

Review



Diffusion Metrics as a Potential Prognostic Biomarker in Cervical Myelopathy

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HIGHLIGHTS

- Diffusion tensor imaging (DTI) metrics are potential predictive biomarker of efficacy of surgical interventions in cervical myelopathy.
- Further efforts to make a consensus on spinal cord DTI are needed.

Review



Diffusion Metrics as a Potential Prognostic Biomarker in Cervical Myelopathy

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Conflict of Interest

The authors have no potential conflicts of interest to disclose.

ABSTRACT

Diffusion tensor imaging (DTI) has a diagnostic value in cervical myelopathy. The usefulness of diffusion metrics as a potential prognostic biomarker was assessed in this review. Various diffusion metrics, such as fractional anisotropy, mean diffusivity, apparent diffusion coefficient, and radial diffusivity, were significant in correlation with functional recovery after surgery. Changes in diffusion metrics not only at the compression level, but also above and below the compression level were confirmed. However, it was difficult to confirm the results owing to the diversity of studies. Further efforts to make a consensus on spinal cord DTI are needed.

Keywords: Diffusion Tensor Imaging; Cervical Myelopathy; Recovery of Function

INTRODUCTION

The incidence of cervical myelopathy, as well as degenerative cervical spinal disease, is increasing. Cervical myelopathy can be caused by compression of the spinal cord by surrounding bony or ligamentous structures and can manifest various clinical symptoms: sensory impairment and motor paralysis (from mild to complete loss) [1-3]. Decompressive surgery is the treatment of choice in symptomatic and progressive cases [4-6]. As an objective diagnostic tool, magnetic resonance imaging (MRI) is essential for the measurement of spinal cord compression and signal change. Intramedullary high signal intensities in T2-weighted (T2W) images might reflect pathological changes in the spinal cord [7-9]. However, accumulating evidence shows that high signal intensities in T2W images alone are not sensitive enough to measure the degree of injury and prognosis accurately [10]. Signal changes in T2W images often appear in the late period of clinical states and do not usually reverse even after successful decompressive surgery [9-11]. Diffusion tensor imaging (DTI), an MRI technique that is based on the diffusion properties of water molecules, has been used in quantifying structural details of the brain, especially the white matter. Recent applications of the DTI technique for the measurement of spinal cord integrity yielded a possibility of exploring the pathological condition in the spinal cord both quantitatively and qualitatively [12-14]. Currently, the use of diffusion metrics (e.g., fractional anisotropy [FA], mean diffusivity [MD], axial diffusivity [AD], and radial diffusivity [RD]) [15] and whether it

has a clinical correlation with symptoms and prognosis are starting to draw great attention among both spinal surgeons and physiatrists. Although only a few previous studies reported on the diagnostic and prognostic values of DTI in cervical myelopathy [16-18], it is adequate for reviewing the possible usefulness of diffusion metrics in the spinal cord as a potential prognostic biomarker in longitudinal studies.

In this review, we analyzed all longitudinal studies that compared the pre-treatment and post-treatment conditions of patients with cervical myelopathy using DTI.

DIFFUSION METRICS IN LONGITUDINAL STUDIES AS A POTENTIAL PROGNOSTIC BIOMARKER

A comprehensive online search was performed to find relevant articles related to diffusion metrics as prognostic marker in cervical myelopathy. The search terms related to cervical myelopathy and DTI used were as follows: (“spinal cord,” “cervical cord,” “myelopathy,” or “spinal cord injury”) and (“diffusion magnetic resonance imaging,” “diffusion tensor imaging,” “diffusion MRI,” or “diffusion weighted MRI”). A filter was set to restrict the search to studies with a cohort design and human studies. Among 24 initially identified articles, 7 were extracted after abstract review. Finally, we found only 3 longitudinal studies related to the predictive utility of diffusion metrics [19-21]. The other 4 studies conducted clinical follow-ups after the treatment; however, DTI was performed only prior to the treatment [22-25]. The details are shown in Tables 1-3.

Subjects

The studies included patients with compressive myelopathy or spondylotic myelopathy who underwent surgical treatment. Compressive myelopathy was diagnosed when there were compression lesions owing to surrounding bony or ligamentous structures. Spondylotic myelopathy was included in cervical myelopathy in a broad sense.

In the 3 longitudinal studies, the average patient ages were 48 years (range: 35–82 years), 52.8 ± 8.0 years, and 56.1 ± 8.8 years. Most of the patients showed high signal intensities on the T2W images (100% in the study by Guan et al. [20] and 90% in that by Yang et al. [19]). Rajasekaran et al. [21] did not describe their patients' conventional MRI findings.

In the other 4 studies that followed up clinical findings only, the subjects were slightly older than those in the longitudinal studies; their average ages were 54.5 years, 61.8 ± 12.3 years, 62.8 years (range: 41–82 years), and 64 years (range: 43–86 years). High signal intensities on the T2W images were observed in fewer patients in these 4 studies than in the longitudinal studies (48% in the study by Vedantam et al. [22]; 30%, Jones et al. [23]; and 29%, Wen et al. [25]). Arima et al. [24] did not describe their patients' conventional MRI findings.

Treatments

Surgical decompression without metallic implant was performed in 2 of the 3 longitudinal studies (laminoplasty with allo-bone graft in the study by Yang et al. [19] and anterior or posterior decompressive procedures in that by Rajasekaran et al. [21]). A titanium implant was used for anterior fixation in the study by Guan et al. [20]. Decompressive surgery was performed using surgical hardware in 2 of the 4 studies that followed up clinical findings only. The use of metal implants was one of the reasons why postoperative DTI was not

Table 1. Summary of studies using DTI as a biomarker in cervical myelopathy - study design

Author (year)	Subject	Surgical procedure	Pre-OP evaluation	Post-OP evaluation	Follow-up interval	Clinical measures
Yang et al. [19] (2018)	20 CM; 20 healthy control	Laminoplasty with allo-bone graft	DTI, clinical measures	DTI, clinical measures	6 months post OP	mJOA
Guan et al. [20] (2017)	7 CSM; 10 healthy control	Anterior cervical discectomy and fusion with titanium alloy implants	DTI, clinical measures	DTI, clinical measures	3 months post OP	mJOA, NDI, questionnaire on daily living activities, VAS
Rajasekaran et al. [21] (2017)	26 CSM	Anterior decompression in 20; posterior decompression in 6	DTI, clinical measures	DTI, clinical measures	12 months post OP	Nurick grade
Vedantam et al. [22] (2017)	27 CSM	No detail description	DTI, clinical measures	Clinical measures	3 months post OP	mJOA, NDI, SF36
Jones et al. [23] (2013)	30 CSM; 15 got surgery	Decompressive surgery with surgical hardware	DTI, clinical measures	Clinical measures	Mean 180 days post OP (range 59–393 days)	mJOA, Nurick, NDI, SF36
Arima et al. [24] (2015)	16 CM	Anterior cervical discectomy and fusion in 10; posterior decompression in 5; anterior and posterior approach in 1	DTI, clinical measures	Clinical measures	3 months post OP	NCSS
Wen et al. [25] (2014)	45 CSM; 22 got surgery; 20 healthy control	Decompression surgery; no further detail description	DTI, clinical measures	Clinical measures	6 months–2 years post OP	mJOA, SEP

DTI, diffusion tensor imaging; pre-OP, preoperative; post-OP, postoperative; CM, cervical compressive myelopathy; mJOA, modified Japanese Orthopedic Association; CSM, cervical spondylotic myelopathy; NDI, Neck Disability Index; VAS, Visual Analogue Scale; SF36, Short Form 36; NCSS, Neurosurgical Cervical Spine Scale; SEP, somatosensory evoked potential.

Table 2. Summary of studies using DTI as a biomarker in cervical myelopathy - DTI analysis

Author (year)	Analyzed level	DTI metrics	ROI	DTI analysis software	Bo; vendor	Slice thickness/slice gap (mm)
Yang et al. [19] (2018)	At maximal compression level; at C7/T1 non-compressed level	FA, MD, AD, RD	Manual, 6 ROIs (bilateral anterior, lateral, posterior)	DTIFit	3T; Philips	3/-
Guan et al. [20] (2017)	At non-compressed upper level; at maximal compression level	FA, MD, AD, RD	Manual, whole spinal cord	DTI studio	3T; Philips	4/0.4
Rajasekaran et al. [21] (2017)	Not described	FA, ADC; relative anisotropy; volume ratio; eigen vectors (E1, E2, E3)	Not described	Not described	1.5T; Siemens	4/-
Vedantam et al. [22] (2017)	At C1/2 non-compressed level; at maximal compression level	FA	Manual, whole spinal cord	AFNI	1.5T; GE	3/3
Jones et al. [23] (2013)	At C2/3; at maximal compression level; at C7/T1	FA	Manual, 3 ROIs (right, center, left); average value was selected	ADW	3T; GE	4/-
Arima et al. [24] (2015)	At maximal compression level	FA, MD	Manual, whole spinal cord	Philips MRI workstation	3T; Philips	3/-
Wen et al. [25] (2014)	At C2/3; at maximal compression level; mean from C3 to C7	FA; eigen values ($\lambda_1, \lambda_2, \lambda_3$)	Manual, whole spinal cord	DTI studio	3T; Philips	7/2.2

DTI, diffusion tensor imaging; ROI, region of interest; FA, fractional anisotropy; MD, mean diffusivity; AD, axial diffusivity; RD, radial diffusivity; ADC, apparent diffusion coefficient; AFNI, Analysis of Functional Neuroimages; ADW, Advantage Workstation; MRI, magnetic resonance imaging.

Table 3. Summary of studies using DTI as a biomarker in cervical myelopathy - acquisition and result

Author (year)	DTI acquisition	FOV (mm ²)	TR/TE (ms)	Key results associated with recovery
Yang et al. [19] (2018)	Single-shot echo-planar imaging; 15 directions; b=500 s/mm ²	250 × 250	6,300/63	Post OP anterior FA at compression and below compression level: correlate with post OP mJOA
Guan et al. [20] (2017)	Multi-shot, high-resolution DTI; sagittal 6 directions; axial 15 directions; b=600 s/mm ²	250 × 250	2,500/72	FA, RD at compressed region: significant differences post-surgery (increased FA, decreased RD post OP)
Rajasekaran et al. [21] (2017)	Axial spine-echo single-shot echo planar parallel imaging; 12 directions; b=500 s/mm ²	220 × 220	6,000/85	Decreased in postoperative ADC, E1, E2: showed neurological improvement
Vedantam et al. [22] (2017)	Standard single-shot, twice-refocused, spin-echo, echo planar image; 12 directions; b=600 s/mm ²	190 × 190	5,000/98.2	FA at max comp level: correlated with change in mJOA score
Jones et al. [23] (2013)	Single-shot echo-planar imaging; 6 directions; b=1,000 s/mm ²	180 × 180	8,100/94.1	Higher FA at stenosis level: NDI improve post OP
Arima et al. [24] (2015)	Single-shot fast-spine-echo-based sequence; 15 directions; b=1,000 s/mm ²	240 × 240	6,000/80	MD-z: correlate with functional recovery rate
Wen et al. [25] (2014)	Single-shot spine-echo echo-planar imaging; 15 directions; b=600 s/mm ²	80 × 80	Not described	Mean FA from C3 to C7: correlate with recovery ratio

DTI, diffusion tensor imaging; FOV, field of view; TR/TE, repetition time/echo time; post OP, postoperative; FA, fractional anisotropy; mJOA, modified Japanese Orthopedic Association; RD, radial diffusivity; ADC, apparent diffusion coefficient; NDI, Neck Disability Index; MD, mean diffusivity.

performed in these studies. There was no specific description of the surgical procedure in the other 2 studies.

Follow-up interval

In the studies that performed DTI after surgery, the follow-up intervals for DTI and clinical evaluation were 3 months in the study by Guan et al. [20]; 6 months, Yang et al. [19]; and 12 months, Rajasekaran et al. [21].

In the studies that performed clinical follow-ups only, the follow-up period was 3 months in 2 studies. The follow-up period was not fixed in the other 2 studies; the follow-up period ranged from 39 to 373 days in the study by Jones et al. [23] and from 6 months to 2 years in that by Wen et al. [25].

Analysis of diffusion metrics

Diffusion metrics

Among the authors of the 3 longitudinal studies, Yang et al. [19] and Guan et al. [20] analyzed FA, MD, AD, and RD. Rajasekaran et al. [21] analyzed FA, apparent diffusion coefficient (ADC), relative anisotropy, volume ratio, and eigen vectors. In the 4 clinical follow-up studies, FA was a common measure, and MD and eigen values were included in one study each.

Level

Among the 3 longitudinal studies, the maximal compression level and C7/T1 non-compressed level were evaluated in the study by Yang et al. [19] and maximal compression level and upper non-compressed level in that by Guan et al. [20]. The included vertebral level was not described in the study by Rajasekaran et al. [21]. In all 4 clinical follow-up studies, the maximal compression level was analyzed. Upper non-compressed areas (C1/2 and C2/3 levels) were included in 3 studies and lower non-compressed areas (C7/T1 level) in one study. One study calculated the mean FA value from C3 to C7.

Region of interest (ROI)

Only Yang et al. [19] defined 6 ROIs (i.e., bilateral anterior, lateral, and posterior) separately at each level. Jones et al. [23] defined 3 ROIs (i.e., right, left, and center) at each level; however, the average value was selected for the statistics. The ROI included the entire cord in the other studies.

DTI analysis software

The analysis software used varied among the studies. Two studies used the DTI studio, which is an open-source diffusion MRI analysis tool [20,25]. FSL's diffusion toolkit, DTIFit, advantage workstation (AW), and analysis of functional neuroimaging processing suite were used in the other studies [19,22-37]. One study did not mention the software used for the analysis. AW is a software offered by GE healthcare, which postprocesses raw DTI data to create FA maps. All the above-mentioned software was first developed for the purpose of studying brain connectivity and activity.

RESULTS

There were 3 longitudinal studies that performed preoperative and postoperative DTI.

Yang et al. [19] analyzed FA, MD, AD, and RD at the maximal compression level and C7/T1 non-compressed level. The postoperative FA at the compression level and below the non-compressed level correlated with the postoperative modified Japanese Orthopedic Association (mJOA) score. More specifically, FA of the anterior ROIs was correlated with recovery. This concrete result was observed because Yang et al. [19] defined 6 ROIs at each of 2 vertebral levels. The reduction of AD was not significant after surgery at the compression level and non-compressed level. Postoperative reduction in RD was noted in some ROIs; however, the changes did not correlate with recovery. There was no significant difference between the preoperative and postoperative MD [19].

Guan et al. [20] analyzed FA, MD, AD, and RD at the maximal compression level and upper non-compressed level. Postoperative increase in FA and decrease in RD at the compression level were observed in association with improvements in the visual analog scale score, mJOA score, and neck disability index. The p value was only 0.048 for RD. At the upper non-compressed level, there were no significant changes in FA and RD. There was no significant difference between the preoperative and postoperative MD and AD at the compression level and upper non-compressed level [20].

Rajasekaran et al. [21] analyzed FA, ADC, relative anisotropy, volume ratio, and eigen vectors. The included vertebral level and selection of ROIs were not described in their study. The decrease in postoperative ADC and eigen vectors correlated with neurological improvement after surgery. The preoperative and postoperative FA did not correlate with neurological improvement. The other diffusion metrics evaluated in their study did not show any clinical significance [21].

Taken together, the postoperative FA at the compressed level seemed to be the most sensitive biomarker for recovery after surgery in these longitudinal studies.

The 4 studies that performed clinical follow-ups after surgery conducted DTI only prior to surgery. In these studies, the correlations between preoperative diffusion metrics and postoperative recovery were studied. A higher FA value at the compression level in the preoperative period had a significant correlation with postoperative recovery in 2 studies [22,23]. The mean FA value from C3 to C7, not at the compression level, was correlated with recovery in one study [25]. Only Arima et al. [24] did not agree on the significance of FA; they did not use the absolute MD and FA values in their analysis and transformed the absolute values into normalized values with z-scores. A normal database from their previous study in

30 healthy subjects was used. They concluded that a higher MD-z value was well correlated with a higher recovery rate. However, the FA-z value had no correlation with preoperative disease severity nor postoperative recovery [24].

Taken together, the preoperative FA at the compressed level seemed to be the most sensitive biomarker for recovery after surgery in these clinical follow-up studies.

Limitations

The small number of participants in each study and lack of control in some studies may weaken the validity of the results. A surgical factor might influence the DTI images obtained after surgery, especially after surgery with metal implantation. The variations in the follow-up periods might affect the comparison of the surgical outcomes. The differences in equipment, image acquisition methods, diffusion metrics, and processing across the studies pose additional challenges.

Nevertheless, the common objective of all these studies was to validate the prognostic value of diffusion metrics in cervical myelopathy. Our effort to extract valid results from these studies has a clinical value.

DISCUSSION

To date, only limited longitudinal DTI studies have been conducted; these mostly showed some correlation between diffusion metrics and prognosis in either the preoperative or postoperative period among patients with cervical myelopathy. Thus, diffusion metrics might be used as a biomarker candidate for prognostication. However, for the general use of DTI in patients with cervical myelopathy, further studies using more sophisticated mapping techniques with enhancement of acquisition protocols are warranted.

Pathophysiological changes, such as apoptotic cell death, loss of neurons, loss of oligodendrocytes, and reactive increase in astrogliosis, occur at the compression level when there are spinal cord lesions [26,27]. Axonal degeneration was more definite in the dorsal funiculus cranial to the compression site and in the ventral funiculus caudal to the compression site in animal models [28]. Similar microstructural changes following spinal cord injury were observed with DTI; changes in FA, generalized FA, and RD were present cranial to the lesion on the dorsal aspect and caudal to the lesion on the ventro-lateral aspect in a previous animal study [29]. The studies included in this review reported similar changes at the lesion level. Nevertheless, there is an important difference between previous animal studies and human DTI studies, which were included in this review. Only one study attempted to measure diffusion metrics separately from the ventral to the dorsal parts of the spinal cord. The remaining studies used the average value of the entire spinal cord at the lesion level; this indicates that DTI could not provide additional information than the presence of T2 high signal intensity in the conventional MRI except possible.

Non-compressed areas were analyzed in most of the studies included in this review. In the 4 studies that performed DTI in the cranial non-compressed areas, none of the diffusion metrics from the cranial to the compression levels were significant in predicting recovery [20,21,23,25]. However, in one study, the preoperative FA above the lesion had a strong correlation with the baseline functional scores [23]. Of the 2 studies that performed DTI in the caudal non-compressed areas, only the study by Yang et al. [19] showed a significance

in the FA value below the lesion level. It is plausible to propose that measuring the motor tract below the lesion level would have a clinical importance as Wallerian degeneration can be present, which can change the diffusion metrics below the lesion level. Another study concluded that there is no correlation between the FA value below the lesion and recovery, which may be because the ROI was defined to cover the entire spinal cord and the anatomical portion of the tracts was not reflected [23].

The surgical intervention changed the diffusion metrics in all 3 longitudinal studies, which might indicate the possibility of using them as a biomarker. The FA value showed a clear correlation with postoperative recovery in all 3 studies. These results support the proposition that microstructural changes occurring after surgical treatment measured by FA clearly reflect the functional outcomes. This result is in line with previous evidence that the FA value is well correlated with its function in other diseases [12,30-32].

Among the 3 longitudinal studies, only 2 studies measured the MD, AD, and RD values. One study did not analyze the diffusion metrics, except for the FA value, which would not be enough to delineate underlying pathological states.

MD is an inverse measure of membrane density and is sensitive to cellularity, edema, and necrosis [33]. Its value is the sum of the AD and RD values [34]. The AD value tends to be variable in white matter changes and pathologies and decreases in axonal injuries [34,35], while the RD value increases in white matter changes with demyelination or dysmyelination. Changes in axonal diameters or density may also influence RD [33,36]. In 2 studies, the MD and AD values did not change significantly after surgery. Only the RD value was reversed after surgery in one study; in this study, the authors interpreted this result as reversed myelinopathy after surgery. The result variations between the 2 studies may be because one study used metallic device during surgery, causing severe artifact. If we exclude this study for possible artifact noise, then the other study would have reported recovery after surgery with plausible pathological changes.

Notably, recent advances in spinal cord imaging tools, such as the Spinal Cord Toolbox (NeuroPoly, École Polytechnique, Université de Montréal campus, Montreal, Canada), may increase the scientific analytical methods using sophisticated acquisition and mapping techniques in the spinal cord.

The detailed analysis process was described elsewhere [37]. As this technique uses meticulous segmentation and registration algorithm specific to the spinal cord, it can provide a good solution for the above-mentioned limitations. There are many physiological and motion artifacts in spinal cord imaging owing to spinal cord pulsation, cardiac pulsation, and respiration; preparing optimal acquisition protocols by reducing field of view approaches (2-dimensional radiofrequency excitation, outer-volume suppression methods, and parallel imaging) [36] would be essential in obtaining reliable scientific data, instead of employing the entire spinal cord as a single ROI or 6 ROIs manually.

CONCLUSION

DTI FA is a potential predictive biomarker of efficacy of surgical interventions in cervical myelopathy. The prognostic value of other diffusion metrics need to be assessed through more structured studies. Further efforts to make a consensus on spinal cord DTI are needed.

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