

# **Cervical cord atrophy and long-term disease progression in primary progressive multiple sclerosis patients**

## **Authors**

F.X. Aymerich<sup>1, 3, \*</sup> PhD, C. Auger<sup>1</sup> MD, J. Alonso<sup>1</sup> PhD, M. Alberich<sup>1</sup> RT, J. Sastre-Garriga<sup>2</sup> PhD, X. Montalban<sup>2</sup> PhD, A. Rovira<sup>1</sup> MD

## **Affiliations**

1. Magnetic Resonance Unit, Department of Radiology, Hospital Universitari Vall d'Hebron, Universitat Autònoma de Barcelona, Barcelona, Spain.
2. Centre d'Esclerosi Múltiple de Catalunya (Cemcat), Department of Neurology/Neuroimmunology, Hospital Universitari Vall d'Hebron, Universitat Autònoma de Barcelona, Barcelona, Spain
3. Department of Automatic Control (ESAII), Universitat Politècnica de Catalunya – Barcelona Tech (UPC), Barcelona, Spain.

## **\*Corresponding author address:**

F. Xavier Aymerich

Magnetic Resonance Unit (IDI), Hospital Universitari Vall d'Hebron

P. Vall d'Hebron 119-129, 08035 Barcelona (Spain)

Tel.: +34934289406

Fax: +34934386059

e-mail: xavier.aymerich@idi.gencat.cat

## **ABSTRACT**

**BACKGROUND AND OBJECTIVE:** Cervical cord atrophy has been associated with clinical disability in multiple sclerosis and is proposed as an outcome measure of neurodegeneration. The aim of this study was to quantify the development of cervical cord atrophy and to evaluate its association with disability progression in patients with primary progressive multiple sclerosis (PPMS).

**MATERIALS AND METHODS:** 31 patients with PPMS underwent 1.5 T brain and spinal cord MRI examination at baseline and at 6-7 years later. The cervical spinal cord from C1 to C5 was segmented to evaluate the normalized overall cross-sectional area (CSA) and the CSA of C2-C3, C3-C4, and C4-C5. The annualized rates of normalized CSA loss were also evaluated. To estimate clinical progression, the expanded disability status scale (EDSS) score was determined at baseline, and at 2 and 14 years after baseline to compute the normalized area under the curve of the EDSS (NAUCEDSS) and the EDSS changes from baseline to the follow-up time points. Associations between the cord CSA and brain MRI and clinical measures were also investigated. Finally, the value of all these measures for predicting long-term disability was evaluated.

**RESULTS:** Some normalized CSA measurements showed moderate correlations with NAUCEDSS, ranging from -0.439 to -0.359 ( $p < 0.05$ ). Moreover, the annualized rate of the normalized mean CSA loss and the baseline EDSS were independent predictors of long-term disability progression.

**CONCLUSIONS:** These data indicate that development of cervical cord atrophy is associated with progression of disability and is predictive of this event in primary progressive MS patients.

## **ABBREVIATIONS**

CSA, cross-sectional area; EDSS, Expanded Disability Status Scale; MS, multiple sclerosis; PPMS, primary progressive multiple sclerosis

## INTRODUCTION

Primary progressive multiple sclerosis (PPMS) is characterized by sustained progression of disability from disease onset and is typically associated with severe motor impairment.<sup>1,2</sup> The rate at which disability progresses is highly variable, but impairment occurs faster early in the disease course and reflects, in part, neuroaxonal loss and spinal cord dysfunction.<sup>3</sup>

The spinal cord is a clinically relevant site of the central nervous system and is often affected in multiple sclerosis (MS). Focal and diffuse cord abnormalities, particularly in the cervical cord segment, have been described in up to 90% of MS patients.<sup>4</sup> MRI measurement of cervical cord atrophy in patients with this disease provides valuable additional information related to disability that cannot be obtained from brain metrics.<sup>5</sup>

A progressive reduction of the cervical cord cross-sectional area (CSA) occurs in PPMS,<sup>6-9</sup> and spinal cord atrophy has been shown to correlate with the severity of clinical disability.<sup>10-12</sup> Moreover, some cross-sectional studies have reported that spinal cord atrophy is an independent predictor of disability progression.<sup>11,12</sup>

Nonetheless, the relationship between spinal cord area changes and worsening of disability has not been consistent between studies: some authors describe an association,<sup>6,9</sup> whereas others do not.<sup>7,8</sup> This discrepancy may be explained by several factors, such as differing sample sizes, follow-up periods, and methods used to measure the cord CSA.<sup>7,13-15</sup>

Although some cross-sectional studies<sup>11,12</sup> have demonstrated the value of spinal cord atrophy as an independent predictor of clinical outcome, only a few longitudinal studies<sup>9,16,17</sup> have specifically focused on analyzing the clinical relevance of this finding in MS patients, and these include a short follow-up or were not focused on PPMS.

Another factor to be taken into account is the method used for measuring the cervical cord CSA, as the optimal approach has not yet been identified. One of the most recently used is the proposed method of Horsfield et al,<sup>18</sup> based on application of active surface (AS) models and known as the AS method. With this approach, the CSA can be measured at specific levels and along extended portions of the cord with lower variability than other methods used in this region, such as the one proposed by Losseff et al.<sup>10</sup> Some recent studies<sup>11,17,19</sup> have used the AS method for this purpose.

The aim of this study is to quantify the development of cervical cord atrophy and evaluate its association with progression of clinical disability at long-term in patients with PPMS.

## MATERIALS AND METHODS

### Subjects

Thirty-one PPMS patients were included in the study. These patients had been initially enrolled in a 2-year, double-blind, placebo-controlled, phase II pilot study, in which patients with PPMS or ‘transitional’ forms of MS received either interferon beta-1b at doses of 8 MIU or placebo for 24 months.<sup>20</sup>

This study was approved by the local Clinical Research Ethics Committee, who waived the requirement of written informed consent.

### Clinical measures

The Expanded Disability Status Scale (EDSS) score and disease duration were the clinical measures included. The EDSS was assessed at 3 time points: at baseline, and at 2 years and approximately 14 years after baseline ( $14.12 \pm 2.88$  years). As EDSS values were not uniformly distributed over time, we used an averaged EDSS over time. To determine this value, the area under the curve of the EDSS (AUCEDSS) was calculated. AUCEDSS values were normalized to the maximum AUCEDSS in the time interval measured to obtain the normalized AUCEDSS (NAUCEDSS) value according to the following expression:

$$NAUCEDSS = \frac{\frac{1}{2} \sum_{k=0}^1 ((t_{k+1} - t_k)(EDSS_{k+1} + EDSS_k))}{10(t_2 - t_0)}$$

where  $t_k$  is the number of months from baseline ( $t_0$ ) in the time point  $k=\{0, 1, 2\}$ , and  $EDSS_k$  is the EDSS measurement in the time point  $k$ .

Moreover, to obtain a prediction of long-term EDSS change ( $\Delta EDSS$ ), the differences between the last measurement and the baseline EDSS measurement were computed for each patient.

## **MRI acquisition**

Two MRIs were analyzed in this group of patients, a baseline examination and a follow-up one obtained  $6.30 \pm 0.23$  years (range, [5.92, 7.17] years) after the baseline study.

All MRI studies were performed on a 1.5 T magnet (Magnetom Vision Plus, Siemens, Erlangen, Germany) using a quadrature transmit/receive head coil for the brain studies and a quadrature receiver only neck phase-array coil for the cervical studies. In each brain examination the following sequences were obtained: 1) a transverse, T2-weighted, dual echo turbo spin-echo sequence (TR, 3000 ms; TE, 14-85 ms; echo train length, 5; acquisitions, 1); and 2) a transverse T1-weighted, spin-echo sequence (TR, 667 ms; TE, 12 ms; acquisitions, 2). For both sequences, 46 interleaved contiguous axial sections with 3-mm thickness were acquired covering the whole brain, with a 192 x 256 matrix and 250 mm field of view, giving an in-plane spatial resolution of approximately  $1 \times 1 \text{ mm}^2$ . Following the brain study, a three-dimensional volume image centered on the cervical spine was obtained using a magnetization-prepared rapid-acquisition gradient-echo sequence (MPRAGE) with 128 partitions in the sagittal plane of 1.25 mm thickness and the following parameters: 9.7 ms/450 ms/4.2 ms (TR/TI/TE), flip angle of  $15^\circ$ , 256 phase encodings in the z direction, one average, 250 mm field of view, and 256x256 matrix.

## **MRI analysis**

Cross-sectional area measurements were assessed using a semi-automatic segmentation method based on an active surface model of the cord surface with intrinsic smoothness constraints,<sup>18</sup> provided in the Jim 6.0 software package (Xinapse Systems Ltd, Essex, UK). Briefly, the sagittal 3D T1-weighted scans of the cervical cord from each patient

were first reformatted in the axial plane and resampled to 1-mm section thickness. Then, the AS method was applied to each scan to estimate the cord surface and cord centerline (see Figure 1). An initial estimate of the cord centerline was manually provided by placing landmarks at the extremes of the cord region to be studied and at approximately each 10 mm between these landmarks. Thus, the region studied comprised the segment from the most cranial section in which the odontoid process was visible down to the C5 superior margin. A single operator placed all landmarks. The cord centerline and cord outlines at each section were calculated using a segmentation algorithm, with steadily increasing refinement of the active surface model describing the cord outline. The total cord length was calculated in each region as the distance along the centerline between the upper and lower landmarks. In each region, the mean cervical cord CSA (MCSA) was calculated as the total cord volume divided by the cord length, and CSA was also measured at the C2-C3 (CSA23), C3-C4 (CSA34), and C4-C5 (CSA45) disks. CSA measurements were then normalized (NMCSA, NCSA23, NCSA34, NCSA45)—in a manner similar to the proposal of Lin et al<sup>21</sup>—to the intracranial cross-sectional area measured at the inferior margins of the corpus callosum in an axial slice of the proton density-weighted image of each patient, as previously suggested.<sup>18</sup> This adjustment was performed because cranial size was found to significantly correlate with the cord area in normal controls.<sup>22</sup> In addition to the normalized CSA measurements, the annualized (normalized) CSA loss rates between the baseline and follow-up examination (aNMCSA, aNCSA23, aNCSA34, aNCSA45) were also evaluated.

To calculate the brain T2 lesion volume (T2LV), lesions found on brain MR imaging were initially analyzed and marked on the PD-weighted hard copies with cross reference to the T2-weighted images, always by the same neuroradiologist. All lesions marked on the hard copies were outlined on the computer image using a semiautomatic local

thresholding contour technique (D.L. Plummer, University College London, England);<sup>23</sup> in cases where the lesion could not be outlined satisfactorily with this approach, manual outlining was carried out. A computer program then summed all the individual lesion volumes and a final T2LV was generated and stored in a database specifically designed for the study. To calculate the T1 lesion volume (T1LV), we used an automatic segmentation algorithm that measures T1LV from the initial T2 lesion segmentation that was used as a lesion mask.<sup>24</sup>

Brain atrophy was evaluated by measuring the brain parenchymal fraction (BPF) according to a previously described algorithm.<sup>25</sup>

### **Statistical analysis**

To evaluate the longitudinal cord CSA changes, differences between the baseline and follow-up CSA measurements were assessed using a *t*-test for paired samples.

Correlations of the cord CSA with the clinical and brain MRI measures were assessed using Pearson's correlation coefficient. To create a predictive model for the  $\Delta$ EDSS, linear regression analysis was carried out. A stepwise method was used to select the most relevant measures among the following: baseline CSA measures, annualized cord CSA loss rates, brain MRI measures, disease duration, and baseline EDSS scores. Age at baseline was also introduced in the model as a covariate. All statistical analyses were performed using SPSS (IBM Corp., USA). *P*-values less than 0.05 were considered statistically significant.

## **RESULTS**

### **Clinical and conventional MRI measures**

The main baseline demographic, clinical, and conventional MRI characteristics of the patients are shown in Table 1. During clinical follow-up, median EDSS was 6.0 (range, 4.0, 8.5) at 24 months, and 7.5 (range, 4.0, 9.5) at last measurement, approximately 14 years after baseline ( $14.12 \pm 2.88$  years) (Table 2). The mean (SD) T2 and T1 lesion volume increased to 21.56 mL (20.65) and 9.53 mL (9.32), respectively, whereas the mean BPF decreased by 3.83% at 6 to 7 years of radiological follow-up (Table 3). The T2LV, T1LV, and BPF changes were statistically significant ( $p < 0.001$ ).

### **Longitudinal changes in cervical cord cross-sectional area**

Baseline CSA measurements, follow-up CSA measurements, and cord area changes averaged by year are shown in Table 4. The normalized CSA values decreased significantly in all the regions studied (Figure 2). The annualized CSA loss rates were similar for all the normalized CSA measurements.

### **Associations between measurements**

According to Evans' categorization system,<sup>26</sup> the normalized CSA measurements showed a weak to moderate negative association with the NAUCEDSS at baseline (NMCSA:  $r = -0.357$ ,  $p = 0.049$ ; NCSA23:  $r = -0.418$ ,  $p = 0.019$ ) and at follow-up (NMCSA:  $r = -0.439$ ,  $p = 0.013$ ; NCSA23:  $r = -0.408$ ,  $p = 0.023$ ; NCSA34:  $r = -0.387$ ,  $p = 0.032$ ). No significant correlations were found between the annualized (normalized) cord CSA loss rates and the NAUCEDSS. Analysis of associations between the normalized CSA and brain MRI measurements showed no associations of the BPF, T2LV, or T1LV with the various CSA measurements. A moderate correlation was found between the baseline

BPF and the annualized (normalized) CSA loss rate at C2-C3 ( $r=-0.419$ ,  $p=0.019$ ), and C3-C4 ( $r=-0.425$ ,  $p=0.017$ ), whereas a trend was observed between the baseline BPF and the aNMCSA ( $r=-0.355$ ,  $p=0.05$ ).

### **Prediction of long-term EDSS change**

The long-term EDSS change ( $\Delta EDSS$ ) was measured in the range of  $14.12 \pm 2.88$  years after baseline to obtain an estimation on a time horizon of around 14 years. In the linear regression analysis to predict this change, the annualized mean cervical cord area loss rate (*aNMCSA*) and baseline EDSS ( $EDSS_0$ ) were introduced in the model using the stepwise method, and age was introduced as a covariate. However, only *aNMCSA* and  $EDSS_0$  with  $p$ -values of 0.007 and 0.025, respectively, were statistically significant variables. The model obtained was then defined by the following expression:

$$\Delta EDSS = 4.0 - 0.628 \text{ aNMCSA} - 0.476 EDSS_0 + 0.006 \text{ Age}$$

The F-test showed a significant  $p$ -value (0.004); thus it was assumed that there was a linear relationship between the variables in our model. Finally,  $R^2=0.390$ , which indicated that the linear regression model explained 39.0% of the total variance in the data.

## DISCUSSION

The present study investigated the role of cervical cord atrophy in a longitudinal study of a cohort of PPMS patients to evaluate the association of this MRI finding with clinical progression of disability and with other MRI measures. We found a significant decrease in the normalized CSA values in all the regions studied. Moreover, some weak to moderate correlations were found between the weighted average EDSS and normalized CSA values both at baseline and at follow-up.

The annual loss of spinal cord tissue in our cohort was lower than has been reported in previous studies.<sup>6,8,9,13,17,21,22</sup> However, Lukas et al<sup>9</sup> recently reported that spinal cord tissue loss may slow down over time, with already highly atrophied structures exhibiting slower atrophy rates. Our results support this notion: over the lengthy follow-up period we found a smaller annualized CSA loss than other studies with a shorter follow-up.

To obtain the weighted average EDSS, we used the area under the curve (AUC). The AUC becomes interesting when the longitudinal time intervals are unequally spaced, as was the case in the present study. Then the AUC reflects the weighted average of a certain outcome variable over the total follow-up period.<sup>27</sup> AUC values were also normalized to facilitate their interpretation by means of an index in the range from 0 to 1, associated with patient disability.

Although the linear regression model predicting the long-term EDSS change showed a strong correlation with the data according to Evans' categorization,<sup>26</sup> the only significant variables remaining in the model were the aNMCSA and baseline EDSS. None of the CSA measures or conventional MRI measures showed high enough significance to be included in the model. The model showed that the greater the progression of cervical cord atrophy, associated with a more negative aNMCSA, the

greater was the long-term EDSS change. Baseline EDSS acted as a limiting factor in the model, as the margin to a long-term EDSS increase was lower when baseline EDSS values were higher.

The lack of association between the BPF and cross-sectional area values is in agreement with a previous study in PPMS patients.<sup>28</sup> At C2-C3 and C3-C4, a moderate negative correlation between the BPF and the annualized rate of spinal cord tissue loss was observed, whereas only a trend was seen between the baseline BPF and aNMCSA. These findings may be an indication that brain and cord pathology evolve differently, and that measurement of brain and cord atrophy can provide complementary information about the severity of PPMS.<sup>28</sup>

The data analysis did not include the effect of treatment. This factor was not considered essential because the study patients were part of a cohort participating in a clinical trial<sup>20</sup> in which one group was treated with interferon beta 1-b and the remainder with placebo during the first two years and there were no differences in EDSS progression or CSA measurements between the groups.

This study is not without limitations. First, the long follow-up made it difficult to enroll a larger sample that fulfilled the clinical and radiological information required for the study. Second, images were acquired using a 1.5T MRI scanner. Most recent studies use 3.0T scanners to acquire cervical cord images, as they provide a better signal-to-noise ratio in the same acquisition time. However, given the duration of our study, a 1.5T scanner was used at the first time point and we decided to maintain the same scanner throughout the study. Third, the sequence used to acquire cervical cord images was a 3D T1-weighted MPRAGE. In a recent study, Kearney et al.<sup>19</sup> proposed use of phase-sensitive inversion recovery (PSIR) sequences to take advantage of their better resolution and higher contrast. It is likely that reproducibility would improve if the AS

method were combined with a PSIR rather than a 3D T1-weighted MPRAGE sequence. However, because of the retrospective nature of the study it was not possible to introduce this sequence in the acquisition. Nonetheless, Kearney et al. mentioned that when PSIR cannot be used, combining AS with 3D MPRAGE may be the most suitable approach. Fourth, EDSS values were not uniformly distributed over time. We tried to resolve this by using a weighted average measurement (normalized AUC), but a uniform distribution would have allowed further analysis. Finally, inclusion of a healthy control group would have helped to differentiate between decreases in cervical cord values due to age and decreases due to MS-induced atrophy.

## **CONCLUSIONS**

The results of this study suggest that cervical cord area measures are associated with disability in PPMS patients. More interestingly, this study supports that MR changes should be taken into account when developing predictive studies. Specifically, we found that the rate of cervical cord area loss could play a relevant role in predicting clinical disability progression at long-term.

Further longitudinal studies focused on evaluation of cervical cord area changes in PPMS patients and their relation to disease progression over long periods would help to define the value of cervical cord atrophy as a surrogate marker in MS clinical trials or for clinical management of these patients.

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## Tables

**Table 1:** Main baseline demographic, clinical, and conventional MRI characteristics

	MS patients
Median age, years, (range)	51 ([33, 61])
Men / women	19 / 12
Mean disease duration at baseline, years, (range)	11.74 ([2, 33])
Median EDSS at baseline (range)	5.5 ([3.0, 6.5])
Mean brain T2LV, mL (SD) at baseline	18.12 (20.63)
Mean brain T1LV, mL, (SD) at baseline	7.41 (8.47)
Mean BPF (SD) at baseline	73.13 % (5.86)

EDSS, expanded disability status scale; T2LV, T2 lesion volume; SD, standard deviation; T1LV, T1 lesion volume; BPF, brain parenchymal fraction

**Table 2:** Evolution of the expanded disability status scale

	Baseline	2 years	14 years
Median EDSS (range)	5.5 ([3.0, 6.5])	6.0([4.0, 8.5])	7.5([4.0,9.5])

EDSS, expanded disability status scale

**Table 3:** MRI characteristics at follow-up

	Follow-up
Mean brain T2LV, mL (SD)	21.56 (20.65)
Mean brain T1LV, mL, (SD)	9.53 (9.32)
Mean BPF (SD)	70.33 % (5.84)

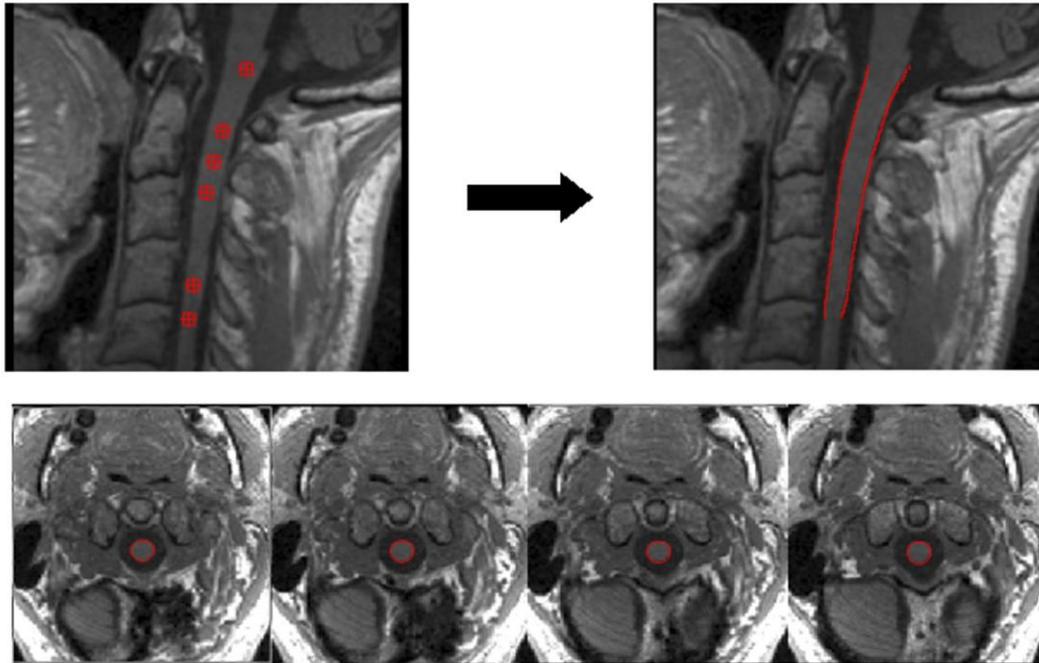
BPF, brain parenchymal fraction; SD, standard deviation; T1LV, T1 lesion volume;  
T2LV, T2 lesion volume

**Table 4:** Longitudinal cross-sectional area measurements

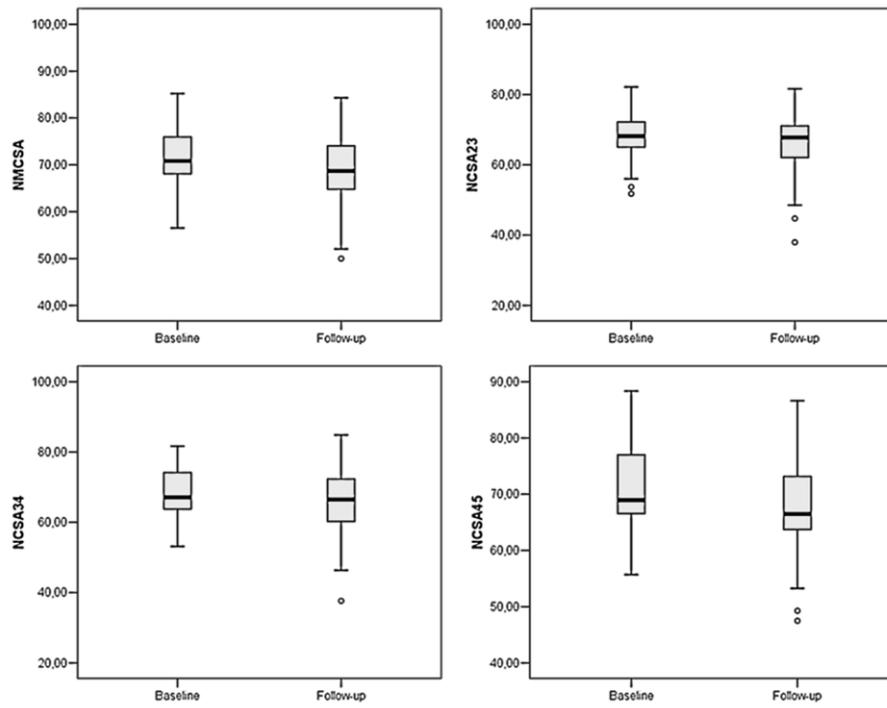
	NMCSA	NCSA23	NCSA34	NCSA45
Mean, mm <sup>2</sup> (SD) at baseline	71.49 (6.37)	67.76 (7.26)	68.21 (7.39)	71.51 (8.27)
Mean, mm <sup>2</sup> (SD) at follow-up	68.12 (8.91)	65.40 (10.27)	65.23 (10.61)	67.95 (9.97)
Cord area change averaged by year, % (SD)	-0.77 (1.14)	-0.62 (1.20)	-0.74 (1.47)	-0.77 (1.61)
p-value	0.001	0.006	0.009	0.006

NMCSA, normalized cross-sectional area; NCSA23, normalized cross-sectional area at C2-C3 level; NCSA34, normalized cross-sectional area at C3-C4 level; NCSA45, normalized cross-sectional area at C4-C5 level; SD, standard deviation

## Figures



**Figure 1.** Example of the cord surface estimation obtained using the active surface method. The top left image shows the location of the landmarks (red markers) that can be visualized in this sagittal slice. These landmarks were manually placed in the axial slices at the center-of-area of the cord with a distance between them of approximately 10 mm. The top right image shows the cord outline estimation (red lines). The bottom axial slices show some examples of the spinal cord segmentation obtained (region within red contour).



**Figure 2.** Box-and-whisker plots of normalized cross-sectional areas: NMCSA (top left), NCSA23 (top right), NCSA34 (bottom left), and NCSA45 (bottom right).