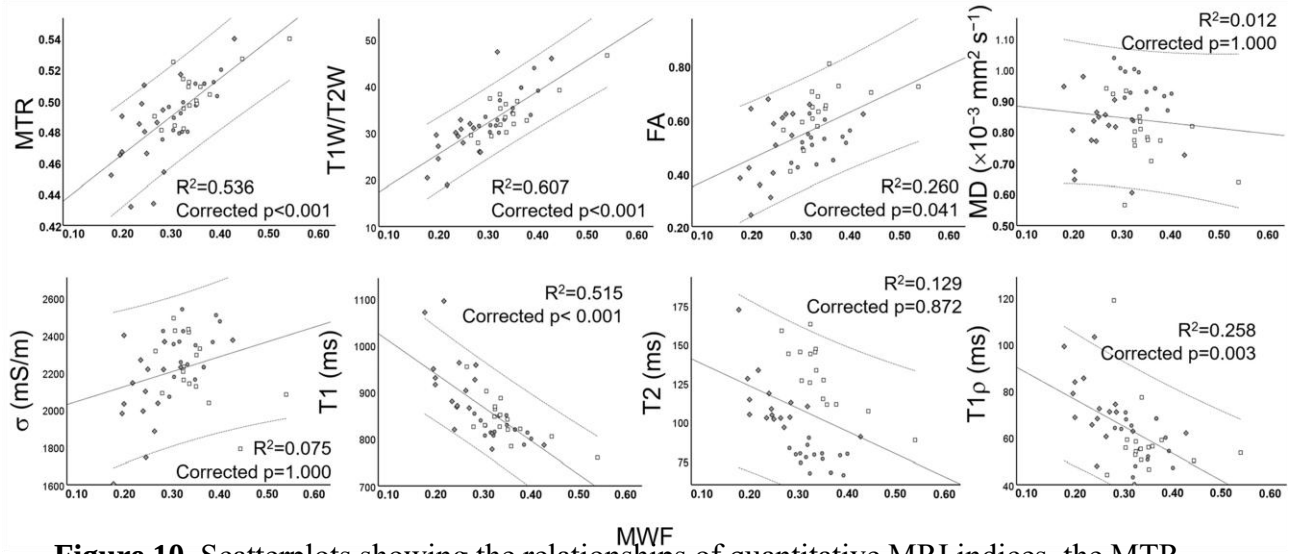


Figure 10. Scatterplots showing the relationships of quantitative MRI indices, the MTR, T1W/T2W, FA, MD, σ , and T1, T2, and T1 ρ relaxation times of WM columns, i.e., the AC, •, LC, □, PC, ♦, with MWF. The mean and 95% confidence interval are given. Abbreviations: MTR, magnetization transfer ratio; T1W/T2W, the ratio between T1-weighted and T2-weighted images; FA, fractional anisotropy; MD, mean diffusivity; σ , electrical conductivity, T1, longitudinal relaxation time; T2, transverse relaxation time; WM, white matter; AC, anterior column; LC, lateral column; PC, posterior column; MWF, myelin water fraction

4. Discussions

Nine quantitative MRI indices were evaluated for their sensitivity in characterizing myelin within the cervical spinal cord of a deer. This comprehensive comparison offers valuable insights into identifying the most effective indices for myelin characterization in the spinal cord. By assessing multiple quantitative indices, the study highlights indices that demonstrate the highest sensitivity to myelin content, providing optimal contrast and reliability. This approach not only enhances understanding of the strengths and limitations of various indices but could also inform the selection of optimal imaging parameters for future research and clinical applications focused on spinal cord myelination.

The choice of ex vivo deer cervical spinal cord tissue was based on factors such as its availability. Quadrupedal CNS tissue is commonly utilized in myelin-related research due to its structural and functional relevance (Werner et al., 1998; Sharif-Alhoseini et al., 2017; Salianni et al., 2017). While interspecies variations in myelin distribution are acknowledged, the primary aim of this study was to evaluate the sensitivity of MRI indices to myelin distribution, which was confirmed through histological analysis. Additionally, with the deer's GM and WM organization closely paralleling that of humans, the findings of this study may offer translational potential.

Ex vivo MRI scans, which allow for extended acquisition times, were essential for this comprehensive comparative study. These scans are free of physiological confounders such as pulsation and respiration, making them ideal for examining intrinsic tissue properties. However, postmortem tissue alterations and microstructural changes associated with cervical spinal cord resection may occur. For instance, the cessation of physiological activity may lead to reduced T1 and T2 relaxation times (Raman et al., 2017; Dawe et al., 2009). Similarly, MWF and MTR signals, which are influenced by metabolic activity and macromolecular interactions with free water protons, may decrease (Schmierer et al., 2004; Birkel et al., 2019). FA and MD values may be affected by slowed water diffusivities (Miller et al., 2011), while σ may decline due to disrupted ion gradients and reduced temperature. Nevertheless, these changes, being global rather

than focal, are unlikely to broadly impact the sensitivity of MRI indices in detecting regional differences in spinal cord signals.

Histological analysis revealed reduced myelin sheath compactness, likely due to paraformaldehyde fixation. While glutaraldehyde fixation might have better preserved myelin compactness, fixation is believed to have had minimal effect on the total myelin density and its contribution to MRI signals. This study did not emphasize the G-ratio, a widely used metric for assessing myelin thickness (Saliani et al., 2017), due to the observed reduction in myelin compactness.

The indices demonstrated varied sensitivity in differentiating spinal cord regions, as reflected by differences in their mean values. Notably, nearly all indices highlighted the contrast between GM and WM columns, demonstrating their responsiveness to variations in myelin content. Across species, GM is known to contain relatively fewer myelinated fibers than WM columns, which are dense with myelinated axons (Anderson et al., 2009; Chung et al., 1985). Distinct sensitivities of MWF, MTR, FA, MD, T1, T2, T1 ρ , and σ were observed across the WM columns, reflecting a heterogeneous myelin distribution within the deer spinal cord. The higher MWF and MTR in LC or AC, along with lower T1, T2, and T1 ρ in AC than PC, suggest higher myelin density in LC or AC. These observations align with myelin density measurements on TEM images. The higher myelin density in LC and AC may likely stem from motor WM tracts running in these columns, such as the pyramidal tract (Saliani et al., 2017). WM tracts, particularly those involved in motor control, tend to have high myelination to support the rapid conduction of motor signals. The observed FA patterns may similarly stem from the same underlying factors, although additional factors, such as fiber arrangement, may contribute (Chang et al., 2017). The lower MD in LC compared to AC could be attributed to the larger pyramidal tract area within the LC. Additionally, the higher MD in the AC relative to the PC might be explained by differences in axonal architecture between these two regions (Saliani et al., 2017). AC typically contains larger, more densely packed axons aligned for motor signal conduction, facilitating diffusion along the direction of these fibers. In contrast, PC primarily comprises sensory tracts with a different microstructural

arrangement, potentially with more hindrance to free diffusion. This organization may account for the higher MD in AC than PC despite a higher myelin density. This may also explain the higher σ in AC, as σ has been shown to have a positive correlation with MD (Gho et al., 2016). The lower T2 in AC compared to LC may indicate differences in iron and protein concentrations or glial cell populations. However, the exact underlying mechanisms remain unclear. The lack of differences in T1WI/T2WI among WM columns may imply that this index is not sufficiently sensitive to characterize variations in WM tissue composition (Sandrone et al., 2023).

The observed multiple correlations among the MRI indices are thought to suggest a shared sensitivity to myelin content, implying that these indices, despite differing in their underlying physical principles and contrast mechanisms, collectively capture aspects of myelin composition and its microstructural organization. Such correlations highlight the potential of integrating multiple indices to enhance the accuracy and reliability of myelin quantification across spinal cord regions. However, the lack of significant correlations between FA and σ in GM, as well as MD, T2, and σ in WM columns with other indices, may indicate that factors other than myelin density, such as fiber arrangement, iron or protein concentration, and glial cell population, play a role in generating WM contrast (Hagiwara et al., 2018; Whittall et al., 1997; Chang et al., 2017).

The study's findings suggest that combining MWF or MTR with a DTI index (FA or MD) or T2 can effectively differentiate GM from all WM columns. Although DTI alone may distinguish all four regions, its sensitivity to non-myelin-related factors warrants caution. The selection of MRI indices for assessing myelin may vary across institutions based on the availability of MRI sequences, post-processing tools, and acquisition time constraints.

With very few reports having directly compared the sensitivity of MRI indices for assessing myelin composition and validated the results with histological findings (Hagiwara et al., 2018), this study provides key contributions to the existing literature. The findings possess potential translational value for human spinal cord studies, where noninvasive MRI methods are essential for evaluating myelin integrity in neurological

conditions, such as multiple sclerosis and spinal cord injuries. Additionally, data on myelin distribution in the spinal cord of quadrupedal mammals, including deer, remain limited (Anderson et al., 2009). Evaluating these indices in a quadrupedal model like the deer offers insights into the evolutionary adaptations in myelin structure relevant to motor and sensory function in quadrupeds, which are also functionally represented in human spinal structures. The existing literature on myelin adaptations across species has demonstrated that four-legged animals have distinct spinal column myelination patterns suited to their locomotive needs, and comparative studies can inform human models by highlighting the conserved and divergent features of spinal cord myelin composition (Anderson et al., 2009; Saliani et al., 2017).

There are a few limitations to this study. First, while the primary focus of identifying the most sensitive MRI index for characterizing myelin composition in spinal cord regions was achieved, a direct correlation with myelin density was not established. Such a correlation would have strengthened the relationship between MRI indices and myelin composition in regions, enhancing the interpretation of the results. Second, ex vivo samples provided a stable medium for evaluating the sensitivity of MRI indices to myelin. However, the potential microstructural alterations in tissue necessitate the need for validation through in-vivo MRI scans. Third, the spatial resolution of some indices was too low to sufficiently capture smaller differences in myelinated regions, potentially introducing partial volume effects that could obscure distinctions between adjacent tissue types. Lastly, the use of a single deer spinal cord sample limits generalizability. As such, further studies with larger sample sizes and higher spatial resolution are needed to confirm the reproducibility and broader applicability of these results.

5. Conclusion

The sensitivity of MRI indices in evaluating myelin across spinal cord regions varied, reflecting these areas' unique structural and functional properties. The comparative analysis indicated that specific MRI indices, such as MWF, FA, MD, and

T2, are responsive to subtle myelin changes in specific regions. In contrast, others provide sensitivity in distinguishing GM from WM. Therefore, by combining two or more indices, the assessment of myelin becomes more comprehensive, facilitating more accurate differentiation between spinal cord regions. Thus, a multimodal approach may improve our understanding of region-specific myelin integrity, offering the potential for improved diagnostics and treatment monitoring for spinal cord pathologies.

Chapter 2.

Diffusion Tensor Imaging Radiomics for Assessing Acute and Early Delayed Brain Parenchyma Microstructural Alterations Associated with Whole Brain Radiotherapy

1. Introduction

Brain metastases arise from the hematogenous dissemination of malignant cells from a primary tumor to the brain and represent a common complication of advanced-stage lung cancer, breast cancer, and melanoma (Im and Muschel, 2000-2013). Among various treatment regimens, WBRT remains the most commonly used treatment for patients with multiple brain metastases and unresectable lesions (Khuntia et al., 2006). It involves the delivery of fractionated radiation doses to the entire brain, targeting disseminated tumors and micrometastatic disease. While effective in alleviating neurological symptoms, reducing recurrence after surgical resection or stereotactic radiosurgery, and serving as prophylactic therapy for cancers with high risk of intracranial spread (Dye et al., 2015), WBRT is associated with deleterious side effects including neurocognitive impairments (Li et al., 2024; Zhang et al., 2016). These impairments affect patients with an expected prognosis of 6 months or longer, reducing QOL, affecting daily activities, relationships, and overall well-being, thereby contributing to social burdens.

WBRT-associated neurocognitive impairments often implicate WM, recognized for its susceptibility to radiation damage and association with multiple cognitive domains (Steen et al., 2001; Bompaire et al., 2018; Welzel et al., 2008; Valk and Dillon, 1991). Although emerging evidence suggests that GM regions, including the hippocampus, thalamus, and basal ganglia, essential for cognitive functions such as memory, learning, awareness, and motor control (Haber and Calzavara, 2009), may also be affected by radiation (Watve et al., 2018), WM vulnerability to radiation remains a central focus of

studies investigating cognitive impairments following WBRT (Steen et al., 2001; Bompaire et al., 2018; Welzel et al., 2008; Valk and Dillon, 1991).

Evaluation of neurocognitive impairments following WBRT combines standardized neuropsychological assessments with MRI to detect acute and early delayed WM microstructural changes and injury (Schuitema et al., 2013). Acute phase injuries (1–6 weeks post-WBRT) are characterized by BBB disruption, oligodendrocyte stress, and glial dysfunction, contributing to myelin instability (Che et al., 2024). In the early-delayed phase (1–6 months), neuroinflammation and transient demyelination may manifest as somnolence, attention deficits, and short-term memory impairment (Green-Schloesser et al., 2012). However, subtle microstructural alterations associated with mild and moderate cognitive dysfunction remain undetected by conventional protocols (Dropcho, 1991). DTI, among advanced techniques such as DKI and NODDI, is clinically preferred due to its widespread availability and relatively shorter acquisition time.

In a study of childhood medulloblastoma and acute lymphoblastic leukemia survivors, Khong et al. (2006) reported a strong correlation between reduced WM FA and cognitive decline following WBRT. Similarly, a study investigating accelerated aging, decreased WM integrity, and neuropsychological dysfunction 25 years after pediatric lymphoid malignancies found that WBRT-treated survivors exhibited significantly reduced FA compared to controls, particularly in the orbitofrontal WM, genu, anterior body, and forceps minor of corpus callosum, cingulum (frontal and parietal), and inferior frontooccipital fasciculus, superior longitudinal fasciculus and uncinate fasciculi. This reduction was correlated with neuropsychological dysfunction assessed by visuomotor accuracy (Schuitema et al., 2013). Elevations in MD have previously been linked to axonal injury followed by demyelination (Kumar et al., 2009). Additionally, changes in the magnitude and directionality of water diffusivity—specifically along (AD) or across (RD) WM fibers—offer insights into axonal and myelin integrity (Song et al 2003, 2005).

Taken together, incorporating FA, MD, AD, and RD into a longitudinal study aimed at examining regional WM alterations within the acute and early delayed phases of WBRT-induced injury may enhance the characterization of region-specific susceptibility. Correlating these diffusion metrics with neuropsychological assessments could further elucidate the relationship between structural alterations and functional outcomes. Such insights may facilitate the development of imaging biomarkers of acute and early delayed WBRT-induced injury.

Towards extracting several quantitative features from DTI maps for assessing WM microstructural alterations associated with WBRT, radiomics analysis of DTI maps is proposed. First-order radiomic features characterize the distribution of voxel intensities within a ROI, while second-order features capture the spatial relationships between voxel pairs of similar or specific intensities. Higher-order features, such as those quantifying pixel runs with consistent intensity along a particular direction, enhance tissue characterization by capturing complex patterns (Abbasian et al.,2022). By identifying these complex spatial patterns, these features improve the detection of subtle tissue changes (Rizzo et al., 2018). Temporal changes in radiomic features may reveal WM alterations, providing insights into regional susceptibility. Thus, DTI-radiomics could be useful for delineating regional WM alterations associated with WBRT.

Integrating DTI radiomics of normal-appearing BP in the acute and early delayed phases with neuropsychological data could improve the assessment of WBRT effects on cognitive function by incorporating a broader range of quantitative features. Although BP may appear normal on conventional MRI, underlying microstructural changes may still exist. Given its sensitivity to tissue microstructural alterations, DTI may detect subtle WBRT-associated changes within these phases. This study proposes that DTI-radiomics can delineate region-specific WM vulnerability and facilitate the development of biomarkers for acute and early delayed WBRT-associated injury. Availability of which could potentially enable timely interventions to mitigate progressive neurocognitive impairments.

2. Materials and Methods

2.1. Participants

This prospective study was approved by the Institutional Review Board (IRB) of Hokkaido University Hospital, and written informed consent was obtained from all participants. Recruitment was conducted over 21 months, from March 2009 to December 2010. Eligible patients were aged 20–80 years, presented with brain metastases (primary tumors included lung [n=16] and breast [n=1]), had a Karnofsky Performance Status (KPS) score $\geq 70\%$ —reflecting the ability to perform daily activities with or without effort (Karnofsky et al., 1948), and an expected survival exceeding 6 months. Eligibility further required a prescribed dose of either 35 Gy in 14 fractions or 30 Gy in 15 fractions, delivered over a two-week course. Exclusion criteria included absolute contraindications for MRI, a history of prior WBRT, and unavailability of follow-up MRI or neuropsychological data up to 4 months, as neurocognitive function at 4 months post-WBRT has been identified as a relevant endpoint in a clinical trial involving brain metastases (Onodera et al., 2014). Of the 17 patients who consented, 2 were excluded due to the unavailability of MRI and neurocognitive data beyond 1.5 months, resulting in a final cohort comprised of 15 patients (11 women, 4 men) aged 53–73 years, with a mean age of 62.33 ± 6.29 years (mean $\pm$ standard deviation [SD]).

2.2. MRI Acquisitions

MRI was performed using a 1.5T scanner (Magnetom Symphony, Siemens Healthcare, Erlangen, Germany) with a standard head coil. MRI sequences included axial DTI and a routine clinical MRI protocol.

Axial DTI was acquired using a fast spin echo echo-planar sequence with the following parameters: repetition time (TR)/echo time (TE) = 5100/139 ms, voxel size = $0.9375 \times 0.9375 \times 5\text{mm}^3$, slice thickness = 5 mm, interslice gap = 1.5 mm, number of slices = 23, number of excitation (NEX) = 2, field of view (FOV) = 240×240 mm, b = 0 and 1000 smm^{-2} , and number of diffusion gradient directions = 12.

Routine clinical MRI protocol comprised of axial pre-contrast enhanced T1-weighted imaging (T1WI) with scan parameters: TR/TE = 700/15 ms, voxel size = $0.9375 \times 0.9375 \times 5 \text{ mm}^3$, slice thickness = 5 mm, interslice gap = 1.5 mm, number of slices = 19, NEX = 1, matrix size = 256×192 , FOV = $240 \times 180 \text{ mm}$; axial gadolinium contrast-enhanced T1-weighted imaging (Gd-T1WI) with scan parameters: TR/TE = 710/17 ms, voxel size = $0.9375 \times 0.9375 \times 5 \text{ mm}^3$, slice thickness = 5 mm, interslice gap = 1.5 mm, number of slices = 19, NEX = 1, matrix = 256×192 , FOV = $240 \times 180 \text{ mm}$; axial contrast-enhanced fluid-attenuated inversion recovery (FLAIR) imaging with scan parameters: TR/TE = 9000/114 ms, voxel size = $0.46875 \times 0.46875 \times 5 \text{ mm}^3$, slice thickness = 5 mm, interslice gap = 1.75 mm, number of slices = 19, inversion time (TI) = 2500 ms, NEX = 1, matrix = 512×384 , FOV = $240 \times 180 \text{ mm}$.

The MRI acquisition timelines included pre-WBRT imaging, which consisted of DTI and the routine protocol (T1WI, Gd-T1WI, and FLAIR) as baseline data. Follow-up imaging was performed immediately after WBRT and included DTI and T1WI. Subsequent follow-up scans were conducted at 1.5 months (DTI, T1WI, and Gd-T1WI) and 4 months (DTI and the routine clinical MRI protocol). A radiologist with 20 years of neuroimaging experience reviewed the DTI and routine MRI images to identify and exclude motion artifacts, as well as other abnormalities or coincidental findings that could impact the results.

2.3. Cognitive Assessment

Among the neurocognitive tests adopted from the repeatable battery for the assessment of neuropsychological status (RBANS) and the trail-making tests (TMT), Onodera et al. (2014) reported a significant decline in neurocognitive performance at 4 and 12 months following WBRT, as assessed by the list recognition subset of the RBANS. The authors suggested that this decline could be attributable to axonal demyelination, although further investigations may be required to confirm this mechanism. The findings further suggest that the list recognition subset may be sensitive

to the WBRT-associated structural damage to axons and, therefore, was adopted in the current study.

The list recognition test evaluates delayed memory performance. In this study, patients were initially presented with a list of 10 words visually and instructed to memorize them. After a short delay, they were presented with another list containing 20 words, including the original words and distractors (non-list items), and asked to identify the words from the original list. The test was administered at baseline (pre-WBRT) and at 4 months post-WBRT. Scores were determined based on the number of correctly identified words from the original list and the number of distractors mistakenly selected. To account for variability in cognitive performance, scores were standardized based on the patient's age and educational level.

2.4. Image Processing

2.4.1 Reconstruction of Diffusion Tensor Imaging Maps

DTI maps were reconstructed by estimating the diffusion tensor D through least square fitting of signal intensities to the Stejskal-Tanner equation (Basser, 1995); $S_k = S_0 e^{-b \hat{g}_k^T D \hat{g}_k}$, where S_0 represents the baseline signal intensity (acquired with no diffusion-sensitizing gradient, i.e., $b = 0$), S_k represents the signal intensity after applying the K^{th} diffusion-sensitizing gradient in a unit direction $\hat{g}_k$. The product $\hat{g}_k^T D \hat{g}_k$ represents diffusivity in the direction $\hat{g}_k$ (O'Donnell and Westin, 2011).

From the fitted tensor, three eigen values, namely λ_1 , λ_2 , λ_3 , which characterize diffusivities along the principal diffusion axes, were derived. Fractional anisotropy (FA) was reconstructed based on the formula (Chang et al., 2017):

$$FA = \sqrt{\frac{3}{2} \frac{\sqrt{(\lambda_1 - MD)^2 + (\lambda_2 - MD)^2 + (\lambda_3 - MD)^2}}{\sqrt{(\lambda_1^2 + \lambda_2^2 + \lambda_3^2)}}}$$

Mean diffusivity (MD) was calculated as $MD = \frac{\lambda_1 + \lambda_2 + \lambda_3}{3}$, and axial diffusivity (AD) as $AD = \lambda_1$. Radial diffusivity (RD) was calculated at a subsequent step described in section 2.4.3 based on the equation $RD = \frac{w\lambda_2 + w\lambda_3}{2}$, where w represents normalized maps of λ_2 and λ_3 .

FA, MD, and AD maps were reconstructed using Dr. View/LINUX R2.5 (Asahi Kasei Corporation, Japan). RD was calculated using statistical parametric mapping version 12 (SPM12) (Wellcome Trust Centre for Neuroimaging, University College of London, Oxford, UK) running on MatLab version 7.9.0 R2009b (The MathWorks, Natick, Massachusetts, USA). The reconstructed maps, FA, MD, λ_1 , λ_2 , and λ_3 are shown in Figure 1.

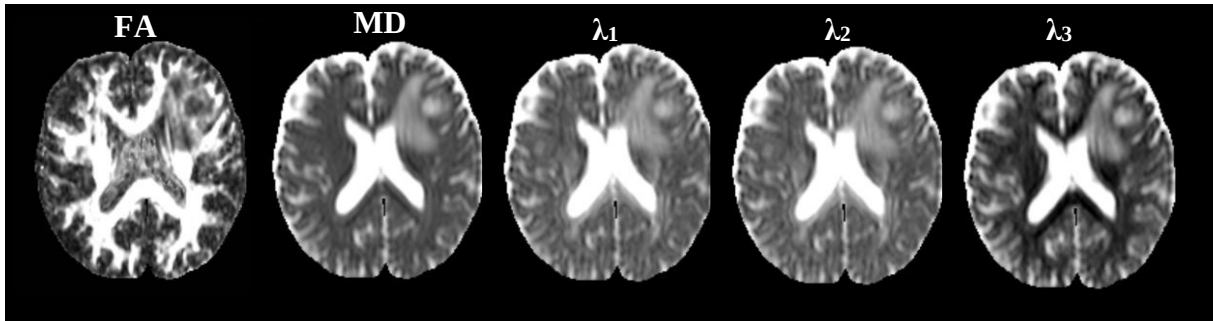


Figure 1. Representative maps of FA, MD, λ_1 , λ_2 , and λ_3 , reconstructed from DTI data. Abbreviations: FA, fractional anisotropy; MD, mean diffusivity; λ_1 , λ_2 , and λ_3 , diffusivities along three diffusion axes; DTI, diffusion tensor imaging.

2.4.2 Image Co-registration

Semiautomated image co-registration was performed to align the echo planar image with no diffusion weighting (b_0), λ_1 , λ_2 , and λ_3 , FA, and MD maps, as well as routine clinical MRI data (T1WI, Gd-T1WI, and FLAIR) at immediate, 1.5, and 4 months' follow-ups to the baseline dataset. Co-registration was conducted using SPM12 implemented in MatLab version 7.9.0 (R2009b). Registration accuracy was visually evaluated by superimposing co-registered images or identifying misaligned voxels by

subtracting their binary-transformed co-registered data. Misregistrations were observed in the DTI and routine clinical MRI datasets of three patients between the immediate and 4-month time points. These discrepancies were associated with large lesions, ranging in size between 11,126 (± 89.01) and 151 (± 1.21) voxels, which caused anatomical deformation of the brain.

2.4.3 Spatial Normalization

All images were spatially normalized using SPM12 to correct misregistration errors and maintain consistency across the dataset. For three patients' brains deformed by large lesions, a lesion mask developed through lesion segmentation outlined in Section 2.4.4 (Paragraph 2) was applied to mask the tumor.

Spatial normalization was performed using a 12-parameter affine transformation optimized for 'East Asian brain anatomy' to improve anatomical alignment with the Montreal Neurological Institute (MNI) East Asian brain template. This transformation step involved image translation, rotation (about the x, y, and z axes), scaling, and shearing to approximate the shape and orientation of the template. Subsequently, non-linear deformations were applied using forward deformation fields (from native to template space) to refine voxel-level alignment—a process known as image warping. For resampling, fourth-degree B-spline interpolation was employed to minimize partial volume effects and preserve tissue boundary integrity. All other normalization parameters were maintained at default settings.

Image spatial normalization using a lesion mask improved alignment and accuracy, ensured consistent transformation of images into a standard reference coordinate system (Schormann and Zilles 1998). The output consisted of spatially normalized b_0 , λ_1 , λ_2 , λ_3 , FA, MD, T1WI, Gd-T1WI, and FLAIR, all normalized within the same MNI space, with coordinates: $X = 40$, $Y = 57$, $Z = 36$. The normalized images were named as wb_0 , $w\lambda_1$, $w\lambda_2$, $w\lambda_3$, wFA , wMD , $wT1WI$, $wGd-T1WI$, and $wFLAIR$ (Figure 2).

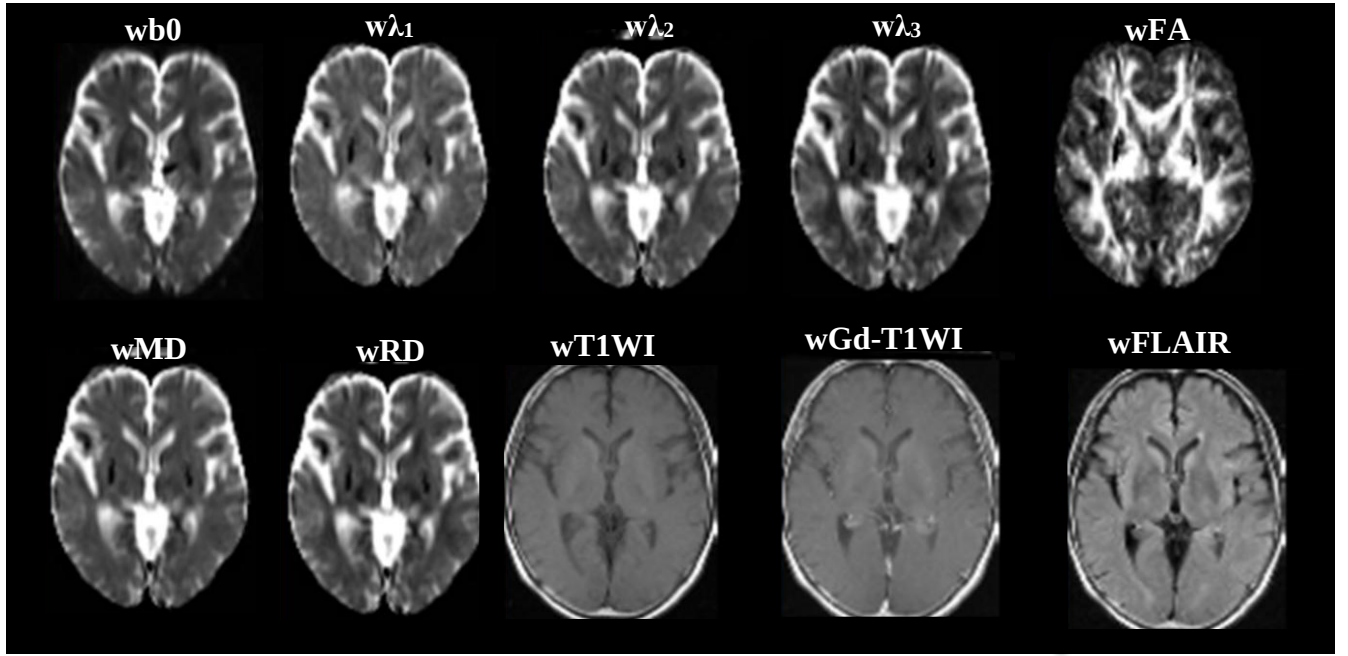


Figure 2. Spatially normalized DTI and anatomical dataset including wb_0 , $w\lambda_1$, $w\lambda_2$, $w\lambda_3$, wFA , wMD , wRD , $wT1WI$, $wGd-T1WI$, and $wFLAIR$ into MNI space across timepoints Abbreviation: FA, fractional anisotropy; MD, mean diffusivity; T1WI, T1-weighted image; Gd-T1WI, Gadolinium contrast-enhanced T1-weighted image.

2.4.4 Segmentation of Normal-Appearing Brain Parenchyma

Normal-appearing BP and lesion volumes were segmented from $wFLAIR$ or from wb_0 images when $wFLAIR$ was unavailable ($wFLAIR$ [n=53] and wb_0 [n=7]) using intensity thresholding in MRICron [version 1.0.20190902] (Rorden et al., 2007). To determine appropriate thresholds, MRI signal intensities were measured across 14 normal-appearing brain regions, including the GM of the bilateral frontal, parietal, temporal, and occipital lobes, as well as the pons, lentiform nucleus, and GM of the cerebellar hemispheres. These GM regions consistently exhibited higher signal intensity across time points, providing more reliable thresholding by minimizing signal intensity variations associated with WM, such as differences in myelin, susceptibility to WBRT-

induced changes, and partial volume effects. The mean and SD of these measurements were calculated at each time point.

Normal-appearing BP was delineated using the threshold defined by the formula: $\text{normal BP}_{\text{signal}} \leq \text{Mean} + (0.5 \times \text{SD})$, where $\text{BP}_{\text{signal}}$ represents the calculated MRI signal intensity for normal BP (Figure 3). These regions appear structurally intact on conventional MRI but may exhibit microstructural or functional abnormalities detectable with advanced MRI techniques such as DTI. Lesion segmentation was based on the formula: $\text{Lesion}_{\text{signal}} > \text{Mean} + (3 \times \text{SD})$, where $\text{Lesion}_{\text{signal}}$ represents the calculated MRI signal intensity that defines the lesion excluding normal-appearing BP.

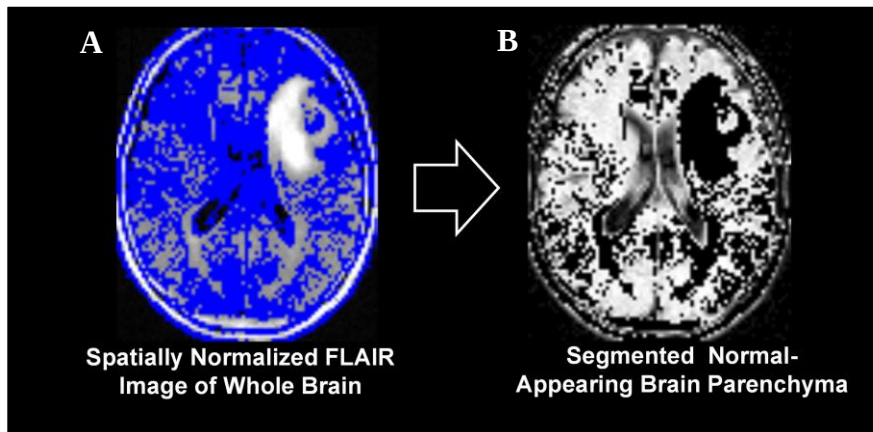


Figure 3. Segmentation of normal-appearing brain parenchyma from wFLAIR image using intensity thresholding. A, spatially normalized FLAIR (wFLAIR) image illustrating the applied intensity threshold (covered by blue voxels); B, segmented normal-appearing brain parenchyma, excluding lesion.

2.4.5 White Matter Template Spatial Normalization

WM atlases provides a standardized anatomical reference map that supports the analysis of brain structure and function. The WM atlas developed by the International Consortium of Brain Mapping 81 (ICBM DTI-81) is a stereotaxic probabilistic atlas that integrates DTI-based WM information with the anatomical template (ICBM 152) derived

from probabilistic tensor maps of 81 healthy, right-handed individuals aged 18–59 years (UCLA Brain Mapping Center).

For each time point, the WM template was spatially normalized to the previous wb0 using SPM12. Normalization parameters included an affine regularization set to the East Asian brain and an interpolation set to nearest neighbor. Spatial normalization accuracy was assessed visually by superimposing images and identifying misaligned voxels through subtraction of binary-transformed data. The step corrected misalignments that occurred after image co-registration.

2.4.6 Segmentation of Normalized White Matter Template

The normalized WM templates across time points were segmented into 50 component tracts using MRICron. Each tract, corresponding to a distinct anatomical region, is assigned a unique reference number. Tract-specific segmentation was performed by adjusting the MRICron's auto-contrast function; for each tract, the maximum contrast value was set to 50, and both minimum and maximum intensity thresholds were fixed at 1. This configuration selectively highlighted the tract associated with the specified reference number (Figure 4). The resulting highlighted region was then preserved as an ROI. This procedure was repeated for all 50 WM tracts by incrementally updating the tract reference number for each segmentation.

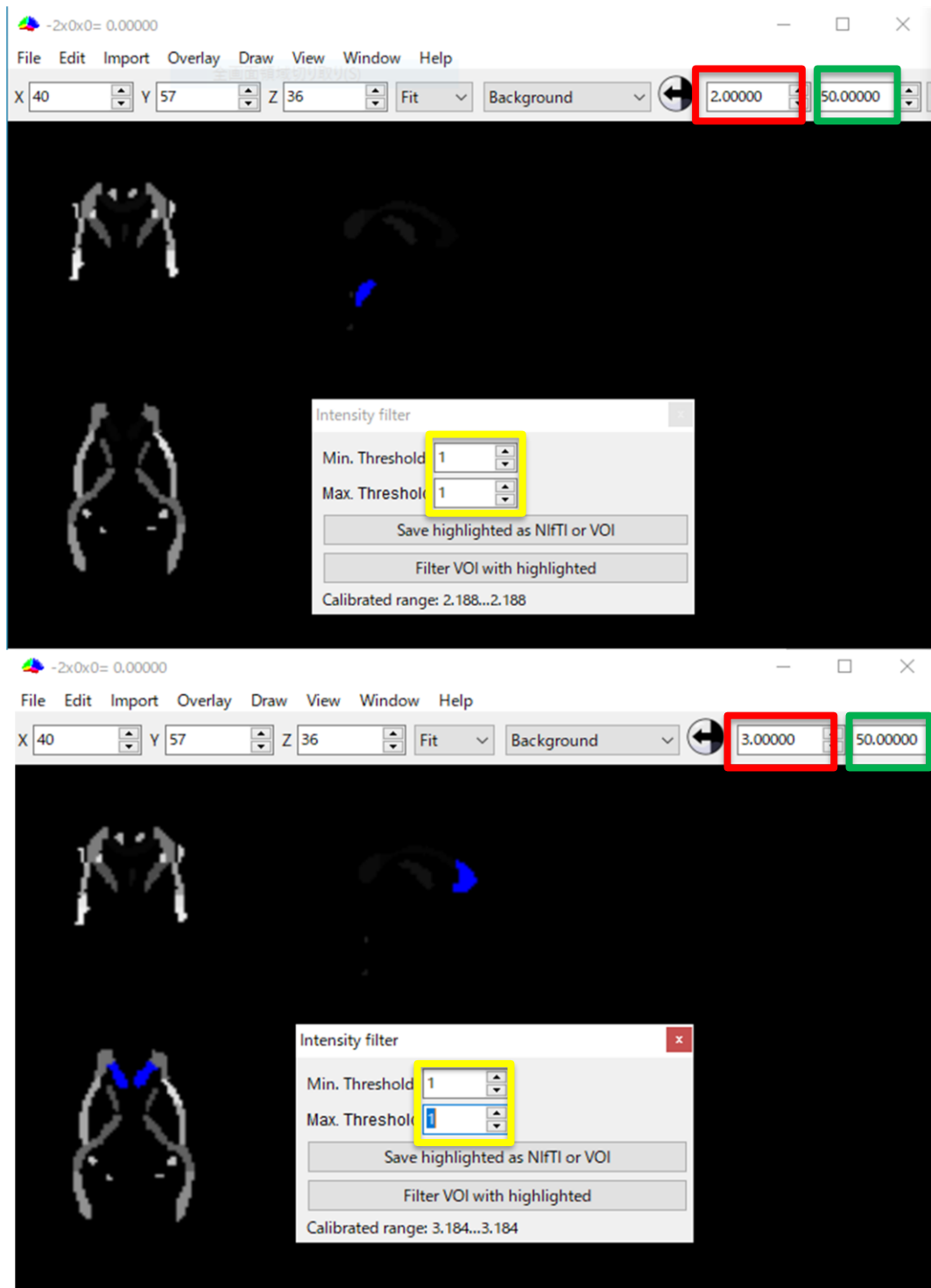


Figure 4. Intensity-based segmentation of spatially normalized WM template using MRICron. The maximum contrast value was set to 50 (green box), the tract reference number is shown in red boxes (2 in top figure showing pontine crossing tract, and 3 in the figure below, showing genu of the corpus callosum), and both minimum and maximum threshold values were set to 1 (yellow box)

2.4.7 Application of White Matter Segments on Normal-Appearing Brain Parenchyma and DTI Maps

To create WM ROIs, the segmented tracts were first sequentially applied on the normal-appearing BP image using MRIcron. The resulting ROIs were preserved and saved for each tract at every time point.

Next, to capture temporal WM microstructural changes and enable subsequent analyses of WBRT-induced alterations as captured by each index at each time point, the same ROIs were applied on the wFA, wMD, wAD, and wRD maps by repeating the above process (Figure 5). The resultant segments were then saved as WM-specific ROIs for each index and time point.

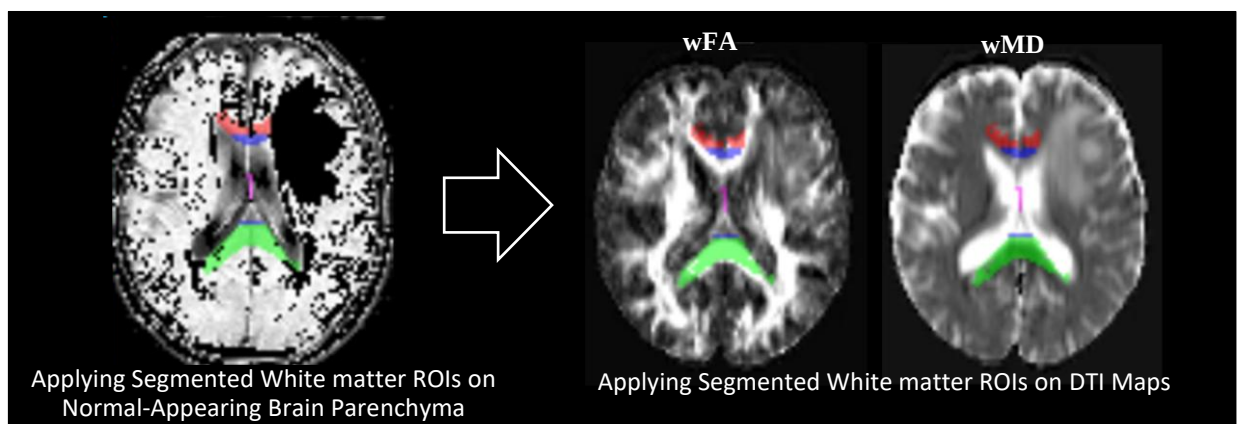


Figure 4. Development of WM ROIs. WM segments were first applied on normal-appearing brain parenchyma. The resultant ROIs were then applied on the normalized DTI maps. Abbreviations: WM, white matter; ROIs, regions of interest; DTI, Diffusion tensor imaging; wFA, normalized fractional anisotropy; wMD, normalized mean diffusivity.

2.4.8 Voxel Erosion

Voxel erosion was performed to mitigate the potential tumor influence of tumor on ROIs using ImageJ (version 1.47, Wayne Rasband and contributors, National Institute of Health, Bethesda, MD, USA). The ROIs were first converted to 8-bit grayscale format,

followed by binary thresholding using the percentile method. A 1-voxel erosion was applied to the perimeter of each ROI. ROIs that were completely eroded after this step were excluded from further analysis.

2.4.9 Extraction of Cerebrospinal Fluid from White Matter ROIs

Following voxel erosion, cerebrospinal fluid (CSF) voxels were removed from the ROIs using MRIcron to ensure that only normal-appearing BP voxels were retained. Similarly, ROIs in which CSF extraction resulted in the complete erosion of voxels were excluded from further analysis.

2.4.10 Selection of WM ROIs

Following CSF extraction, variations in the minimum voxel count across ROIs at time points were observed. To maintain consistency in subsequent analysis, inclusion criteria based on defined rules were established. These were: each ROI was required to contain at least three voxels, with ROI availability for at least two timepoints, including baseline. ROIs satisfying these criteria were selected for onward analysis.

Fifteen ROIs were consequently selected including: right anterior corona radiata (ACR-R), left anterior corona radiata (ACR-L), left anterior limb of internal capsule (ALIC-L), right posterior limb of internal capsule (PLIC-R), left posterior limb of internal capsule (PLIC-L), middle cerebellar peduncle (MCP), genu of corpus callosum (GCC), body of corpus callosum (BCC), splenium of corpus callosum (SCC), right superior longitudinal fasciculus (SLF-R), left superior longitudinal fasciculus (SLF-L), right superior corona radiata (SCR-R), left superior corona radiata (SCR-L), right retrolenticular part of internal capsule (RLIC-R), left retrolenticular part of internal capsule (RLIC-L) were selected. These ROI are identified by red voxels in Figure 5.

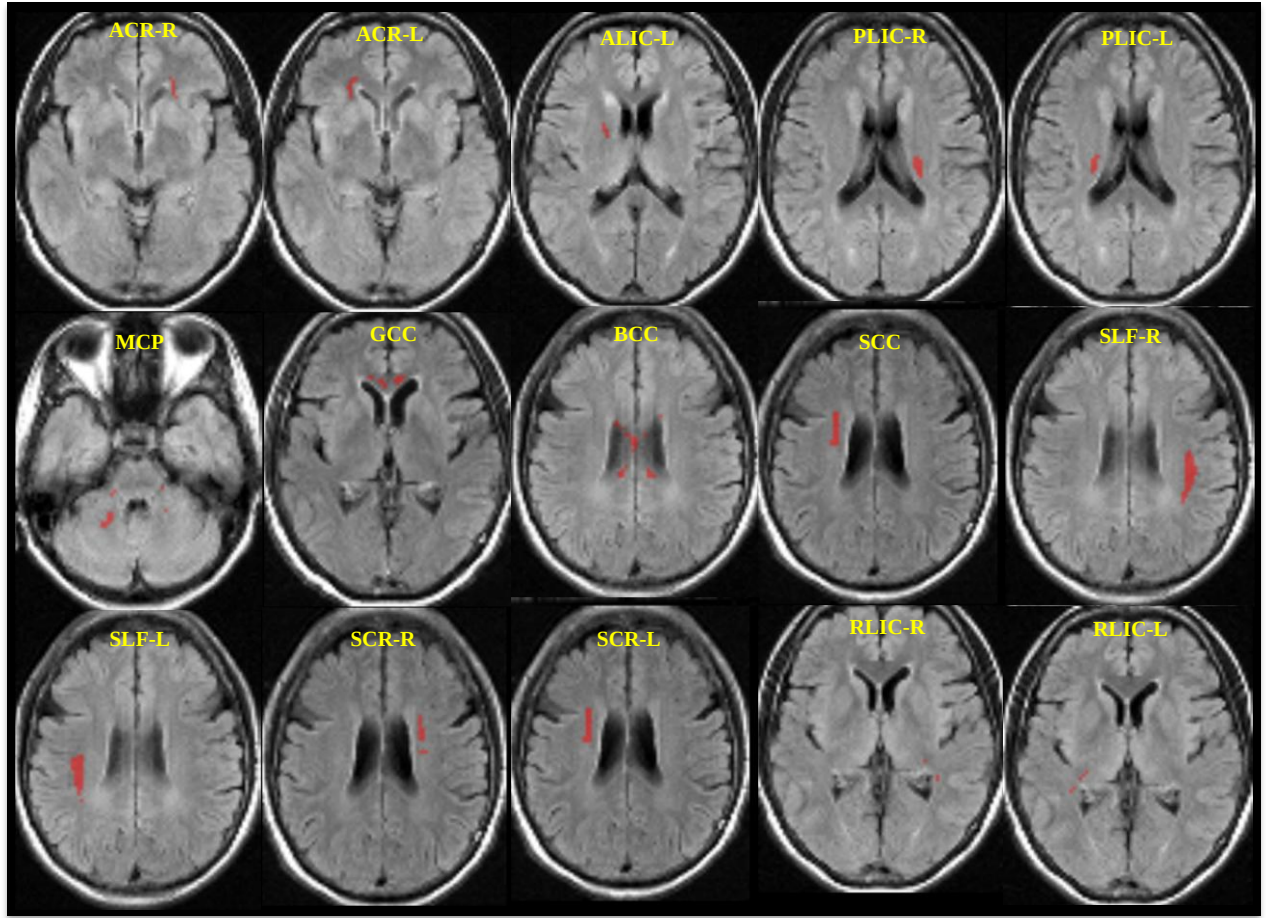


Figure 5: WM ROIs overlaid on normalized FLAIR image. Abbreviations: WM, white matter; ROIs, regions of interest; ACR-R, right anterior corona radiata; ACR-L, left anterior corona radiata; ALIC-L, left limb of anterior internal capsule; PLIC-R, right posterior limb of internal capsule; PLIC-L, left posterior limb of internal capsule; MCP, middle cerebellar peduncle; GCC, genu of corpus callosum; BCC, body of corpus callosum; SCC, splenium of corpus callosum; SLF-R, right superior longitudinal fasciculus; SLF-L, left superior longitudinal fasciculus; SCR-R, right superior corona radiata; SCR-L, left superior corona radiata; RLIC-R, right retrolenticular part of internal capsule; RLIC-L, left retrolenticular part of internal capsule.

2.5 Radiomic Analysis

2.5.1. Radiomic Feature Extraction

A customized radiomic feature extraction workflow was implemented in Python (version 3.9.18) within the Spyder IDE environment to extract quantitative features from ROIs, including histogram and GLCM features. The selection of histogram and GLCM features was guided by previous studies highlighting their utility in differentiating schizophrenia patients from healthy controls, as well as repeatability and reproducibility of measurements (Bang et al., 2021; Traverso et al., 2018).

Histogram features represent the simplest information contained in an image, which characterizes the distribution and frequency of voxels with specific intensity (Castellano et al., 2004). Commonly used histogram features in the literature include mean, standard deviation, variance, percentiles, kurtosis, skewness, energy, and entropy (Abbasian et al., 2022). Standard deviation quantifies the amount of variation or dispersion from the mean intensity value. 10th and 90th percentiles describe the intensity below which 10% and 90% of voxel intensities fall, respectively. The 90th percentile reflects the upper intensity distribution, with higher values suggesting brighter voxels potentially linked to increased tissue signal (Zwanenburg et al., 2020). Others include kurtosis—a measure that quantifies the ‘peakedness’ of the intensity distribution within an ROI, skewness, which quantifies the asymmetry of the intensity value distribution relative to the mean value. Energy and entropy describe the measure of the magnitude of voxel values and uncertainty/randomness in the image values, respectively (Zwanenburg et al., 2016).

Texture features capture spatial relationships between pixel pairs with similar intensity (Abbasian et al., 2022). For instance, the GLCM joint average (GLCM Jav) calculates the average intensity of pixel pairs in a given spatial relationship, providing insights into the uniformity or heterogeneity of intensities in an ROI. The GLCM cluster shade (GLCM cS) measures the skewness and uniformity of the GLCM, with higher cluster shade implying greater asymmetry about the mean. The GLCM cluster tendency (GLCM cT) quantifies the groupings of voxels with similar gray-level values. The GLCM

difference average (GLCM Diff.v) measures the relationship between occurrences of pairs with similar intensity values and occurrences of pairs with differing intensity values. The correlation between the intensity distributions of neighboring pixel pairs in an image, reflecting the complexity of the texture, is described by the GLCM informational measure of correlation 1 (GLCM ImC1), with higher values indicative of stronger linear relationships between pixel intensities (Zwanenburg et al., 2016).

From each ROI, 18 histogram and 24 texture features were extracted across four DTI indices and time points, resulting in a total of 10,080 features.

2.5.2. Radiomics Feature Reduction

Feature reduction was performed to remove redundant features using intercorrelation analysis based on Pearson's correlation coefficient (r), with a threshold of $r > 0.7$, implemented via the caret package in R software (Kuhn, 2008). This threshold was selected to identify and eliminate highly correlated features, thereby mitigating multicollinearity while preserving informative variability among features. The approach reduced the initial set of 10,080 features to 462 relatively independent features.

2.5.3. Statistical Analysis

To evaluate WBRT-induced WM microstructural alterations across regions, temporal changes in DTI-radiomic features were analyzed using one-sample t -tests. Uncorrected $p < 0.05$ was considered statistically significant.

Pearson's correlation was used to examine the potential predictive relationship between DTI-radiomic features and delayed memory performance by correlating DTI-radiomic features across time points with delayed memory scores at baseline and 4 months. Uncorrected $p < 0.01$ was chosen to minimize the influence of Type II error, considering the exploratory nature of the study.

3. Results

3.1. WBRT-Associated White Matter Changes

Figures 6—11 present regional changes in DTI-radiomic features. The 10th percentile of AD in the left anterior limb of the internal capsule (ALIC-L) increased significantly immediately after WBRT (Figure 6). In contrast the 90th percentile of AD decreased significantly at the same time point (Figure 7).

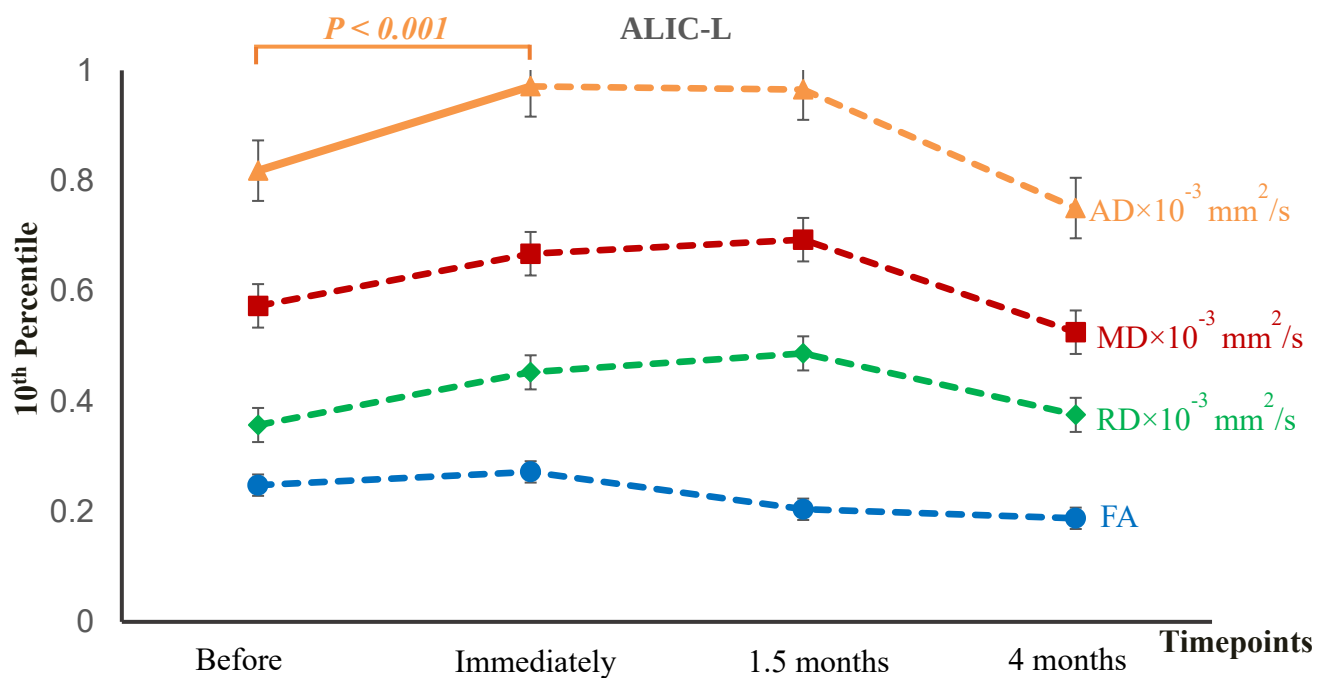


Figure 6. Significant increase in the 10th percentile of AD in the left anterior limb of internal capsule immediately after WBRT. Abbreviation: AD, axial diffusivity; MD, mean diffusivity; FA, fractional anisotropy; RD, radial diffusivity.

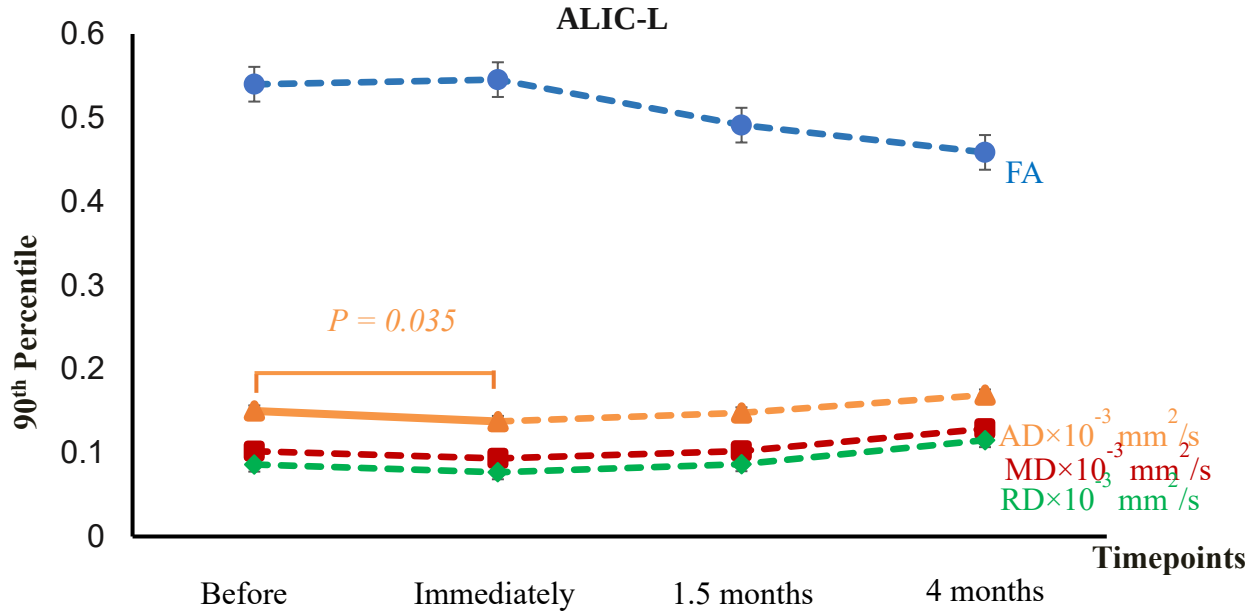


Figure 7. Significant decrease in the 90th percentile of AD in the left anterior limb of internal capsule immediately after radiotherapy. Abbreviation: AD, axial diffusivity; MD, mean diffusivity; FA, fractional anisotropy; RD, radial diffusivity.

Within the left posterior limb of internal capsule (PLIC-L), kurtosis of AD declined, while GLCM difference variance of FA increased significantly at 1.5 months post-WBRT (Figure 8 and Figure 9), respectively.

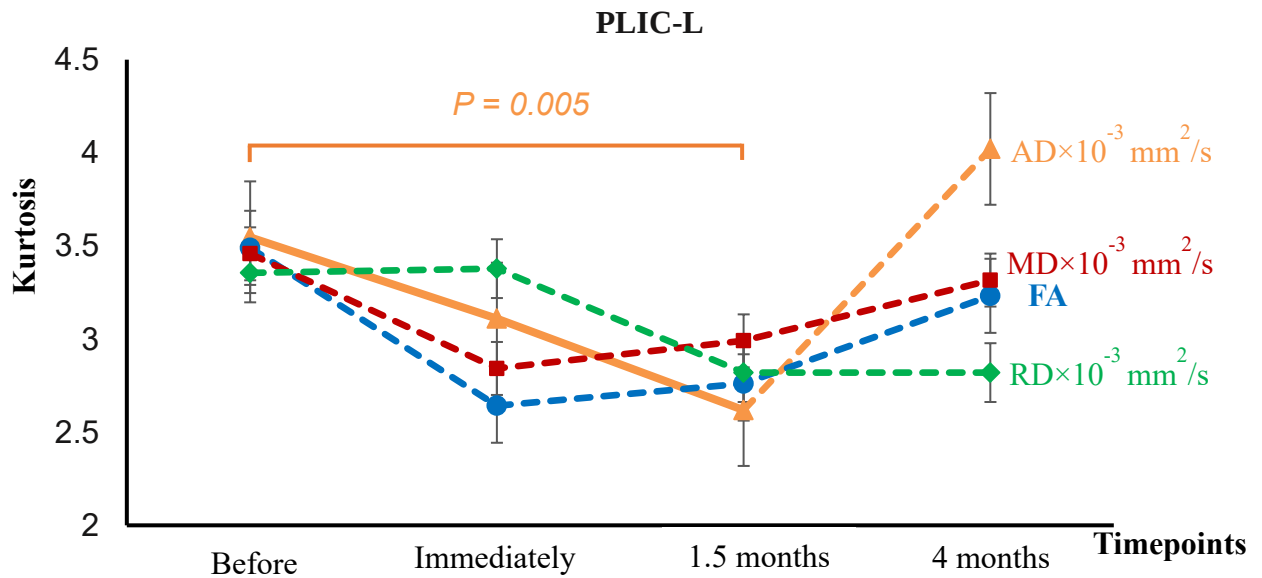


Figure 8. Significant decrease in the kurtosis of AD in the left posterior limb of internal capsule 1.5 months post-WBRT. Abbreviation: AD, axial diffusivity; MD, mean diffusivity; FA, fractional anisotropy; RD, radial diffusivity.

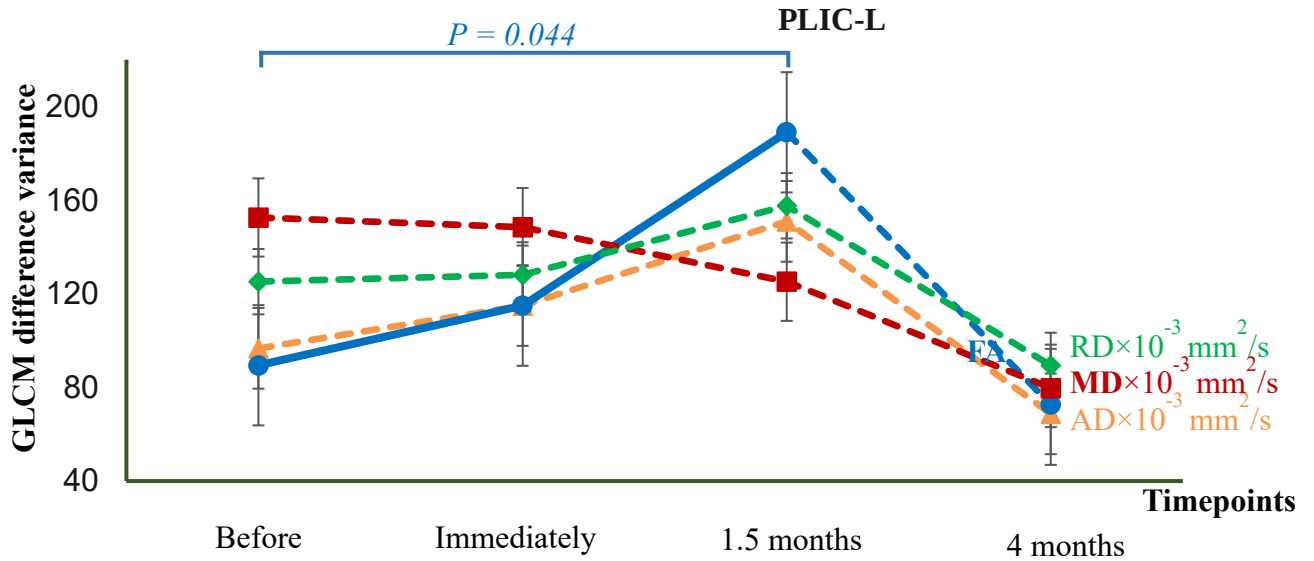


Figure 9. Significant increase in GLCM Difference variance of FA in the left posterior limb of internal capsule 1.5 months post-WBRT. Abbreviation: GLCM, gray level co-occurrence matrix; AD, axial diffusivity; MD, mean diffusivity; FA, fractional anisotropy; RD, radial diffusivity.

A significant decline in GLCM cluster tendency of MD was observed within the left superior corona radiata at 4 months, while an increase in GLCM difference variance was observed in the right superior corona radiata at 1.5 months post-WBRT (Figure 10 and Figure 11, respectively).

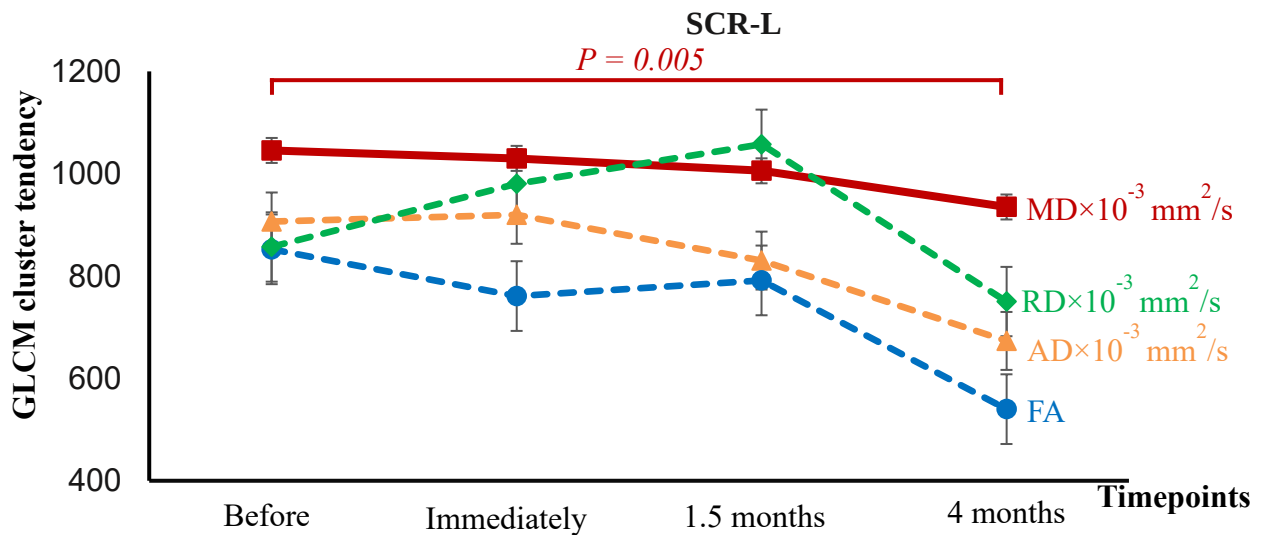


Figure 10. Significant decrease in GLCM cluster tendency of MD in the left superior corona radiata at 4 months post-WBRT. Abbreviation: GLCM, gray level co-occurrence matrix; AD, axial diffusivity; MD, mean diffusivity; FA, fractional anisotropy; RD, radial diffusivity.

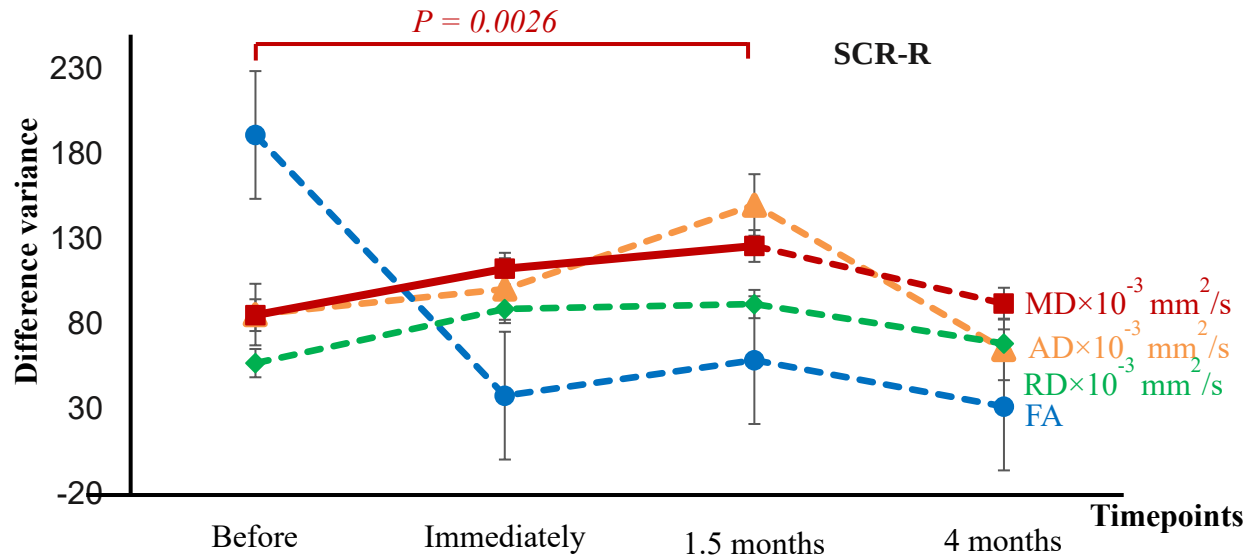


Figure 11. Significant decrease in GLCM difference variance of MD in the right superior corona radiata 1.5 months post-WBRT. Abbreviation: GLCM, gray level co-occurrence matrix; AD, axial diffusivity; MD, mean diffusivity; FA, fractional anisotropy; RD, radial diffusivity.

3.2. Predictive Value of DTI-Radiomics for Delayed Memory Performance

Tests of correlations revealed that the skewness of FA within the right superior longitudinal fasciculus and the 90th percentile of RD in the left superior corona radiata at 1.5 months post-WBRT had strong and moderate positive correlations with delayed memory scores at 4 months, respectively (Figure 12). Additionally, a strong negative correlation was observed between the 10th percentile of FA in the body of the corpus callosum and delayed memory scores at 4 months (Figure 13).

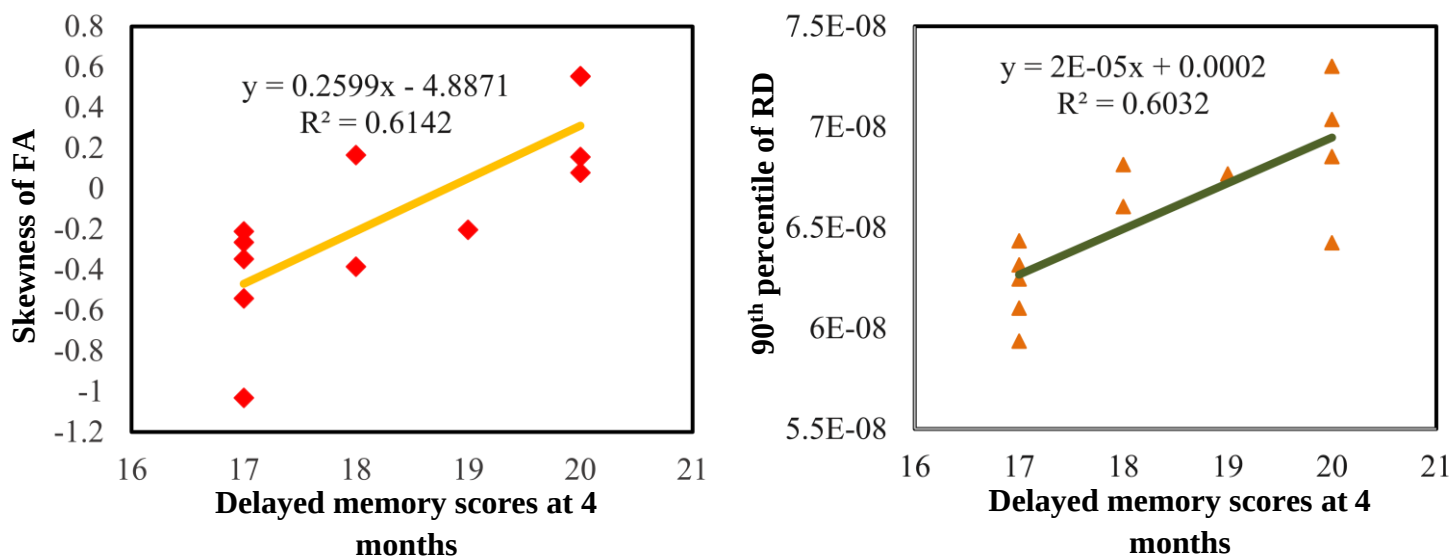


Figure 12. Correlations between DTI-radiomic features at 1.5 months and delayed memory scores at 4 months. A strong positive correlation was observed between skewness of FA in the right superior longitudinal fasciculus and delayed memory scores. A moderate correlation was found between 90th percentile of RD in the left superior corona radiata and delayed memory scores. Abbreviation: DTI, diffusion tensor imaging; FA, fractional anisotropy; RD, radial diffusivity.

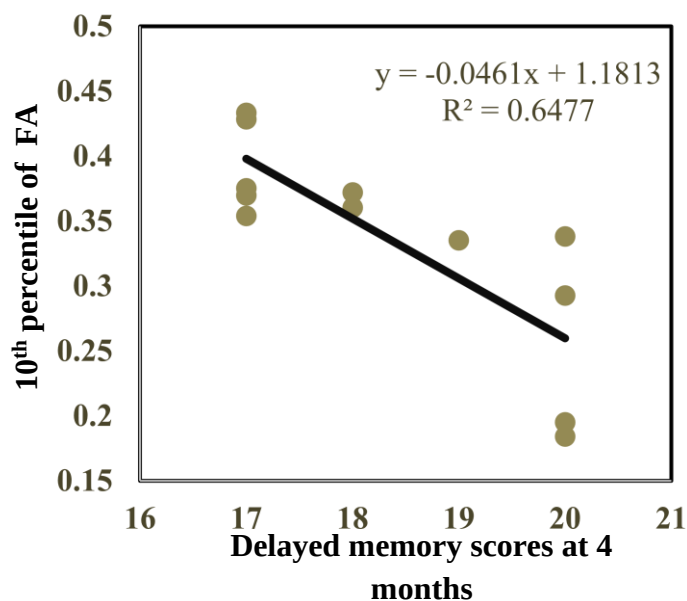


Figure 13. Correlations between 10th percentile of FA and cognition performance at 4 months. A strong negative correlation was observed between the 10th percentile of FA in the body of the corpus callosum and delayed memory scores at 4 months.

4. Discussions

This study assessed the value of DTI-radiomics in characterizing regional WM alterations post-WBRT within the acute and early delayed phases of WBRT-induced injury. Temporal variations in FA, MD, AD, and RD histogram and GLCM features were observed across time points relative to baseline, suggesting differential susceptibility of WM ROIs to WBRT-induced alterations. Significant changes were observed in the ALIC-L, PLIC-L, and bilateral SCR. Correlation analysis revealed strong and moderate associations between delayed memory performance and time point DTI-radiomic features, suggesting the potential predictive value of these biomarkers for delayed memory performance following WBRT.

Histogram feature analysis offers a sensitive method for detecting subtle tissue changes by evaluating voxel intensity distribution, enabling the detection of microstructural variations (Dai et al., 2025), with whole brain histogram-DTI described by Cercignani et al (2000) as capable of revealing microscopic changes in the normal appearing BP. In this study, histogram feature analysis revealed a significant increase in the 10th percentile and a decrease in the 90th percentile of AD within the ALIC-L immediately after WBRT. The 10th and 90th percentiles reflect the lower and higher ends of the signal intensity distribution, representing the values below which 10% and 90% of the signal intensities fall, respectively (Zwanenburg et al., 2020). Thus, the concurrent increase and decrease of these percentiles result in the narrowing of the signal intensity distribution of AD. Given that AD is considered a surrogate marker for axonal integrity (Song et al., 2003), these changes may be the result of concurrent axonal swelling and degeneration or cessation of peritumoral edema.

The observed reduction in kurtosis of AD within the PLIC-L at 1.5 months post-WBRT likely reflects the cessation of tumor-related and peritumoral edema, which compressed local axons, or a partial recovery of axonal swelling, both of which can lead to increased water mobility. Kurtosis quantifies the deviation from Gaussian diffusion; higher values indicate more restricted diffusion and sharper voxel intensity peak (Jensen et al., 2010). The significant decrease in kurtosis of AD suggests a shift towards more

Gaussian-like diffusion, characterized by broader voxel intensity distributions and reduced peak sharpness. The concurrent increase in GLCM difference variance of FA supports this interpretation, reflecting elevated diffusivity in PLIC-L. GLCM-based texture features, such as difference variance, are sensitive to spatial heterogeneity in voxel intensities and can detect subtle microstructural alterations (Kim et al., 2022). The rise in FA difference variance indicates greater variability in FA values across neighboring voxels, potentially resulting from the cessation of tumor compression or partial axonal recovery of axonal swelling following WBRT-induced injury.

Within the bilateral SCR, notable alterations in texture features were observed. In particular, the GLCM cluster tendency, which quantifies the propensity of similar gray-level intensities to form clusters within a ROI, showed a decline at 4 months post-WBRT. An increased cluster tendency typically reflects greater local homogeneity, where neighboring voxels share similar intensities. Conversely, the observed decrease in cluster tendency of MD in the SCR-L implies increased textural heterogeneity, with less clustering of similar gray-level values (Zwanenburg et al., 2016). At 1.5 months, the increased difference variance of MD within the SCR-R further supports the occurrence of increased texture heterogeneity. This metric reflects greater variation in intensity difference between neighboring voxels, aligning with diffusivity patterns in altered tissue microstructure. Taken together, the decrease in cluster tendency and increase in difference variance of MD in the bilateral SCR suggest an increased degree of tissue heterogeneity, which may be indicative of partial recovery of radiation-induced injury or the appearance new tumor in the region.

In this DTI-radiomic study of WBRT-induced WM changes within the acute and early delayed phases, no significant alterations in RD-derived radiomic features were observed. The absence of such changes suggests that myelin remained relatively preserved at these time points. This observation appears to align with early phase WM response mechanisms to WBRT, which are predominantly characterized by endothelial injury, BBB disruption, cerebral edema, and transient demyelination (Greene-Schloesser et al., 2012). Notably, increased RD has been associated with severe demyelination and

axonal loss (Klawiter et al., 2011; Naismith et al., 2010). Thus, the lack of significant RD alterations in our study may indicate minimal or potentially reversible myelin disruptions within the acute and early delayed phases.

Given the exploratory nature of this study, correlation analyses were performed without correction for multiple comparisons. Significant correlations were identified between time point DTI-radiomic features and delayed memory scores at 4 months. Notably, a strong positive correlation was observed between the skewness of FA in the SLF-R at 1.5 months and delayed memory performance at 4 months. Skewness of FA reflects the asymmetry of the voxel-wise FA intensity distribution within the SLF-R. This observation implies that the lesser the degree of microstructural damage in the SLF-R at 1.5 months, the better the delayed memory scores at 4 months. The SLF is a major associative fiber bundle known to support memory functions, including verbal and working components, and its integrity disruption has been linked to cognitive decline (Makris, 2005). Similarly, the moderate positive correlation between the 90th percentile of RD within the SCR-L at 1.5 months and delayed memory at 4 months may be explained by similar reasoning.

In contrast, a strong negative correlation was observed between the 10th percentile of FA within the body of corpus callosum and delayed memory scores at 4 months. This finding may be interpreted as a rightward shift in the FA histogram, with decreasing tumor compression, which may result in improved delayed memory.

Taken together, these findings suggest that early post-WBRT DTI-radiomic features, particularly histogram metrics such as skewness and percentiles (10th and 90th), may serve as sensitive indicators of delayed memory performance following WBRT. While the lack of corrections for multiple comparisons warrants cautious interpretation, the results offer promising insights for future longitudinal studies aimed at predicting cognitive changes associated with brain tumor radiotherapy.

Several limitations should be considered. First, while DTI adequately served the purpose of this study, the advent of advanced diffusion imaging techniques, capable of resolving multiple diffusion directions, offering higher resolution within a voxel could

enhance the replicability of these findings. Second, tumors influence the diffusion patterns within their local environment. To mitigate this potential bias, we segmented the normal-appearing BP and eroded 1 voxel around the ROIs to account for potential tumor confounds. Third, with several WM tracts excluded from the study due to the ROI selection criteria, future studies could benefit from alternative methods that maximize the exclusion of more WM regions.

5. Conclusions

This study demonstrated significant WM microstructural changes following WBRT, as assessed through DTI-radiomic analysis. The findings highlight acute and early-delayed WBRT-induced alterations in the ALIC-L, PLIC-L, and bilateral SCR, with DTI histogram and GLCM features underscoring the value of radiomics in assessing regional WM alterations following WBRT. Future studies should evaluate the performance of these radiomic features with advanced diffusion MRI techniques.

Summary and Conclusion

This research study assessed the performance of MRI indices in evaluating myelin and brain injury following WBRT within the acute and early-delayed phases. Structured into two themes, chapter 1 investigated the relative sensitivity of nine MRI indices to myelin, aimed at identifying the most sensitive index for myelin characterization. The findings from this study are expected to have valuable implications for the noninvasive assessment of CNS myelin. The key findings are as follows:

In chapter 1,

1. MRI indices including MWF, MTR, T1W/T2W, FA, MD, T1, T2, T1 ρ relaxation times, and σ showed varied sensitivities in distinguishing spinal cord regions, based on their measured mean values.
2. The myelin distributions observed across the cervical spinal cord tissue using the MRI indices were consistent with myelin density measurements obtained from TEM.

3. Nearly all indices highlighted the contrast between GM and WM columns, reflecting their sensitivity to variations in myelin content, as well as the diversity of myelin distributions within WM columns and GM.
4. All indices, except σ , differentiated GM from all columns.
5. Two WM columns had significantly different MWF, FA, MD, and T2 values.
6. MWF, MTR, T1W/T2W, FA values were consistently lower in GM, while MD, T1, T2, and T1 ρ were higher.
7. Higher MWF and MTR in the LC or AC, along with lower T1, T2, and T1 ρ in the AC compared to the PC, suggest that higher myelin density is localized within the LC or AC, which agrees well with myelin density measured on TEM images.
8. Correlation analysis among the indices revealed moderate to strong associations, suggesting shared sensitivity across the different techniques for myelin characterization.
9. The findings suggest that combining MWF or MTR with a DTI index (FA or MD) or T2 offers a particularly sensitive combination for accurate differentiation of all WM columns and GM.

Building on the demonstrated sensitivity of DTI indices—FA and MD—to myelin *ex vivo* studies, chapter 2 further incorporated RD and AD to evaluate regional variations in WM vulnerability to WBRT-induced injury within the acute and early-delayed phases. Radiomics analysis of these indices revealed significant microstructural alterations in WM regions and their associations with delayed memory. The key findings are as follows:

In chapter 2

1. A significant increase in the 10th percentile and a decrease in the 90th percentile of AD were observed within the left anterior limb of the internal capsule between baseline and immediate time points.

2. Between baseline and 1.5 months post-WBRT, a significant decline in kurtosis of AD and an increase in GLCM difference variance of FA within the left posterior limb of the internal capsule were observed.
3. Across the bilateral superior corona radiata, significant changes in GLCM features were observed. Specifically, GLCM cluster tendency of MD declined within the left superior corona radiata between baseline and 4 months, while GLCM difference variance of MD increased in the right superior corona radiata between baseline and 1.5 months.
4. The study revealed that DTI-radiomic features at 1.5 or 4 months may predict delayed memory performance at 4 months post-WBRT.
5. Skewness of FA at 1.5 months within the SLF-R was strongly associated with delayed memory at 4 months.
6. The 90th percentile of RD within the SCR-L at 4 months was moderately associated with delayed memory at 4 months.
7. The 10th percentile of FA within the BCC was strongly associated with delayed memory at 4 months.
8. DTI imaging indices are sensitive to detecting WM changes, which may or may not be myelin injury.

Acknowledgments

This paper is a summary of research results obtained under the guidance of Associate Professor Khin Khin Tha of the Laboratory for Biomarker Imaging Science, Graduate School of Biomedical Science and Engineering, Hokkaido University.

First, I would like to express my profound gratitude to Associate Professor Khin Khin Tha, who offered me an opportunity to study as a doctoral student at the Laboratory for Biomarker Imaging Science, Graduate School of Biomedical Science and Engineering. The immense support throughout the study period is greatly appreciated. Thanks to the excellent guidance, I have developed a strong interest in MRI imaging analysis, and I look forward to an exciting future. To Professor Takayuki Hashimoto, I am so thankful for the direction and guidance offered to me throughout the study period. I am very grateful. I am incredibly grateful to Dr. Takahiro Kanehira for his time, advice, and guidance as my EXEX (formerly DX) Doctoral Fellowship mentor. I would also like to express my sincerest appreciation to the EXEX Doctoral Fellowship for the funding support offered to me throughout the study period. Also, I am deeply grateful to professors Nina Patzke and Kevin C Wakeman for the guidance and support in major sections of chapter 1.

Next, I would also like to extend my heartfelt appreciation to former and current laboratory members whose collaboration has enriched my experience. Special thanks to Ms Sanoe Takayama, whose assistance with numerous administrative tasks and paper-related matters has been invaluable throughout this journey. Working alongside such talented and supportive colleagues during these past years has been an immense pleasure. Also, I would like to express my sincere gratitude to the staff of the Global Center for Biomedical Science and Engineering (GCB), Eba Murai and Funakoshi Nana, for the administrative services and support offered to me during the study period.

Lastly, I express my deepest gratitude to my family back home. Their constant love, encouragement, and unwavering support have been my greatest source of strength, and I am forever indebted to them for standing by me throughout this academic journey.

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