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## **Prognostic value of spinal cord MRI in Multiple Sclerosis patients**

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## **Abstract**

Multiple sclerosis (MS) is a common inflammatory, demyelinating and neurodegenerative disease of the central nervous system that affects both the brain and the spinal cord. In clinical practice, spinal cord MRI is performed far less frequently than brain MRI, mainly owing to technical limitations and time constraints. However, improvements of acquisition techniques, combined with a strong diagnosis and prognostic value, suggest an increasing use of spinal cord MRI in the near future. This review summarizes the current data from the literature on the prognostic value of spinal cord MRI in MS patients in the early and later stages of their disease. Both conventional and quantitative MRI techniques are discussed. The prognostic value of spinal cord lesions is clearly established at the onset of disease, underlining the interest of spinal cord conventional MRI at this stage. However, studies are currently lacking to affirm the prognostic role of spinal cord lesions later in the disease, and therefore the added value of regular follow-up with spinal cord MRI in addition to brain MRI. Besides, spinal cord atrophy, as measured by the loss of cervical spinal cord area, is also associated with disability progression, independently of other clinical and MRI factors including spinal cord lesions. Although potentially interesting, this measurement is not currently performed as a routine clinical procedure. Finally, other measures extracted from quantitative MRI have been established as valuable for a better understanding of the physiopathology of MS, but still remain a field of research.

**Keywords:** multiple sclerosis; spinal cord; MRI; prognosis

## **Introduction**

Multiple sclerosis (MS) is a common inflammatory, demyelinating and degenerative disease of the central nervous system that affects both the brain and the spinal cord. While the brain damage has been extensively explored since the development of MRI, spinal cord damage has been less studied, mainly due to MR acquisition challenges. These challenges are due to the geometry and the anatomical location of the spinal cord, which is a very thin and mobile structure surrounded by cerebrospinal fluid and bones, responsible for spatial inhomogeneity of the magnetic field strength. Moreover, intrinsic motion caused by cardiac and respiratory cycles can interfere and create artefacts [1]. The past few years have seen substantial improvements in spinal cord imaging, both qualitative (increased detection of focal lesions on conventional MRI sequences) and quantitative (atrophy measurement, quantitative metrics extracted from magnetization transfer and diffusion imaging, MR spectroscopy, functional MRI). Despite these developments, the use of spinal cord MRI in clinical routine remains limited compared to brain MRI, and quantitative techniques remain in the field of research.

Nonetheless, spinal cord damage is common in MS and the presence of spinal cord lesions has been demonstrated in up to 90% of patients with early relapsing-remitting multiple sclerosis (RRMS) [2–5]. The spinal cord involvement is sometimes even predominant in the clinical course of the disease [6–10]. In addition, spinal cord lesions are relatively specific to MS and have therefore been included in the diagnostic criteria for MS since their first version [11]. In the last version published in 2017, the spinal cord is one of the four localizations considered as eloquent and prone to fulfill conditions of dissemination in space, whether the lesion is symptomatic or not [12]. Spinal cord imaging is particularly useful when brain imaging does not meet diagnostic criteria. Finally, the spinal cord is a small and compact structure containing all sensory and motor nerve pathways for the limbs. A strong prognostic value of spinal cord damage on physical disability worsening can therefore be suspected.

In this review, we aim to expose the current data from the literature on the prognostic value of spinal cord MRI in MS patients. The first part will focus on the description of spinal cord pathology in MS patients, from the anatomopathological and the radiological point of view. The second part will focus on the prognostic value of spinal cord MRI, in the early and

later stages of the disease. Both conventional and quantitative MRI techniques will be discussed.

### **Spinal cord pathology in MS**

#### **Histopathological data**

In post-mortem studies, spinal cord lesions are highly prevalent and affect the entire spinal cord from the cervical to the lumbar portion [13–16]. In the axial plane, their predominant location are the posterior and lateral columns of the white matter, while the anterior columns are less affected. Grey matter is also affected by demyelination [17], and even more importantly than white matter, especially at the thoracic level [18]. Axonal loss is the other essential histopathological feature of MS. In particular, a loss of 57 to 62% across all levels of the spinal cord, independently from axonal size and spinal cord level have been observed in patients with well established MS (mean disease duration=29 years, sd=11 years) [18]. The association between axonal loss and demyelination in chronic MS remains unclear [18,19].

#### **Radiological data**

Two different types of MRI signal abnormalities have been observed in the spinal cord of MS patients : focal lesions and diffuse abnormalities [20,2]. On T2 weighted images, focal lesions are typically described as areas of hyperintensity of small size (less than two vertebral segments and half of the cross section), with a cigar-like shape on sagittal plane and wedge-shaped in axial images, seen along the entire spinal cord (cervical, thoracic or lumbar levels) but with a predominance in the cervical portion. Diffuse abnormalities are defined as areas without sharp edge, with increase of signal intensity but not as brightly as focal lesions. They are best detected on PD-weighted sequences. They are found mostly in primary progressive patients, less frequently in secondary progressive patients and rarely in relapsing–remitting patients [21, 2, 16, 22].

#### **Various MRI sequences to evaluate spinal cord lesions**

Specific MRI sequences have been developed and evaluated for years for the detection of lesions of MS. T2-FSE (Fast Spin Echo) is the most commonly used T2-weighted sequence. It could be used in combination with a Short Tau Inversion Recovery

(STIR) sequence which has been shown to be more sensitive than T2-weighted sequence in detecting spinal cord lesions but is more susceptible to flow-related artefacts [23–25]. More recently, the T1-weighted phase-sensitive inversion recovery (PSIR) [26] sequence has been proposed, and allows a better delineation of lesions. The sensitivity of these sequences varies according to the imaged level: in cervical cord, STIR and PSIR have a higher sensitivity than T2-FSE whereas in thoracic cord STIR has a higher sensitivity than T2-FSE, itself more sensitive than PSIR [27,28]. The 3D-T1-weighted MPRAGE sequence, in which MS lesions appear as hyposignals compared to the surrounding spinal cord, has also been evaluated, revealing lesions with a better contrast as compared to T2-FSE or STIR [29]. Finally, lesions located in the lateral part of the spinal cord are often missed on sagittal scans [30] and the combination of axial and sagittal acquisition improves lesion detection, compared to sagittal scans alone [30–32].

An optimum imaging protocol for spinal cord lesion identification has been recently defined, comprising at least two sagittal sequences (STIR, T2-FSE, PD-FSE, PSIR or 3DT1 MPRAGE) or two different planes (i.e. sagittal + axial) to be confident that the identified spinal cord lesions are not artefacts [33]. These acquisitions should cover both the cervical and thoracic levels. Concerning magnetic field strengths, if 3T MRI is the preferred magnet strength in the current MAGNIMS criteria, both 1,5T and 3T can be used. Figure 1 illustrates the visualization of spinal cord MS lesions using different conventional sequences available in clinical practice.

### **Correlation between histopathological and radiological data**

Several post-mortem studies have assessed the correlation between histopathological damages observed in the spinal cord of MS patients and the abnormalities visualized on the corresponding MR images. They have shown a good correlation when focusing on white matter demyelination [14,34]. However, grey matter lesions are not visualized as well as those in white matter [27,35], and the number of lesions in the spinal cord is underestimated by using sagittal view alone [15]. In addition, axonal damage and loss correlate poorly with abnormal signals on T2-weighted images [34,36]. This could be one of the explanations for the « clinico-radiological paradox in MS » [37], described as the surprisingly poor relationship between clinical status and radiological abnormalities. Interestingly, the correlation between axonal density in the spinal cord and spinal cord cross sectional area is low [18]. It is also important to note that if a high correlation between white matter

demyelination and signal intensity changes was reported in post-mortem studies, these results have to be moderated by the fact that MRI protocols used higher resolution MRI than in clinical routine and were not disturbed by motions artefacts encountered with *in-vivo* MRI imaging.

### **Prognostic value of conventional spinal cord MRI**

Two main markers of spinal cord pathology are explored using conventional MRI: focal lesions and atrophy. Many of the studies using these metrics are cross-sectional and therefore seek to link the level of disability of patients at a given time to the spinal cord injury at the same time. There are fewer prognostic studies, i.e. longitudinal studies whose main objective is to link the initial spinal cord lesion load or atrophy to the progression of disability several years later. Furthermore, MS evolves over several decades, and the majority of prognostic studies involving spinal cord MRI propose a short (2 years) or medium-term (5 years) follow-up. In this section we will highlight - when available - longitudinal studies proposing long-term follow-up, as they are particularly informative. Nonetheless, it is important to bear in mind that prognostic studies with longer follow-up, do not take into account recent technical developments to better visualize and quantify the initial lesion load. The prognostic role of spinal cord MRI can therefore probably be further improved.

#### **Focal lesions**

For a long time, a relationship between MS focal lesion load and disability has been hypothesized. However, results were disappointing with poor to moderate correlation when brain MRI was used alone, and a predominant involvement of the spinal cord in physical disability was suggested. Several studies have been led since the early 2000s and their findings were concordant with a correlation between spinal cord lesion load and disability at each stage of the disease, even in the earliest time. In addition, longitudinal studies have demonstrated the prognostic role of spinal cord MRI at the onset of disease, whereas it is less well evaluated later in the disease. These studies, grouped by disease phenotypes, are detailed below.

#### **Radiologically isolated syndrome**

In radiologically isolated syndrome (RIS), spinal cord lesions are associated with an increased risk of conversion to MS. In a recent meta-analysis, the spinal cord T2 lesions

number was the most predictive factor of early clinical conversion to MS [38]. This result was reported in 9 studies, including a total of 1193 RIS patients [39–47]. Moreover, the presence of spinal cord lesions was associated with an increased risk of developing primary progressive MS (PPMS) in RIS patients [45]. In particular, 100% of the 15 RIS patients who went on to develop PPMS had spinal cord lesions prior to the progressive phase, compared with 64% of the 113 who converted to clinically isolated syndrome (CIS) or RRMS, and 23% of the 324 who remained asymptomatic. Other MRI characteristics in the pre-progressive phase of PPMS were observed to be indistinguishable from CIS/MS.

### **Clinically isolated syndrome**

In CIS patients, the spinal cord lesion load has been consistently associated with an increased risk of conversion to MS and of disability progression [48–55]. Similar results were obtained in the presence of infratentorial lesions [56]. The risk of developing MS in presence of spinal cord lesions has been specifically evaluated in a cohort of 207 CIS patients who were followed for two years [54]. The risk of conversion to MS (McDonald 2010) [11] was increased from 2.0 to 2.6 times in case of spinal cord lesions, independently of factors like brain lesions, and was associated with the number of spinal cord lesions (1.6 to 2.1 for one lesion ; 2.4 to 3.3 for 2 lesions or more). Moreover, the risk of short-term disability progression (EDSS = 3 or more at 2 years) was observed to be 5 times higher in presence of spinal cord lesions. These results have been confirmed recently in a cohort of 178 patients with a follow-up of 15 years [55]. Patients were recruited prospectively and underwent MRI scans of the brain and spinal cord at baseline and after 1 and 3 years. They were followed clinically over 15 years. Both baseline brain gadolinium-enhancing lesion number and spinal cord lesion number were significantly associated with EDSS progression at 15 years. The analysis of MRI metrics at baseline, 1 and 3 years revealed that both new spinal cord lesions over time and baseline spinal cord lesions were associated with conversion to secondary progressive multiple sclerosis (SPMS). These results support the assumption that early focal inflammatory disease activity and spinal cord lesions are suitable predictors of very long-term disease outcomes in CIS patients.

### **Relapsing remitting patients**

Although fewer studies - essentially cross-sectional - have been conducted in RRMS patients, results are concordant and indicate an association between spinal cord lesion load



and disability [21,57–63]. Moreover, lesion location seems to contribute to disease course. In a recent cross sectional study including 642 patients with a majority of RRMS patients, lesions in central and lateral cervical spine regions were associated with a more severe EDSS score [64]. In a subgroup of the same cohort followed at 2 years, spinal cord motor tracts lesions were the only factor associated with disability progression [65]. Interestingly, a longitudinal study including 103 RRMS patients assessed the relevance of spinal cord MRI in asymptomatic patients [66]. One-quarter of clinically stable RRMS presented a new asymptomatic spinal cord lesions. The presence of at least one asymptomatic lesion in the brain or the spinal cord, was significantly predictive of an increased risk of future relapses with a Hazard Ratio of 2.31 (95% CI = 1.13-4.72,  $p = 0.02$ ). Another longitudinal study, involving 239 early RRMS patients (disease duration of less than 2 years) followed for at least 7 years, evaluated the impact of spinal cord injury on the development of severe disability [67]. The presence of spinal cord lesions at baseline was the best predictor for reaching EDSS 4.0 during follow-up, compared to other predictors such as the number of brain T2 lesions.

### **Primary progressive MS patients**

Cross sectional studies have consistently shown a higher correlation between spinal cord lesion load and disability scored by the EDSS compared to brain lesion load in PPMS patients [21,68–74]. Furthermore, a specific profile of lesion location in spinal cord for progressive MS patients was described, with more frequent damages in central and lateral column as well as spinal cord grey matter involvement [62,64,75]. A key role of spinal cord lesions in disability progression is also suggested by the recent description of progressive solitary sclerosis. Thus, patients with a solitary demyelinating lesion in the corticospinal tract, mainly in the spinal cord lateral columns, can develop progressive motor impairment, clinically very similar to progressive multiple sclerosis [8,10]. Similar observations were reported in progressive multiple sclerosis patients with few (i.e. 2-5) lesions [76].

### Atrophy

Spinal cord atrophy can be investigated from MR images using two different approaches. A first approach consists in using a baseline and a follow-up acquisition and in estimating the loss of spinal cord volume or cross sectional area (CSA) from one session to

the other [77,78]. A second and widely used approach consists in using a single acquisition, in computing the patient spinal cord volume or CSA and in comparing this value to a reference value (or in comparing the values measured from different populations) [79]. While this second approach is simple, its ability to detect subtle changes is limited due to the high natural inter-subject variability of spinal cord volumes and cross sectional areas. The anatomopathological substrate of spinal cord atrophy measured on MRI remains uncertain. Indeed, in recent histological studies, no significant correlation was found between the spinal cord CSA and the axonal loss [18]. Despite this lack of specificity, spinal cord atrophy has been consistently described in MS patients after a few years of disease duration and is related with disability. Its prognostic value has been demonstrated in short and medium term studies. However, longitudinal studies with a long follow-up duration are limited. Despite these results at the population level, the measurement of spinal cord atrophy is not currently used in clinical routine. Standardization of the acquisition protocols and the methods to measure spinal cord atrophy could contribute to the definition of pathological thresholds that could be used at the individual level.

### **Association between spinal cord atrophy and disability**

At the onset of the disease, i.e. in CIS and early RRMS patients, the existence of spinal cord atrophy remains unclear [53,77,78,80–86]. These inconsistent results are probably related to different measurement methodologies and patient inclusion criteria. In addition, edema is associated with acute MS lesions, which may mask atrophy. On the contrary, the occurrence of spinal cord atrophy has been consistently demonstrated in latter stage of the disease, in RRMS [82,87], SPMS [70,88,89] as well as PPMS patients [68,70,71,90]. Similarly, numerous studies have consistently reported an association between spinal cord atrophy and physical disability [75,83,91–98]. In particular, spinal cord gray matter atrophy is more pronounced in progressive MS patients and more associated with disability than spinal cord white matter atrophy or brain gray matter atrophy [99]. These results were confirmed in a meta-analysis across 94 studies in 2018 [100]. The magnitude of spinal cord atrophy was greater in progressive MS patients compared to RRMS patients, correlated with disability, and was greater than reported rates of brain atrophy (–1.78% versus –0.5% per year).

### **Prognostic value of spinal cord atrophy**

The prognostic value of spinal cord atrophy on conversion to definite MS was evaluated in a cohort of 131 non-spinal CIS patients followed over 5 years [53]. The annualized rate of spinal cord atrophy was significantly higher in patients who developed MS compared to those who remained CIS. The change in the upper cervical cord CSA was independently associated with EDSS at follow-up. The prognostic value of spinal cord atrophy on subsequent disability was also evaluated in a cohort of 352 patients across different MS phenotypes (RRMS: 256, SPMS: 73, PPMS: 23) with clinical and MRI evaluations at baseline, 12 months and 24 months [95]. Baseline upper cervical cord CSA and the number of spinal cord segments presenting lesions at baseline were found to be relevant contributors of disease progression at 2 years. A progressive upper cervical cord atrophy was found in all MS subtypes at 24 months, but a higher rate of cervical spinal cord volume loss was observed in patients with disease progression after 24 months (-2.3% per year) compared to stable patients (-1.2% per year). In another study including 231 MS patients with 5 years follow-up, the cervical spinal cord volume was found to be the strongest MRI predictor for EDSS score change. An increase of 1% of the annual spinal cord volume loss rate was associated with an increase of 28% of the risk progression in the following year [101].

### **Quantitative MRI techniques**

Different quantitative MRI techniques have been applied to the spinal cord in MS patients, in order to assess the microstructure (demyelination, axonal loss) inside and outside focal lesions. These techniques include diffusion imaging, magnetization transfer imaging (MTI), magnetic resonance spectroscopy and functional MRI. They remain technically challenging, and limited to a research context. Their general principles and the components being evaluated are summarized in Table 1. To date, only a limited number of studies have used these techniques for prognostic purposes. These are summarized in Table 2.

### **Conclusion**

Spinal cord MRI is performed far less frequently than brain MRI in MS patients mainly owing to technical limitations. Recent improvements in MRI acquisition protocols should lead to the growing use of spinal cord MRI in clinical practice in the near future [114, 115].

Spinal cord involvement is frequently observed in patients with MS, and has a clear diagnostic and prognostic value. In particular, the prognostic value of spinal cord lesions is clearly established at the onset of disease, in RIS, CIS and early RRMS patients. Spinal cord

lesions are associated with an increased risk of conversion to MS, aggravation of disability and conversion to progressive phenotype. Later in the disease, studies are lacking to affirm the prognostic role of spinal cord lesions and therefore the added value of regular follow-up with spinal cord MRI. Spinal cord atrophy, as measured by loss of cervical spinal cord area, is also associated with disability progression, independently of other clinical and MRI factors including spinal cord lesions. Although potentially interesting, this measurement is not currently performed as a routine clinical procedure. Finally, other measures extracted from quantitative MRI have been established as valuable for a better understanding of the pathophysiology of MS, but remain a field of research.

### **Disclosures of interest**

S Leguy, B Combès, E Bannier and A Kerbrat have nothing to disclose

## References :

- [1] Stroman PW, Wheeler-Kingshott C, Bacon M, Schwab JM, Bosma R, Brooks J, et al. The current state-of-the-art of spinal cord imaging: Methods. *NeuroImage* 2014;84:1070–81. <https://doi.org/10.1016/j.neuroimage.2013.04.124>.
- [2] Lycklama G, Thompson A, Filippi M, Miller D, Polman C, Fazekas F, et al. Spinal-cord MRI in multiple sclerosis. *Lancet Neurol* 2003;2(9):555-62. [https://doi.org/10.1016/s1474-4422\(03\)00504-0](https://doi.org/10.1016/s1474-4422(03)00504-0).
- [3] Bot JCJ, Barkhof F, Polman CH, Lycklama à Nijeholt GJ, de Groot V, Bergers E, et al. Spinal cord abnormalities in recently diagnosed MS patients: added value of spinal MRI examination. *Neurology* 2004;62:226–33. <https://doi.org/10.1212/wnl.62.2.226>.
- [4] Katz Sand I. Classification, diagnosis, and differential diagnosis of multiple sclerosis: Current Opinion in Neurology 2015;28:193–205. <https://doi.org/10.1097/WCO.0000000000000206>.
- [5] Ciccarelli O, Cohen JA, Reingold SC, Weinshenker BG, Amato MP, Banwell B, et al. Spinal cord involvement in multiple sclerosis and neuromyelitis optica spectrum disorders. *The Lancet Neurology* 2019;18:185–97. [https://doi.org/10.1016/S1474-4422\(18\)30460-5](https://doi.org/10.1016/S1474-4422(18)30460-5).
- [6] Weinshenker BG, Gilbert JJ, Ebers GC. Some clinical and pathologic observations on chronic myelopathy: a variant of multiple sclerosis. *Journal of Neurology, Neurosurgery & Psychiatry* 1990;53:146–9. <https://doi.org/10.1136/jnnp.53.2.146>.
- [7] Lattanzi S, Schmalstieg WF. Solitary sclerosis: Progressive myelopathy from solitary demyelinating lesion. *Neurology* 2012;79:393–393. <https://doi.org/10.1212/01.wnl.0000418061.10382.f7>.
- [8] Lattanzi S, Logullo F, Di Bella P, Silvestrini M, Provinciali L. Multiple sclerosis, solitary sclerosis or something else? *Mult Scler* 2014;20:1819–24. <https://doi.org/10.1177/1352458514535129>.
- [9] Cohen M, Lebrun C, Ayrignac X, Labauge P, Assouad R. Solitary sclerosis: Experience from three French tertiary care centres. *Mult Scler* 2015;21:1216–1216. <https://doi.org/10.1177/1352458515570405>.
- [10] Keegan BM, Kaufmann TJ, Weinshenker BG, Kantarci OH, Schmalstieg WF, Paz Soldan MM, et al. Progressive solitary sclerosis: Gradual motor impairment from a single CNS demyelinating lesion. *Neurology* 2016;87:1713–9. <https://doi.org/10.1212/WNL.00000000000003235>.
- [11] McDonald WI, Compston A, Edan G, Goodkin D, Hartung H-P, Lublin FD, et al. Recommended diagnostic criteria for multiple sclerosis: Guidelines from the international panel on the diagnosis of multiple sclerosis. *Ann Neurol* 2001;50:121–7. <https://doi.org/10.1002/ana.1032>.
- [12] Thompson AJ, Banwell BL, Barkhof F, Carroll WM, Coetzee T, Comi G, et al. Diagnosis of multiple sclerosis: 2017 revisions of the McDonald criteria. *The Lancet Neurology* 2018;17:162–73. [https://doi.org/10.1016/S1474-4422\(17\)30470-2](https://doi.org/10.1016/S1474-4422(17)30470-2).
- [13] Ikuta F, Zimmerman HM. Distribution of plaques in seventy autopsy cases of multiple sclerosis in the United States. *Neurology* 1976;26:26–8. [https://doi.org/10.1212/wnl.26.6\\_part\\_2.26](https://doi.org/10.1212/wnl.26.6_part_2.26).
- [14] Nijeholt GJ, Bergers E, Kamphorst W, Bot J, Nicolay K, Castelijns JA, et al. Post-mortem high-resolution MRI of the spinal cord in multiple sclerosis: a correlative study with conventional MRI, histopathology and clinical phenotype. *Brain* 2001;124:154–66. <https://doi.org/10.1093/brain/124.1.154>.
- [15] Bergers E, Bot JCJ, Valk P van der, Castelijns JA, Nijeholt GJLA, Kamphorst W, et al. Diffuse signal abnormalities in the spinal cord in multiple sclerosis: Direct postmortem in situ magnetic resonance imaging correlated with in vitro high-resolution magnetic resonance imaging and histopathology. *Annals of Neurology* 2002;51:652–6. <https://doi.org/10.1002/ana.10170>.
- [16] Bot JCJ, Blezer ELA, Kamphorst W, Lycklama à Nijeholt GJ, Ader HJ, Castelijns JA,

- et al. The Spinal Cord in Multiple Sclerosis: Relationship of High-Spatial-Resolution Quantitative MR Imaging Findings to Histopathologic Results. *Radiology* 2004;233:531–40. <https://doi.org/10.1148/radiol.2332031572>.
- [17] Gilmore CP, Bö L, Owens T, Lowe J, Esiri MM, Evangelou N. Spinal Cord Gray Matter Demyelination in Multiple Sclerosis—A Novel Pattern of Residual Plaque Morphology. *Brain Pathology* 2006;16:202–8. <https://doi.org/10.1111/j.1750-3639.2006.00018.x>.
- [18] Petrova N, Carassiti D, Altmann DR, Baker D, Schmierer K. Axonal loss in the multiple sclerosis spinal cord revisited. *Brain Pathology* 2018;28:334–48. <https://doi.org/10.1111/bpa.12516>.
- [19] DeLuca GC, Williams K, Evangelou N, Ebers GC, Esiri MM. The contribution of demyelination to axonal loss in multiple sclerosis. *Brain* 2006;129:1507–16. <https://doi.org/10.1093/brain/awl074>.
- [20] Tartaglino LM, Friedman DP, Flanders AE, Lublin FD, Knobler RL, Liem M. Multiple sclerosis in the spinal cord: MR appearance and correlation with clinical parameters. *Radiology* 1995;195:725–32. <https://doi.org/10.1148/radiology.195.3.7754002>.
- [21] Nijeholt GJ, van Walderveen MA, Castelijns JA, van Waesberghe JH, Polman C, Scheltens P, et al. Brain and spinal cord abnormalities in multiple sclerosis. Correlation between MRI parameters, clinical subtypes and symptoms. *Brain* 1998;121 ( Pt 4):687–97. <https://doi.org/10.1093/brain/121.4.687>.
- [22] Agosta F, Absinta M, Sormani MP, Ghezzi A, Bertolotto A, Montanari E, et al. In vivo assessment of cervical cord damage in MS patients: a longitudinal diffusion tensor MRI study. *Brain* 2007;130:2211–9. <https://doi.org/10.1093/brain/awm110>.
- [23] Hittmair K, Mallek R, Prayer D, Schindler EG, Kollegger H. Spinal cord lesions in patients with multiple sclerosis: comparison of MR pulse sequences. *AJNR Am J Neuroradiol* 1996;17:1555–65.
- [24] Bot JCJ, Barkhof F, Lycklama à Nijeholt GJ, Bergers E, Polman CH, Adèr HJ, et al. Comparison of a conventional cardiac-triggered dual spin-echo and a fast STIR sequence in detection of spinal cord lesions in multiple sclerosis. *European Radiology* 2000;10:753–8. <https://doi.org/10.1007/s003300050998>.
- [25] Campi A, Pontesilli S, Gerevini S, Scotti G. Comparison of MRI pulse sequences for investigation of lesions of the cervical spinal cord. *Neuroradiology* 2000;42:669–75. <https://doi.org/10.1007/s002340000368>.
- [26] Poonawalla AH, Hou P, Nelson FA, Wolinsky JS, Narayana PA. Cervical Spinal Cord Lesions in Multiple Sclerosis: T1-weighted Inversion-Recovery MR Imaging with Phase-Sensitive Reconstruction. *Radiology* 2008;246:258–64. <https://doi.org/10.1148/radiol.2463061900>.
- [27] Kearney H, Miszkiel KA, Yiannakas MC, Ciccarelli O, Miller DH. A pilot MRI study of white and grey matter involvement by multiple sclerosis spinal cord lesions. *Multiple Sclerosis and Related Disorders* 2013;2:103–8. <https://doi.org/10.1016/j.msard.2012.09.005>.
- [28] Alcaide-Leon P, Pauranik A, Alshafai L, Rawal S, Oh J, Montanera W, et al. Comparison of Sagittal FSE T2, STIR, and T1-Weighted Phase-Sensitive Inversion Recovery in the Detection of Spinal Cord Lesions in MS at 3T. *American Journal of Neuroradiology* 2016;37:970–5. <https://doi.org/10.3174/ajnr.A4656>.
- [29] Nair G, Absinta M, Reich DS. Optimized T1-MPRAGE Sequence for Better Visualization of Spinal Cord Multiple Sclerosis Lesions at 3T. *AJNR Am J Neuroradiol* 2013;34:2215–22. <https://doi.org/10.3174/ajnr.A3637>.
- [30] Breckwoldt MO, Gradl J, Hähnel S, Hielscher T, Wildemann B, Diem R, et al. Increasing the sensitivity of MRI for the detection of multiple sclerosis lesions by long axial coverage of the spinal cord: a prospective study in 119 patients. *J Neurol* 2017;264:341–9. <https://doi.org/10.1007/s00415-016-8353-3>.
- [31] Weier K, Mazraeh J, Naegelin Y, Thoeni A, Hirsch JG, Fabbro T, et al. Biplanar MRI for the assessment of the spinal cord in multiple sclerosis. *Mult Scler* 2012;18:1560–9. <https://doi.org/10.1177/1352458512442754>.
- [32] Galler S, Stellmann J-P, Young KL, Kutzner D, Heesen C, Fiehler J, et al. Improved

- Lesion Detection by Using Axial T2-Weighted MRI with Full Spinal Cord Coverage in Multiple Sclerosis. *AJNR Am J Neuroradiol* 2016;37:963–9.  
<https://doi.org/10.3174/ajnr.A4638>.
- [33] Filippi M, Preziosa P, Banwell BL, Barkhof F, Ciccarelli O, De Stefano N, et al. Assessment of lesions on magnetic resonance imaging in multiple sclerosis: practical guidelines. *Brain* 2019;142:1858–75. <https://doi.org/10.1093/brain/awz144>.
- [34] Bergers E, Bot JCJ, De Groot CJA, Polman CH, Lycklama a Nijeholt GJ, Castelijns JA, et al. Axonal damage in the spinal cord of MS patients occurs largely independent of T2 MRI lesions. *Neurology* 2002;59:1766–71.  
<https://doi.org/10.1212/01.WNL.0000036566.00866.26>.
- [35] Gilmore CP, Geurts JGG, Evangelou N, Bot JCJ, van Schijndel RA, Pouwels PJW, et al. Spinal cord grey matter lesions in multiple sclerosis detected by post-mortem high field MR imaging. *Mult Scler* 2009;15:180–8.  
<https://doi.org/10.1177/1352458508096876>.
- [36] Lovas G, Szilagyi N, Majtenyi K, Palkovits M, Komoly S. Axonal changes in chronic demyelinated cervical spinal cord plaques. *Brain* 2000;123:308–17.  
<https://doi.org/10.1093/brain/123.2.308>.
- [37] Barkhof F. The clinico-radiological paradox in multiple sclerosis revisited: Current Opinion in Neurology 2002;15:239–45. <https://doi.org/10.1097/00019052-200206000-00003>.
- [38] Bisulca J, De Lury A, Coyle PK, Syrityna O, Peyster R, Bangiyev L, et al. MRI features associated with high likelihood of conversion of radiologically isolated syndrome to multiple sclerosis. *Mult Scler Relat Disord* 2019;36:101381.  
<https://doi.org/10.1016/j.msard.2019.101381>.
- [39] Lebrun C, Bensa C, Debouverie M, Wiertlevski S, Brassat D, Seze J de, et al. Association Between Clinical Conversion to Multiple Sclerosis in Radiologically Isolated Syndrome and Magnetic Resonance Imaging, Cerebrospinal Fluid, and Visual Evoked Potential: Follow-up of 70 Patients. *Arch Neurol* 2009;66:841–6.  
<https://doi.org/10.1001/archneurol.2009.119>.
- [40] De Stefano N, Stromillo ML, Rossi F, Battaglini M, Giorgio A, Portaccio E, et al. Improving the characterization of radiologically isolated syndrome suggestive of multiple sclerosis. *PLoS ONE* 2011;6:e19452.  
<https://doi.org/10.1371/journal.pone.0019452>.
- [41] De Stefano N, Giorgio A, Tintoré M, Pia Amato M, Kappos L, Palace J, et al. Radiologically isolated syndrome or subclinical multiple sclerosis: MAGNIMS consensus recommendations. *Mult Scler* 2018;24:214–21.  
<https://doi.org/10.1177/1352458517717808>.
- [42] Okuda DT, Mowry EM, Cree BAC, Crabtree EC, Goodin DS, Waubant E, et al. Asymptomatic spinal cord lesions predict disease progression in radiologically isolated syndrome. *Neurology* 2011;76:686–92.  
<https://doi.org/10.1212/WNL.0b013e31820d8b1d>.
- [43] Okuda DT, Siva A, Kantarci O, Inglese M, Katz I, Tutuncu M, et al. Radiologically Isolated Syndrome: 5-Year Risk for an Initial Clinical Event. *PLoS ONE* 2014;9:e90509. <https://doi.org/10.1371/journal.pone.0090509>.
- [44] Maia ACM, Rocha AJ da, Barros BR, Tilbery CP. Incidental demyelinating inflammatory lesions in asymptomatic patients: a Brazilian cohort with radiologically isolated syndrome and a critical review of current literature. *Arq Neuropsiquiatr* 2012;70:5–11. <https://doi.org/10.1590/s0004-282x2012000100003>.
- [45] Kantarci OH, Lebrun C, Siva A, Keegan MB, Azevedo CJ, Inglese M, et al. Primary Progressive Multiple Sclerosis Evolving From Radiologically Isolated Syndrome: Preprogressive Phase of PPMS. *Ann Neurol* 2016;79:288–94.  
<https://doi.org/10.1002/ana.24564>.
- [46] Makhani N, Lebrun C, Siva A, Brassat D, Carra Dallièrè C, de Seze J, et al. Radiologically isolated syndrome in children: Clinical and radiologic outcomes. *Neurol Neuroimmunol Neuroinflamm* 2017;4:e395.

- <https://doi.org/10.1212/NXI.0000000000000395>.
- [47] Thouvenot E, Hinsinger G, Demattei C, Uygunoglu U, Castelnovo G, Pittion-Vouyovitch S, et al. Cerebrospinal fluid chitinase-3-like protein 1 level is not an independent predictive factor for the risk of clinical conversion in radiologically isolated syndrome. *Mult Scler* 2019;25:669–77. <https://doi.org/10.1177/1352458518767043>.
- [48] Cordonnier C, de Seze J, Breteau G, Ferriby D, Michelin E, Stojkovic T, et al. Prospective study of patients presenting with acute partial transverse myelopathy. *J Neurol* 2003;250:1447–52. <https://doi.org/10.1007/s00415-003-0242-x>.
- [49] Minneboo A, Barkhof F, Polman CH, Uitdehaag BMJ, Knol DL, Castelijns JA. Infratentorial lesions predict long-term disability in patients with initial findings suggestive of multiple sclerosis. *Arch Neurol* 2004;61:217–21. <https://doi.org/10.1001/archneur.61.2.217>.
- [50] Swanton JK, Fernando KT, Dalton CM, Miszkiel KA, Altmann DR, Plant GT, et al. Early MRI in optic neuritis: The risk for disability. *Neurology* 2009;72:542–50. <https://doi.org/10.1212/01.wnl.0000341935.41852.82>.
- [51] Patrucco L, Rojas JI, Cristiano E. Assessing the value of spinal cord lesions in predicting development of multiple sclerosis in patients with clinically isolated syndromes. *J Neurol* 2012;259:1317–20. <https://doi.org/10.1007/s00415-011-6345-x>.
- [52] Sombekke MH, Wattjes MP, Balk LJ, Nielsen JM, Vrenken H, Uitdehaag BMJ, et al. Spinal cord lesions in patients with clinically isolated syndrome: A powerful tool in diagnosis and prognosis. *Neurology* 2013;80:69–75. <https://doi.org/10.1212/WNL.0b013e31827b1a67>.
- [53] Brownlee WJ, Altmann DR, Alves Da Mota P, Swanton JK, Miszkiel KA, Wheeler-Kingshott CG, et al. Association of asymptomatic spinal cord lesions and atrophy with disability 5 years after a clinically isolated syndrome. *Mult Scler* 2017;23:665–74. <https://doi.org/10.1177/1352458516663034>.
- [54] Arrambide G, Rovira A, Sastre-Garriga J, Tur C, Castelló J, Río J, et al. Spinal cord lesions: A modest contributor to diagnosis in clinically isolated syndromes but a relevant prognostic factor. *Mult Scler* 2018;24:301–12. <https://doi.org/10.1177/1352458517697830>.
- [55] Brownlee WJ, Altmann DR, Prados F, Miszkiel KA, Eshaghi A, Gandini Wheeler-Kingshott CAM, et al. Early imaging predictors of long-term outcomes in relapse-onset multiple sclerosis. *Brain* 2019;142:2276–87. <https://doi.org/10.1093/brain/awz156>.
- [56] Tintore M, Rovira A, Arrambide G, Mitjana R, Río J, Auger C, et al. Brainstem lesions in clinically isolated syndromes. *Neurology* 2010;75:1933–8. <https://doi.org/10.1212/WNL.0b013e3181feb26f>.
- [57] Honig LS, Sheremata WA. Magnetic resonance imaging of spinal cord lesions in multiple sclerosis. *J Neurol Neurosurg Psychiatry* 1989;52:459–66.
- [58] Trop I, Bourgouin PM, Lapierre Y, Duquette P, Wolfson CM, Duong HD, et al. Multiple Sclerosis of the Spinal Cord: Diagnosis and Follow-up with Contrast-Enhanced MR and Correlation with Clinical Activity 1998:9.
- [59] Coret F, Bosca I, Landete L, Magraner MJ, Navarré A, León JL, et al. Early diffuse demyelinating lesion in the cervical spinal cord predicts a worse prognosis in relapsing-remitting multiple sclerosis. *Mult Scler* 2010;16:935–41. <https://doi.org/10.1177/1352458510371960>.
- [60] Kearney H, Altmann DR, Samson RS, Yiannakas MC, Wheeler-Kingshott CAM, Ciccarelli O, et al. Cervical cord lesion load is associated with disability independently from atrophy in MS. *Neurology* 2015;84:367–73. <https://doi.org/10.1212/WNL.0000000000001186>.
- [61] Kearney H, Schneider T, Yiannakas MC, Altmann DR, Wheeler-Kingshott CAM, Ciccarelli O, et al. Spinal cord grey matter abnormalities are associated with secondary progression and physical disability in multiple sclerosis. *J Neurol Neurosurg Psychiatry* 2015;86:608–14. <https://doi.org/10.1136/jnnp-2014-308241>.
- [62] Kearney H, Miszkiel KA, Yiannakas MC, Altmann DR, Ciccarelli O, Miller DH. Grey matter involvement by focal cervical spinal cord lesions is associated with progressive



- multiple sclerosis. *Mult Scler* 2016;22:910–20. <https://doi.org/10.1177/1352458515604905>.
- [63] Valsasina P, Aboulwafa M, Preziosa P, Messina R, Falini A, Comi G, et al. Cervical Cord T1-weighted Hypointense Lesions at MR Imaging in Multiple Sclerosis: Relationship to Cord Atrophy and Disability. *Radiology* 2018;288:234–44. <https://doi.org/10.1148/radiol.2018172311>.
- [64] Eden D, Gros C, Badji A, Dupont SM, De Leener B, Maranzano J, et al. Spatial distribution of multiple sclerosis lesions in the cervical spinal cord. *Brain* 2019;142:633–46. <https://doi.org/10.1093/brain/awy352>.
- [65] Kerbrat A, Gros C, Badji A, Bannier E, Galassi F, Combès B, et al. Multiple sclerosis lesions in motor tracts from brain to cervical cord: spatial distribution and correlation with disability. *Brain* 2020. <https://doi.org/10.1093/brain/awaa162>.
- [66] Zecca C, Disanto G, Sormani M, Riccitelli G, Cianfoni A, Del Grande F, et al. Relevance of asymptomatic spinal MRI lesions in patients with multiple sclerosis. *Mult Scler* 2016;22:782–91. <https://doi.org/10.1177/1352458515599246>.
- [67] D'Amico E, Patti F, Leone C, Lo Fermo S, Zappia M. Negative prognostic impact of MRI spinal lesions in the early stages of relapsing-remitting multiple sclerosis. *Mult Scler J Exp Transl Clin* 2016;2:2055217316631565. <https://doi.org/10.1177/2055217316631565>.
- [68] Stevenson VL, Miller DH, Rovaris M, Barkhof F, Brochet B, Dousset V, et al. Primary and transitional progressive MS: A clinical and MRI cross-sectional study. *Neurology* 1999;52:839–839. <https://doi.org/10.1212/WNL.52.4.839>.
- [69] Filippi M. The role of magnetization transfer and diffusion-weighted MRI in the understanding of multiple sclerosis evolution. *Neurological Sciences* 2000;21:S877–81. <https://doi.org/10.1007/s100720070030>.
- [70] Rovaris M. In vivo assessment of the brain and cervical cord pathology of patients with primary progressive multiple sclerosis. *Brain* 2001;124:2540–9. <https://doi.org/10.1093/brain/124.12.2540>.
- [71] Ingle GT, Stevenson VL, Miller DH, Leary SM, Rovaris M, Barkhof F, et al. Two-year follow-up study of primary and transitional progressive multiple sclerosis. *Mult Scler* 2002;8:108–14. <https://doi.org/10.1191/1352458502ms778oa>.
- [72] Oh J, Zackowski K, Chen M, Newsome S, Saidha S, Smith SA, et al. Multiparametric MRI correlates of sensorimotor function in the spinal cord in multiple sclerosis. *Mult Scler* 2013;19:427–35. <https://doi.org/10.1177/1352458512456614>.
- [73] Healy BC, Buckle GJ, Ali EN, Egorova S, Khalid F, Tauhid S, et al. Characterizing Clinical and MRI Dissociation in Patients with Multiple Sclerosis. *J Neuroimaging* 2017;27:481–5. <https://doi.org/10.1111/jon.12433>.
- [74] Dastagir A, Healy BC, Chua AS, Chitnis T, Weiner HL, Bakshi R, et al. Brain and spinal cord MRI lesions in primary progressive vs. relapsing-remitting multiple sclerosis. *ENeurologicalSci* 2018;12:42–6. <https://doi.org/10.1016/j.ensci.2018.07.002>.
- [75] Valsasina P, Rocca MA, Horsfield MA, Absinta M, Messina R, Caputo D, et al. Regional Cervical Cord Atrophy and Disability in Multiple Sclerosis: A Voxel-based Analysis. *Radiology* 2013;266:853–61. <https://doi.org/10.1148/radiol.12120813>.
- [76] Keegan BM, Kaufmann TJ, Weinshenker BG, Kantarci OH, Schmalstieg WF, Paz Soldan MM, et al. Progressive motor impairment from a critically located lesion in highly restricted CNS-demyelinating disease. *Mult Scler* 2018;24:1445–52. <https://doi.org/10.1177/1352458518781979>.
- [77] Hagström IT, Schneider R, Bellenberg B, Salmen A, Weiler F, Köster O, et al. Relevance of early cervical cord volume loss in the disease evolution of clinically isolated syndrome and early multiple sclerosis: a 2-year follow-up study. *J Neurol* 2017;264:1402–12. <https://doi.org/10.1007/s00415-017-8537-5>.
- [78] Moccia M, Prados F, Filippi M, Rocca MA, Valsasina P, Brownlee WJ, et al. Longitudinal spinal cord atrophy in multiple sclerosis using the generalized boundary shift integral. *Ann Neurol* 2019;86:704–13. <https://doi.org/10.1002/ana.25571>.
- [79] Horsfield MA, Sala S, Neema M, Absinta M, Bakshi A, Sormani MP, et al. Rapid semi-

- automatic segmentation of the spinal cord from magnetic resonance images: application in multiple sclerosis. *Neuroimage* 2010;50:446–55. <https://doi.org/10.1016/j.neuroimage.2009.12.121>.
- [80] Combès B, Kerbrat A, Ferré JC, Callot V, Maranzano J, Badji A, et al. Focal and diffuse cervical spinal cord damage in patients with early relapsing-remitting MS: A multicentre magnetisation transfer ratio study. *Mult Scler* 2019;25:1113–23. <https://doi.org/10.1177/1352458518781999>.
- [81] Brex PA. Measurement of spinal cord area in clinically isolated syndromes suggestive of multiple sclerosis. *Journal of Neurology, Neurosurgery & Psychiatry* 2001;70:544–7. <https://doi.org/10.1136/jnnp.70.4.544>.
- [82] Biberacher V, Boucard CC, Schmidt P, Engl C, Buck D, Berthele A, et al. Atrophy and structural variability of the upper cervical cord in early multiple sclerosis. *Mult Scler* 2015;21:875–84. <https://doi.org/10.1177/1352458514546514>.
- [83] Rocca MA, Horsfield MA, Sala S, Copetti M, Valsasina P, Mesaros S, et al. A multicenter assessment of cervical cord atrophy among MS clinical phenotypes. *Neurology* 2011;76:2096–102. <https://doi.org/10.1212/WNL.0b013e31821f46b8>.
- [84] Rocca MA, Valsasina P, Damjanovic D, Horsfield MA, Mesaros S, Stosic-Opincal T, et al. Voxel-wise mapping of cervical cord damage in multiple sclerosis patients with different clinical phenotypes. *J Neurol Neurosurg Psychiatry* 2013;84:35–41. <https://doi.org/10.1136/jnnp-2012-303821>.
- [85] Rocca MA, Preziosa P, Filippi M. What role should spinal cord MRI take in the future of multiple sclerosis surveillance? *Expert Review of Neurotherapeutics* 2020;0:1–15. <https://doi.org/10.1080/14737175.2020.1739524>.
- [86] Song X, Li D, Qiu Z, Su S, Wu Y, Wang J, et al. Correlation between EDSS scores and cervical spinal cord atrophy at 3T MRI in multiple sclerosis: A systematic review and meta-analysis. *Multiple Sclerosis and Related Disorders* 2020;37:101426. <https://doi.org/10.1016/j.msard.2019.101426>.
- [87] Rashid W. Increasing cord atrophy in early relapsing-remitting multiple sclerosis: a 3 year study. *Journal of Neurology, Neurosurgery & Psychiatry* 2006;77:51–5. <https://doi.org/10.1136/jnnp.2005.068338>.
- [88] Lin X, Blumhardt LD, Constantinescu CS. The relationship of brain and cervical cord volume to disability in clinical subtypes of multiple sclerosis: a three-dimensional MRI study. *Acta Neurol Scand* 2003;108:401–6. <https://doi.org/10.1034/j.1600-0404.2003.00160.x>.
- [89] Furby J, Hayton T, Anderson V, Altmann D, Brenner R, Chataway J, et al. Magnetic resonance imaging measures of brain and spinal cord atrophy correlate with clinical impairment in secondary progressive multiple sclerosis. *Mult Scler* 2008;14:1068–75. <https://doi.org/10.1177/1352458508093617>.
- [90] Kidd D, Thorpe JW, Kendall BE, Barker GJ, Miller DH, McDonald WI, et al. MRI dynamics of brain and spinal cord in progressive multiple sclerosis. *Journal of Neurology, Neurosurgery & Psychiatry* 1996;60:15–9. <https://doi.org/10.1136/jnnp.60.1.15>.
- [91] Ingle GT. Primary progressive multiple sclerosis: a 5-year clinical and MR study. *Brain* 2003;126:2528–36. <https://doi.org/10.1093/brain/awg261>.
- [92] Cohen AB, Neema M, Arora A, Dell’Oglio E, Benedict RHB, Tauhid S, et al. The Relationships among MRI-Defined Spinal Cord Involvement, Brain Involvement, and Disability in Multiple Sclerosis. *Journal of Neuroimaging* 2012;22:122–8. <https://doi.org/10.1111/j.1552-6569.2011.00589.x>.
- [93] Lukas C, Sombekke MH, Bellenberg B, Hahn HK, Popescu V, Bendfeldt K, et al. Relevance of spinal cord abnormalities to clinical disability in multiple sclerosis: MR imaging findings in a large cohort of patients. *Radiology* 2013;269:542–52. <https://doi.org/10.1148/radiol.13122566>.
- [94] Kearney H, Yiannakas MC, Abdel-Aziz K, Wheeler-Kingshott CAM, Altmann DR, Ciccarelli O, et al. Improved MRI quantification of spinal cord atrophy in multiple sclerosis: Cord Atrophy in MS. *J Magn Reson Imaging* 2014;39:617–23.

- <https://doi.org/10.1002/jmri.24194>.
- [95] Lukas C, Knol DL, Sombekke MH, Bellenberg B, Hahn HK, Popescu V, et al. Cervical spinal cord volume loss is related to clinical disability progression in multiple sclerosis. *J Neurol Neurosurg Psychiatry* 2015;86:410–8. <https://doi.org/10.1136/jnnp-2014-308021>.
- [96] Kearney H, Rocca M, Valsasina P, Balk L, Sastre-Garriga J, Reinhardt J, et al. Magnetic resonance imaging correlates of physical disability in relapse onset multiple sclerosis of long disease duration. *Mult Scler* 2014;20:72–80. <https://doi.org/10.1177/1352458513492245>.
- [97] Daams M, Weiler F, Steenwijk MD, Hahn HK, Geurts JJ, Vrenken H, et al. Mean upper cervical cord area (MUCCA) measurement in long-standing multiple sclerosis: Relation to brain findings and clinical disability. *Mult Scler* 2014;20:1860–5. <https://doi.org/10.1177/1352458514533399>.
- [98] Bernitsas E, Bao F, Seraji-Bozorgzad N, Chorostecki J, Santiago C, Tselis A, et al. Spinal cord atrophy in multiple sclerosis and relationship with disability across clinical phenotypes. *Mult Scler Relat Disord* 2015;4:47–51. <https://doi.org/10.1016/j.msard.2014.11.002>.
- [99] Schlaeger R, Papinutto N, Panara V, Bevan C, Lobach IV, Bucci M, et al. Spinal cord gray matter atrophy correlates with multiple sclerosis disability: GM Atrophy and MS Disability. *Ann Neurol* 2014;76:568–80. <https://doi.org/10.1002/ana.24241>.
- [100] Casserly C, Seyman EE, Alcaide-Leon P, Guenette M, Lyons C, Sankar S, et al. Spinal Cord Atrophy in Multiple Sclerosis: A Systematic Review and Meta-Analysis: Spinal Cord Atrophy in Multiple Sclerosis: Systematic Review. *Journal of Neuroimaging* 2018;28:556–86. <https://doi.org/10.1111/jon.12553>.
- [101] Tsagkas C, Magon S, Gaetano L, Pezold S, Naegelin Y, Amann M, et al. Spinal cord volume loss: A marker of disease progression in multiple sclerosis. *Neurology* 2018;91:e349–58. <https://doi.org/10.1212/WNL.0000000000005853>.
- [102] Schmierer K, Wheeler-Kingshott CAM, Boulby PA, Scaravilli F, Altmann DR, Barker GJ, et al. Diffusion tensor imaging of post mortem multiple sclerosis brain. *NeuroImage* 2007;35:467–77. <https://doi.org/10.1016/j.neuroimage.2006.12.010>.
- [103] Budde MD, Kim JH, Liang H-F, Russell JH, Cross AH, Song S-K. Axonal injury detected by in vivo diffusion tensor imaging correlates with neurological disability in a mouse model of multiple sclerosis. *NMR Biomed* 2008;21:589–97. <https://doi.org/10.1002/nbm.1229>.
- [104] Boretius S, Escher A, Dallenga T, Wrzos C, Tammer R, Brück W, et al. Assessment of lesion pathology in a new animal model of MS by multiparametric MRI and DTI. *NeuroImage* 2012;59:2678–88. <https://doi.org/10.1016/j.neuroimage.2011.08.051>.
- [105] Klawiter EC, Schmidt RE, Trinkaus K, Liang H-F, Budde MD, Naismith RT, et al. Radial diffusivity predicts demyelination in ex vivo multiple sclerosis spinal cords. *NeuroImage* 2011;55:1454–60. <https://doi.org/10.1016/j.neuroimage.2011.01.007>.
- [106] Dousset V, Grossman RI, Ramer KN, Schnall MD, Young LH, Gonzalez-Scarano F, et al. Experimental allergic encephalomyelitis and multiple sclerosis: lesion characterization with magnetization transfer imaging. *Radiology* 1992;182:483–91. <https://doi.org/10.1148/radiology.182.2.1732968>.
- [107] Bjartmar C, Kidd G, Mörk S, Rudick R, Trapp BD. Neurological disability correlates with spinal cord axonal loss and reduced N-acetyl aspartate in chronic multiple sclerosis patients. *Ann Neurol* 2000;48:893–901.
- [108] Stroman PW, Ryner LN. Functional MRI of motor and sensory activation in the human spinal cord. *Magnetic Resonance Imaging* 2001;19:27–32. [https://doi.org/10.1016/S0730-725X\(01\)00226-0](https://doi.org/10.1016/S0730-725X(01)00226-0).
- [109] Charil A, Caputo D, Cavarretta R, Sormani MP, Ferrante P, Filippi M. Cervical cord magnetization transfer ratio and clinical changes over 18 months in patients with relapsing-remitting multiple sclerosis: a preliminary study. *Mult Scler* 2006;12:662–5. <https://doi.org/10.1177/1352458506070714>.
- [110] Oh J, Chen M, Cybulsky K, Suthiphosuwat S, Seyman E, Dewey B, et al. Five-year

- longitudinal changes in quantitative spinal cord MRI in multiple sclerosis. *Mult Scler* 2020;1352458520923970. <https://doi.org/10.1177/1352458520923970>.
- [111] Freund P, Wheeler-Kingshott C, Jackson J, Miller D, Thompson A, Ciccarelli O. Recovery after spinal cord relapse in multiple sclerosis is predicted by radial diffusivity. *Mult Scler* 2010;16:1193–202. <https://doi.org/10.1177/1352458510376180>.
- [112] Théaudin M, Saliou G, Ducot B, Deiva K, Denier C, Adams D, et al. Short-term Evolution of Spinal Cord Damage in Multiple Sclerosis: A Diffusion Tensor MRI Study. *Neuroradiology* 2012;54. <https://doi.org/10.1007/s00234-012-1057-1>.
- [113] Ciccarelli O, Altmann DR, McLean MA, Wheeler-Kingshott CA, Wimpey K, Miller DH, et al. Spinal cord repair in MS: does mitochondrial metabolism play a role? *Neurology* 2010;74:721–7. <https://doi.org/10.1212/WNL.0b013e3181d26968>.
- [114] Bellenberg B, Busch M, Trampe N, Gold R, Chan A, Lukas C. <sup>1</sup>H-Magnetic Resonance Spectroscopy in diffuse and focal cervical cord lesions in Multiple Sclerosis. *Eur Radiol* 2013;23:3379–92. <https://doi.org/10.1007/s00330-013-2942-7>.
- [115] Yetkin MF, Mirza M, Dönmez H. Monitoring interferon  $\beta$  treatment response with magnetic resonance spectroscopy in relapsing remitting multiple sclerosis. *Medicine (Baltimore)* 2016;95:e4782. <https://doi.org/10.1097/MD.0000000000004782>.

**Table 1** : Quantitative MRI techniques

Technique	Principle – Based on	Parameter	Association with the microstructure
DTI	Molecular diffusion of water, constrained by the anatomy, i.e. white matter bundles.  Voxel-based information about the orientation and anisotropy of WM bundles in the brain or spinal cord, and thus about their integrity.	MD: mean water diffusivity	Post-mortem evidence of association with gliosis [100]
		FA: fractional (degree of) anisotropy of the diffusion directions (zero : isotropic diffusion, increases when anisotropic)	Association with axonal pathology [100]
		AD: axial diffusivity : diffusion along the principal axis of diffusion	Association with acute axonal loss in experimental model of MS [101,102]
		RD: radial diffusivity, orthogonal to the principal axis of diffusion	Association with demyelination in ex vivo spinal cords [103]
MTI	Proton mobility, depending on environment (free water <sup>1</sup> H/rotationally-restricted <sup>1</sup> H linked within macromolecules i.e with myelin in WM). Application of a magnetization transfer (MT) radiofrequency pulse to saturate the magnetization of linked <sup>1</sup> H then transferred to free water <sup>1</sup> H, reducing the measured signal intensity.	MTR: magnetization transfer ratio	Association with demyelination [16] and with inflammation [104]

<sup>1</sup> H-MRS	Quantify metabolite relative concentrations reflecting specific pathological processes	NAA: marker for neuronal metabolism	Reduced NAA level correlates with axonal loss [105]
fMRI	T2* signal changes reflecting the local blood flow and oxygenation changes with neuronal activity	BOLD contrast	Provides an indirect mapping of neuronal activity [106]

AD (axial diffusivity); BOLD (Blood Oxygen Level Dependent); DTI (diffusion tensor imaging); fMRI (functional MRI); <sup>1</sup>H-MRS (proton magnetic resonance spectroscopy); MD (mean diffusivity); MTI (magnetization transfer imaging); MTR (magnetization transfer ratio); NAA (N-acetylaspartate ); RD (radial diffusivity)

**Table 2:** Quantitative spinal cord MRI and prognostic studies

Study	Patients	Longitudinal	Main results
<b>MTR</b>			
<u>Charil and al., 2006</u> Cervical cord magnetization transfer ratio and clinical changes over 18 months in patients with RRMS: a preliminary study. [107]	14 RRMS	<u>18 months</u> - At baseline: MRI, EDSS - At 18 months: EDSS, relapses	Baseline average cervical cord MTR was correlated with relapse rate during follow-up.
<u>Oh and al., 2020</u> Five-year longitudinal changes in quantitative spinal cord MRI in MS [108]	75 MS - 45 RRMS - 30 PMS	<u>5 years</u> At baseline, 1.8 year, 5 years : clinical data (EDSS), MRI	At 2 years, MTR decreased ( $p = 0.04$ ) and at 5 years, both MTR ( $p = 0.03$ ) and spinal cord CSA ( $p = 0.009$ ) decreased. Robust correlations were found between the 2-year trajectories of change in quantitative spinal cord MRI measures and 5-year trajectories of change.
<b>DTI</b>			
<u>Agosta and al., 2007</u> In vivo assessment of spinal cord damage in MS patients: a longitudinal DT MRI study [22]	42 MS - 13 RRMS - 14 SPMS - 15 PPMS 9 HCs	<u>2.4 years</u> At baseline and after a mean follow-up of 2.4years : clinical data (EDSS), MRI	Baseline spinal cord cross-sectional area ( $r = -0.40$ , $p = 0.01$ ) and FA ( $r = -0.40$ , $p = 0.03$ ) was correlated with increase in disability at follow-up.
<u>Freund and al., 2010</u> Recovery after spinal cord relapse in MS is predicted by radial diffusivity [109]	14 MS with acute lesion 13 HCs	<u>6 months</u> At baseline, 1, 3, 6 months: clinical data (EDSS, 9HPT, TWT), MRI	Lower radial diffusivity of the spinal cord corticospinal tract at onset of spinal cord relapse was associated with better clinical outcome.
<u>Théaudin and al., 2012</u> Short-term evolution of spinal cord damage in MS: a DT MRI study [110]	16 RRMS with acute lesion	<u>3 months</u> At baseline and 3 months : clinical data (EDSS, ASIA), MRI	A baseline less marked decrease in FA value and more marked decrease in radial diffusivity inside the inflammatory lesion were associated with better clinical outcome.

<u>Oh and al., 2020</u> Five-year longitudinal changes in quantitative spinal cord MRI in MS [108]	75 MS - 45 RRMS - 30 PMS	<u>5 years</u> At baseline, 1.8 year, 5 years : clinical data (EDSS, MSFC), MRI	Results found a limited correlation between changes in DTI metrics and disability, not statistically significant, but robust correlations between the 2-year trajectories of change of quantitative spinal cord MRI measures and 5-year trajectories of change ( $r = 0.97$ ( $p < 0.001$ ) for FA; $r = 0.75$ ( $p < 0.001$ ) for mean diffusivity; $r = 0.97$ ( $p < 0.001$ ) for axial diffusivity).
MR spectroscopy			
<u>Ciccarelli and al., 2010</u> Spinal cord repair in MS: does mitochondrial metabolism play a role? [111]	14 MS - 13 RRMS - 1 SPMS 13 HCs	<u>6 months</u> At baseline and at 1, 3, and 6 months : clinical data (EDSS), MRI	Patients who recovered showed a sustained increase in NAA after 1 month. In the whole patient group, a greater increase of NAA after 1 month was associated with greater clinical recovery.
<u>Bellenberg and al., 2013</u> 1H-MR spectroscopy in diffuse and focal cervical cord lesions in MS [112]	22 MS patients with persistent spinal cord symptoms. 17 HCs	<u>24 months</u> - MS: At baseline and 12 months, +/- 24 months if available : clinical data (EDSS, TWT and 9HPT), MR (MRS) - HC : baseline and 6 months : MRI/S	NAA/Cr at baseline was associated significantly with cord atrophy and with disability progression during follow-up.
<u>Yetkin and al., 2016</u> Monitoring interferon $\beta$ treatment response with MRS in RRMS [113]	36 RRMS recently diagnosed, never treated with interferon $\beta$ . 15 HCs	<u>12 months</u> - MS : Before, at 6 and 12 months after the initiation of treatment : clinical data (EDSS), MRS - HCs : MRS	In patients treated with interferon $\beta$ NAA/Cr ratios remained stable. No significant correlation between EDSS scores and MRS metabolite ratios at baseline or during follow-up
fMRI			
No longitudinal study found			

DTI (diffusion tensor imaging); EDSS (Expanded Disability Status Scale); MRS (magnetic resonance spectroscopy); MTI (magnetization transfer imaging); MTR (magnetization transfer ratio); NAA/Cr (N-acetylaspartate/Creatinine); PPMS (primary progressive MS); RRMS (relapsing remitting MS); SPMS (secondary progressive MS); TWT (Timed 25-Foot Walk test); 9HPT= (9-Hole Peg Test).



**Legend of figure 1**

**Figure 1:** Visualization of spinal cord MS lesions using different conventional sequences available in clinical practice. A : sagittal T2 TSE ; B : sagittal T1 MPRAGE ; C : sagittal PSIR; D : axial T2 TSE ; E : axial T1+ GADOLINIUM; F : sagittal STIR

