Vall d'Hebron Hospital

Institut Català de la Salut

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IDI INSTITUT DE DIAGNÒSTIC PER LA IMATGE

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"Spinal cord MR imaging in Multiple Sclerosis"

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SFNR SOCIETE FRANCAISE DE NEURORADIOLOGIE

Disclosures

I have no disclosures in relation to the content of this presentation

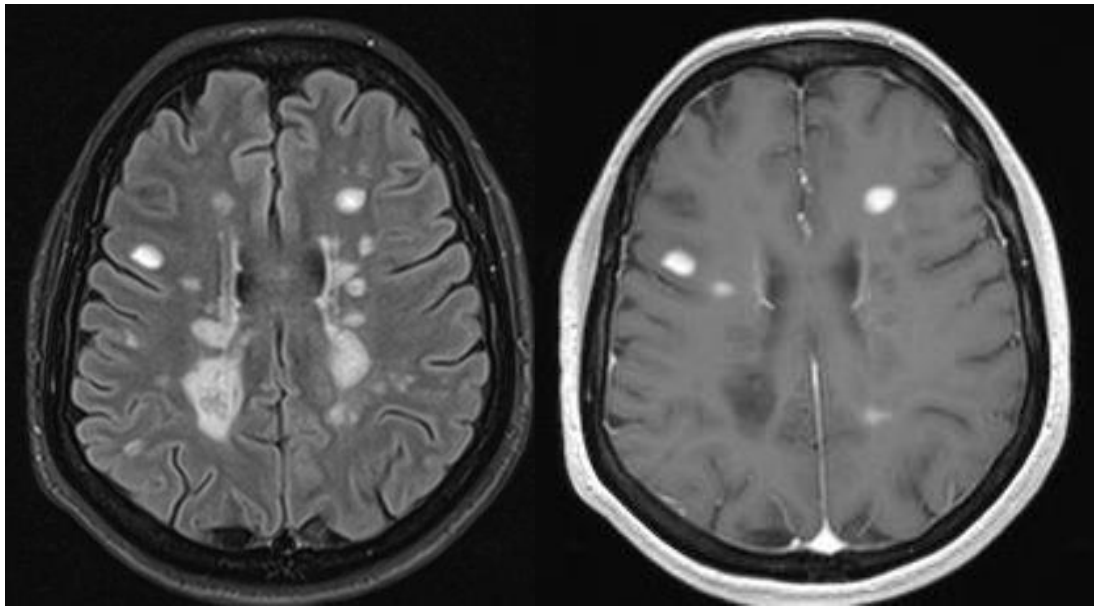
Summary

- Introduction
- Technical features
- MR imaging features
- Spinal cord MRI for the diagnosis and prognosis of MS
- Spinal cord MRI for monitoring MS
- Conclusions

Brain MR imaging in MS

T2 and CE T1-WI

T2-weighted (FLAIR)



Post-contrast T1-weighted

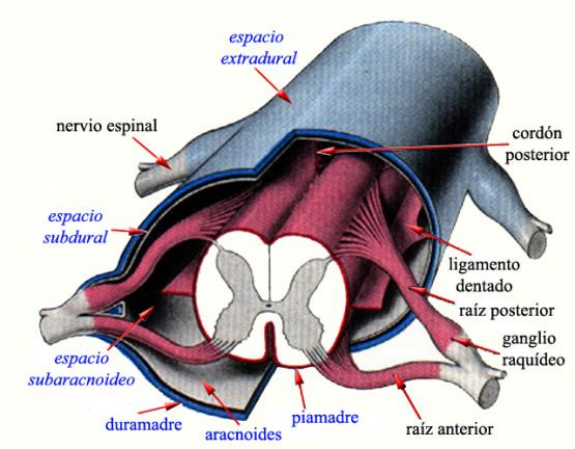
- Highly sensitive for detecting MS plaques
- Provide quantitative assessment of inflammatory activity and lesion load
- Most important paraclinical tool for diagnosing and monitoring MS

Spinal cord MR imaging in MS

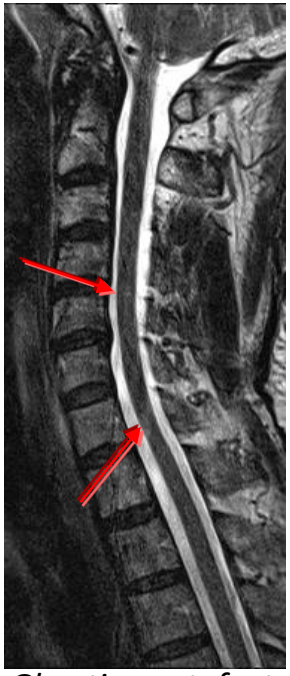
Spinal cord MRI is not performed as commonly as brain MRI, mainly because of certain technical difficulties and the increase in total acquisition time.

Technical issues

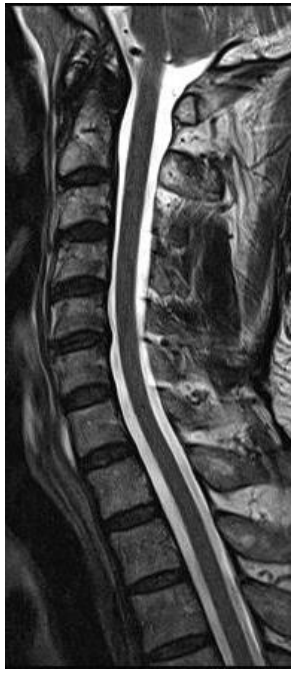
- Small, long and mobile structure
- Ghosting artefacts from heart and great vessels
- Truncation artifacts (tissue interface)
- Patient movement artifacts



35-48 mm transverse diameter



Ghosting artefacts from swallowing



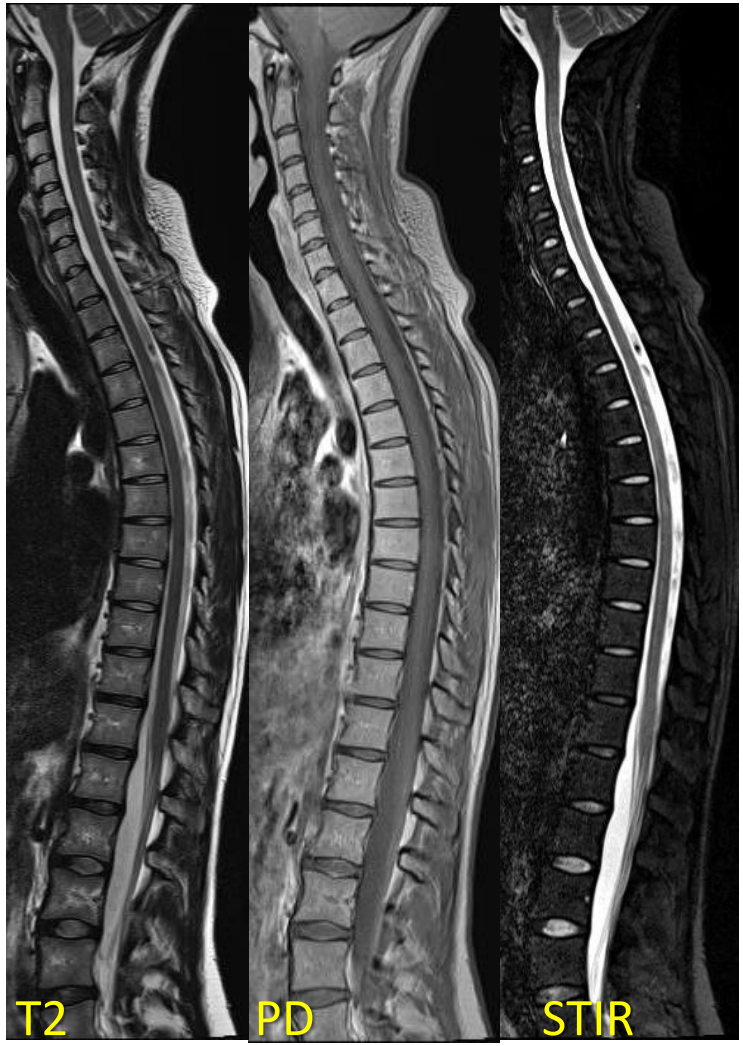
Absence of artefacts

Spinal cord MR imaging in MS

Solutions

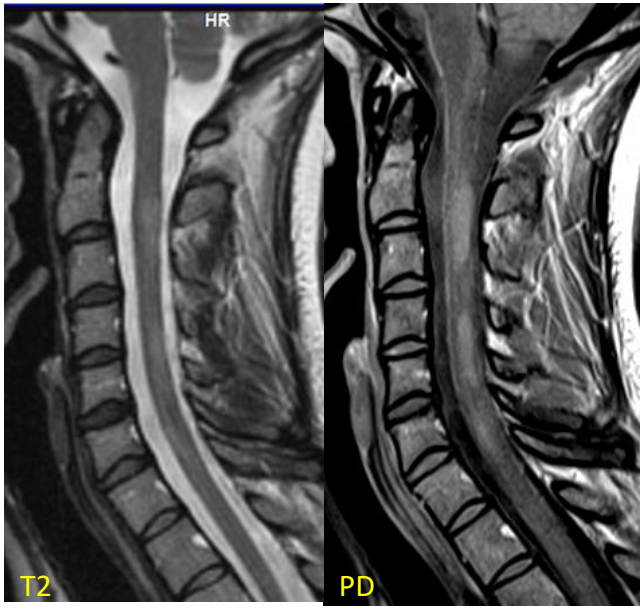
- Cardiac gating (SE)
- Presaturation slabs
- Fast imaging sequences
- Phased-array coils

Fast double-echo and STIR sequences obtained with phase-array coils covering the entire spinal cord



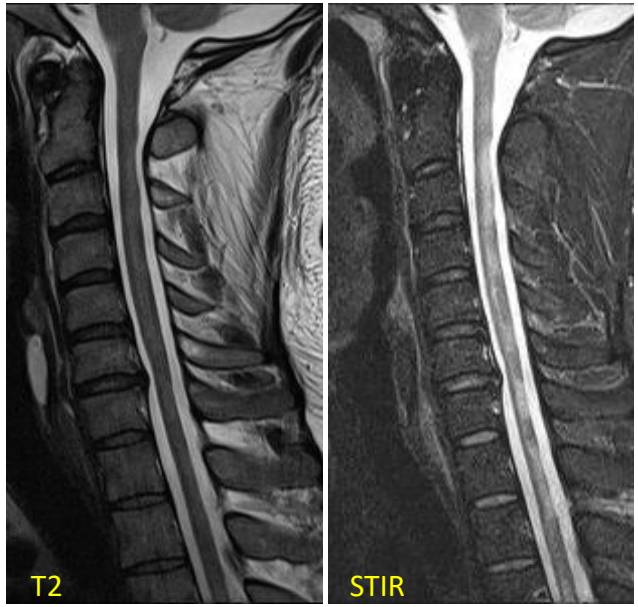
Selection of T2w MR sequences

PD > T2



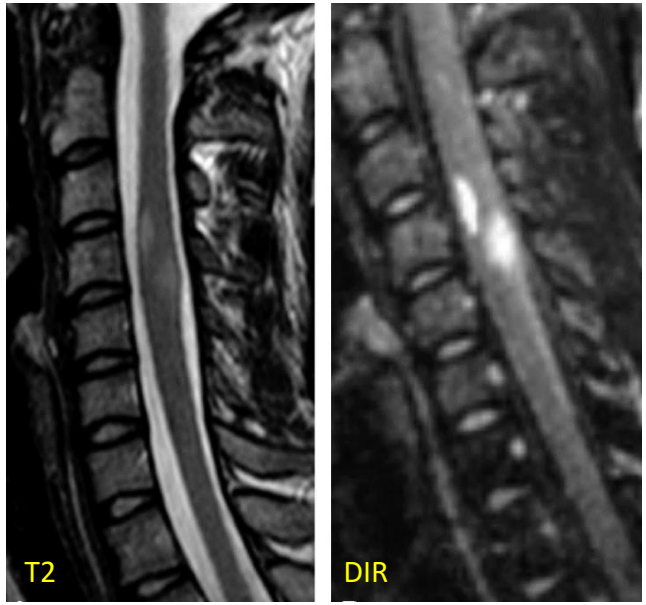
Cord almost isointense with surrounding CSF
Easy identification of any increase in signal

STIR > T2



Higher sensitivity compared to T2 SE
More susceptible to artifacts (false positive)
Use it in combination with T2

DIR > T2



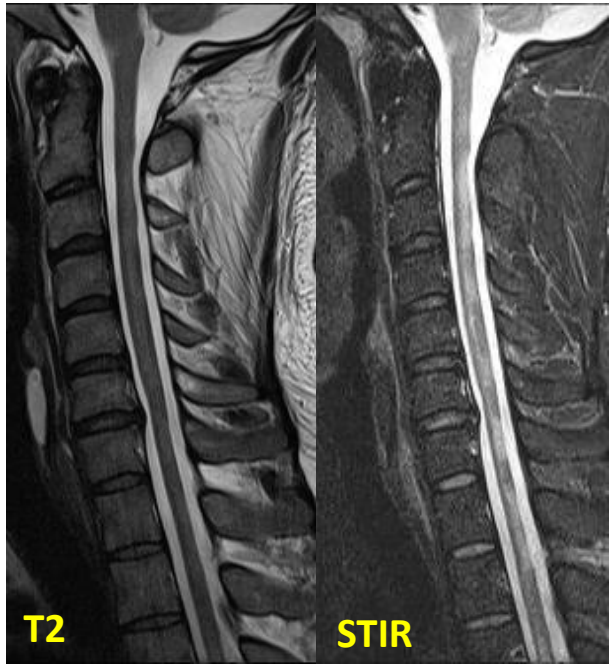
Nayak et al. Acta Neurol Scand 2014; Riederer et al. Am J Neuroradiol 2015; Chong et al. Am J Neuroradiol 2016

Selection of T2w MR sequences

Single echo heavily T2 weighted[1-2] :

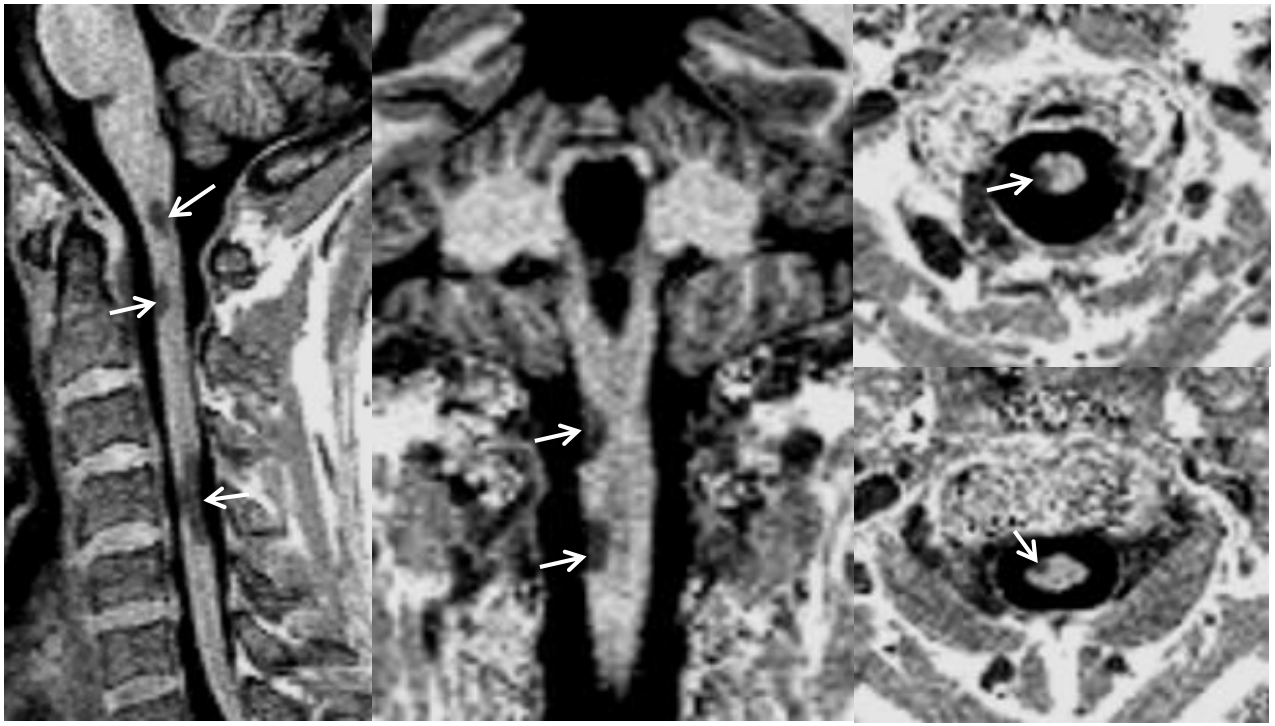
- limited sensitivity in depicting signal abnormalities[1-2]
- should not be obtained as a stand-alone sequence[3]

Combination of at least two T2w sequences[3]: T2, PD, STIR

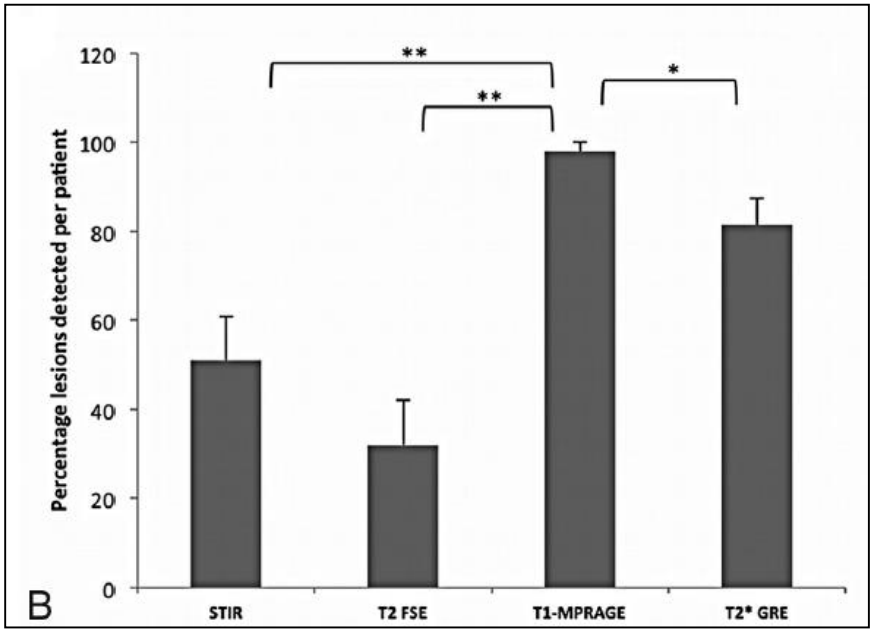


1.) Philpott et al. Eur J Radiol 2011; 80:780-5; 2.) Bot et al. Eur Radiol 2000; 10:753-8; 3.) Rovira et al. Nat Rev Neurol 2015; ;11:471-82.

Selection of MR sequences



Images from Alex Rovira



Heavily T1-weighted sequences, such as **PSIR** (phase-sensitive inversion recovery) or **MPRAGE /MP2RAGE** (two inversion-contrast magnetization-prepared rapid gradient echo), improve MS lesion detection

Nair et al. Am J Neuroradiol 2013; Alcaide-Leon P, et al. Am J Neuroradiol. 2016 Jan 21. [Epub ahead of print]

Standardised MRI acquisition protocol

Field strength: 1.5 or 3.0T

Sequences:

Mandatory

- Axial proton density; 2D /3D T2-FLAIR; T2-weighted
- Axial 2D or 3D contrast-enhanced T1-weighted (single dose, minimum delay 5 min)

Optional

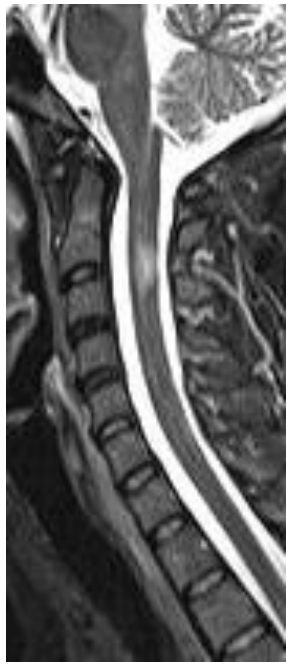
- Unenhanced 2D or high-resolution isotropic 3D T1-weighted (brain atrophy)
- 2D/3D double inversion recovery (cortical lesions)
- Diffusion-weighted imaging (PML)
- Spinal cord imaging:
  - **Sagittal contrast-enhanced T1-weighted**
  - **Sagittal proton density (STIR) / T2-weigthed**
  - **Axial T2-weighted**

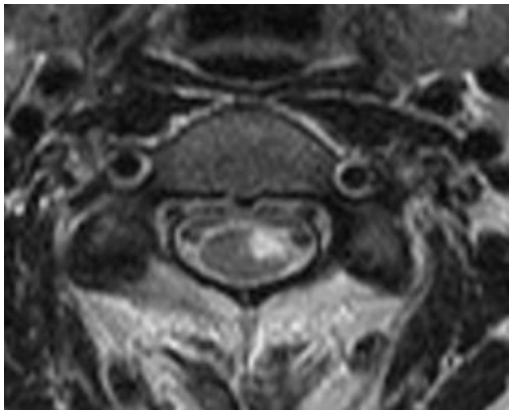
Magnims: Magnetic Resonance Imaging in Multiple Sclerosis network

Rovira et al. Nat Rev Neurol 2015;11:471-82.

Typical MR imaging findings: spinal cord

- ✓ No cord swelling (unless active)
- ✓ Unequivocal hyperintense T2 or Gd-enhancing; focal lesions
- ✓ ≥3mm in size; <2 vertebral segments long
- ✓ Peripheral location, cigar shaped
- ✓ Occupying only part of cord cross-section (less than 50%)





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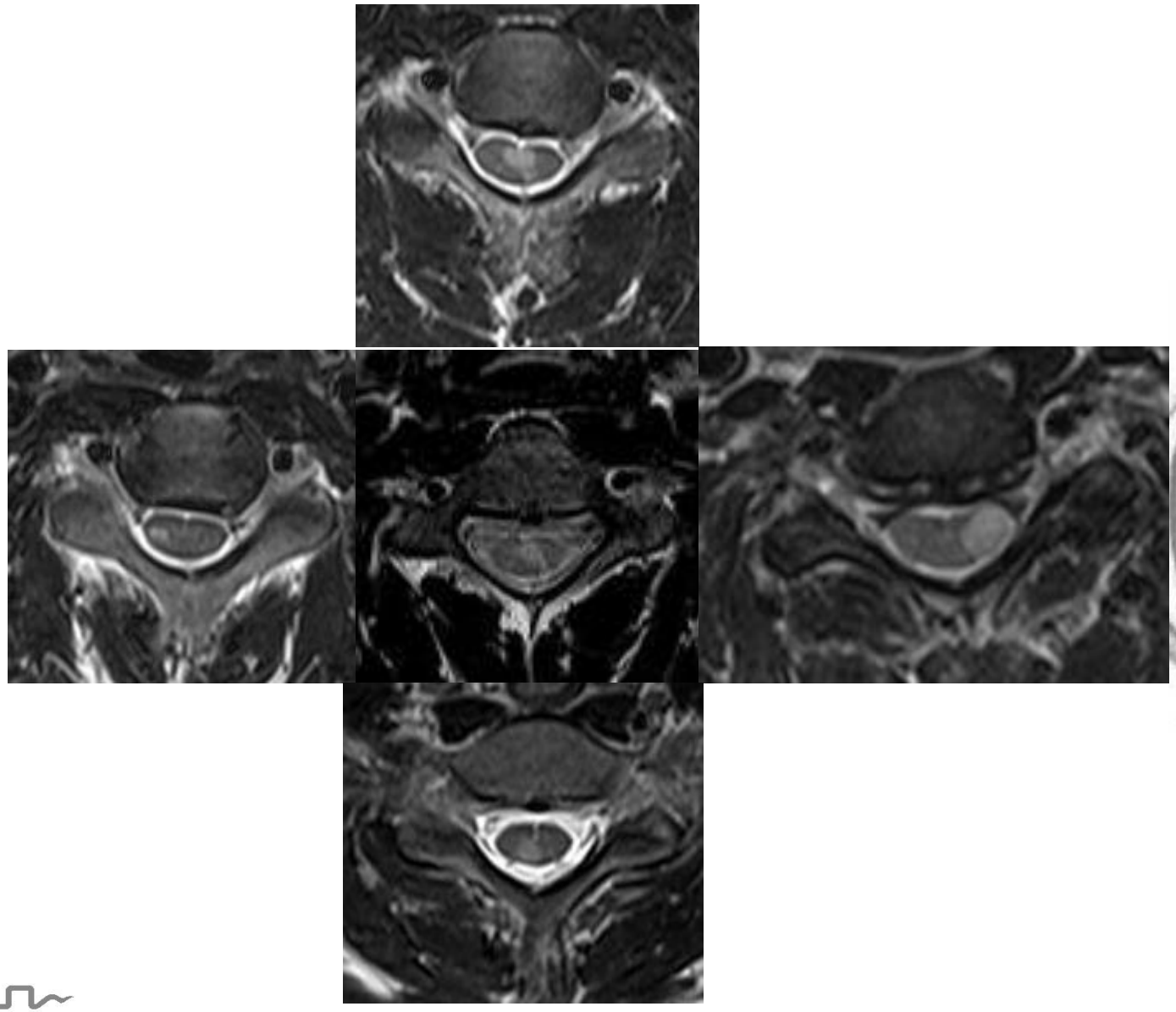
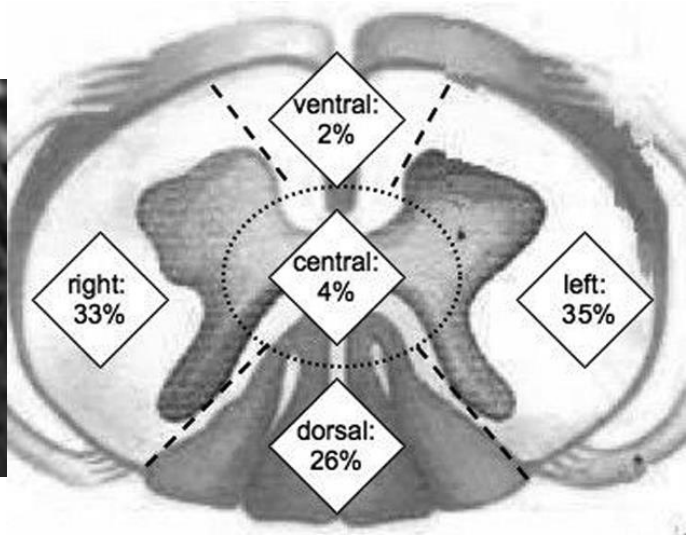
Bot et al. Neurology. 2004; 62:226-33; Weier et al. Mult Scler 2012;18:1560-9; Gass et al. Lancet Neurol 2015;14:443-54

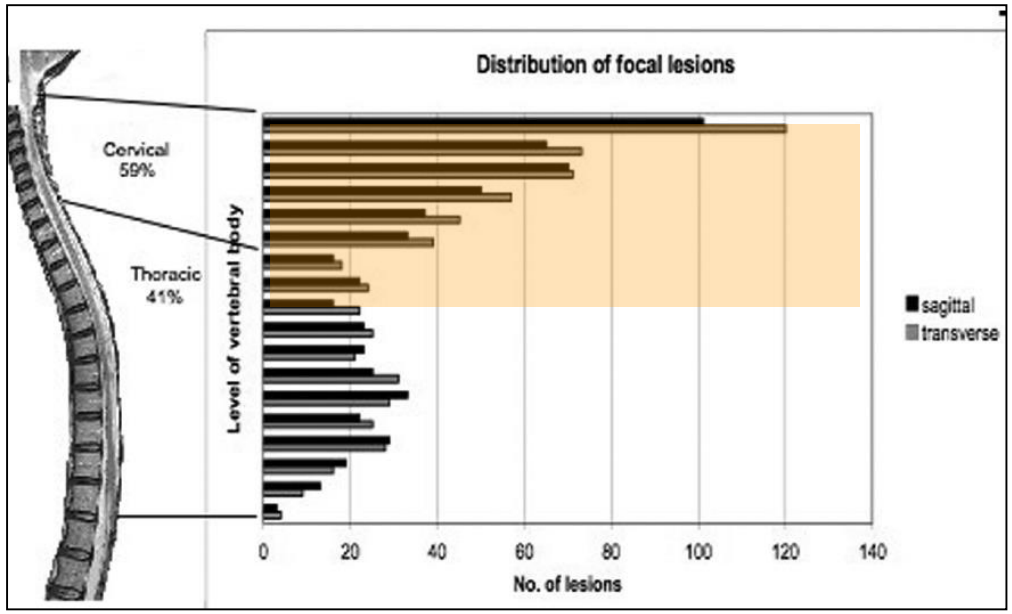
Typical MR imaging findings: spinal cord





Weier et al. Mult Scler 2012;18:1560-9

Distribution of focal lesions in the spinal cord

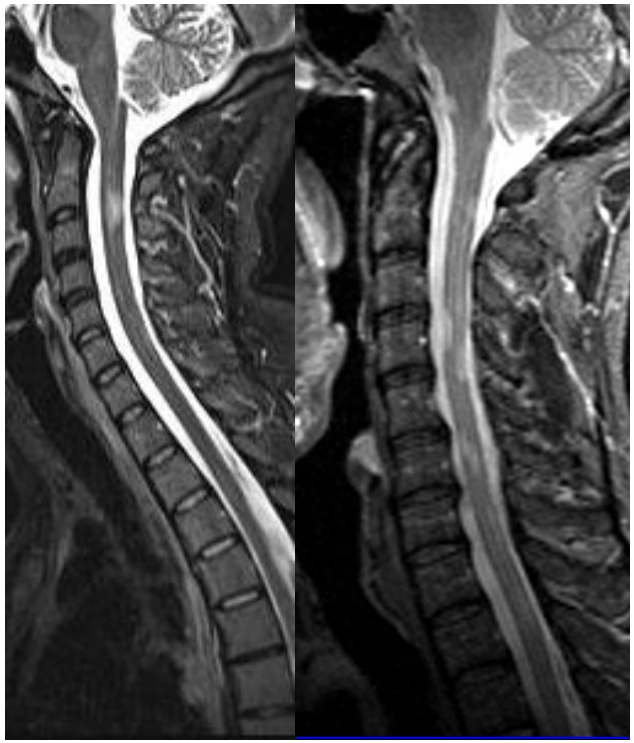


- Focal lesions primarily located in the cervical cord: **59%**
- Only in 16% of patients the lesions are exclusively located in the cervical cord
- Lesions are also quite frequently (**20%**) in the lower thoracic spinal segments (Th7–12).
- **In 8% of patients**, lesions are found either exclusively, or at least one of only two lesions, below the level of the Th5.

Weier et al. Mult Scler 2012

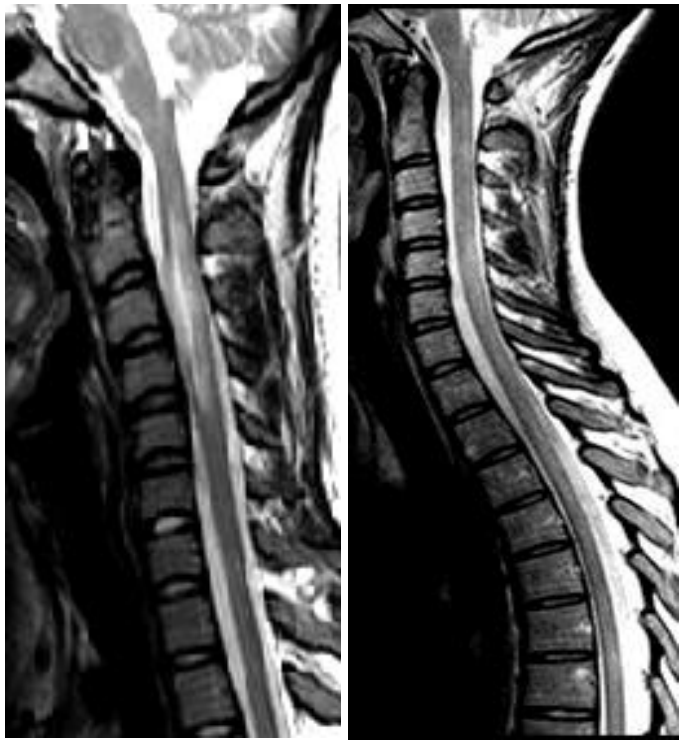
Lesion patterns in spinal cord MRI

Typical MRI patterns



unifocal multifocal

Atypical MRI patterns



tumefactive diffuse

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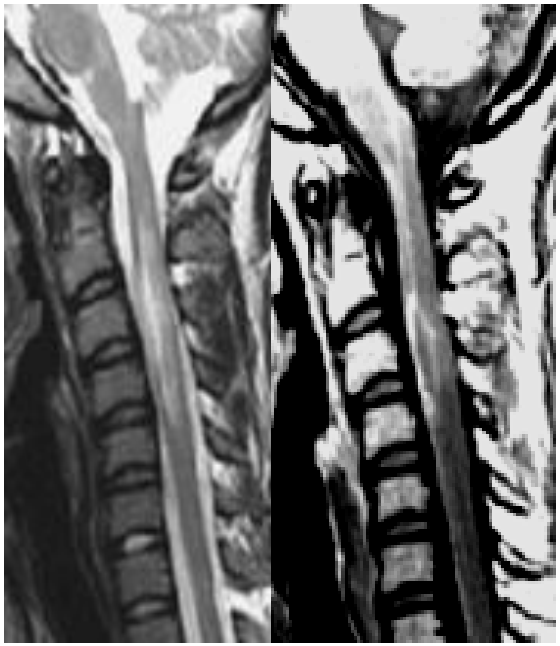
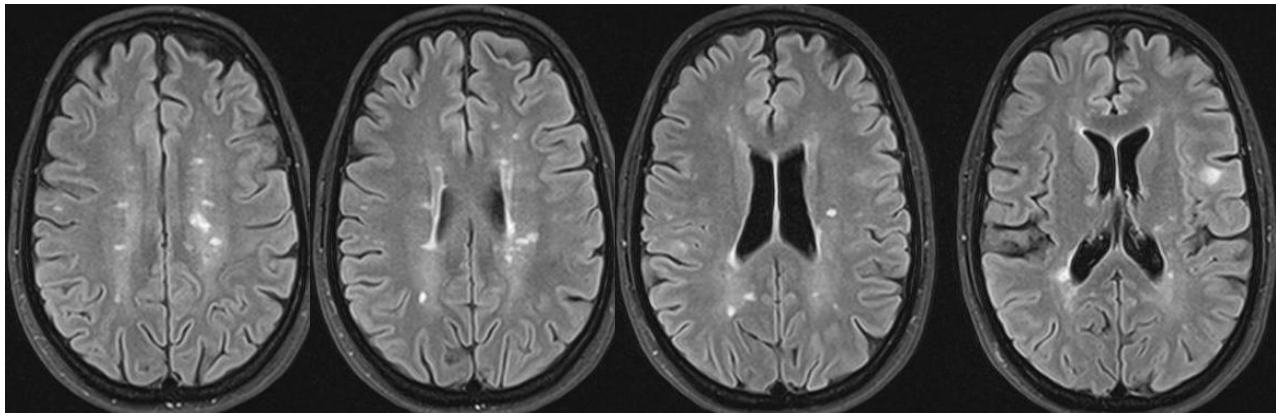
Tumefactive pattern

The tumefactive pattern represents a diagnostic challenge, as in addition to spinal cord tumors, different non-MS inflammatory diseases may present with expansive spinal cord lesions



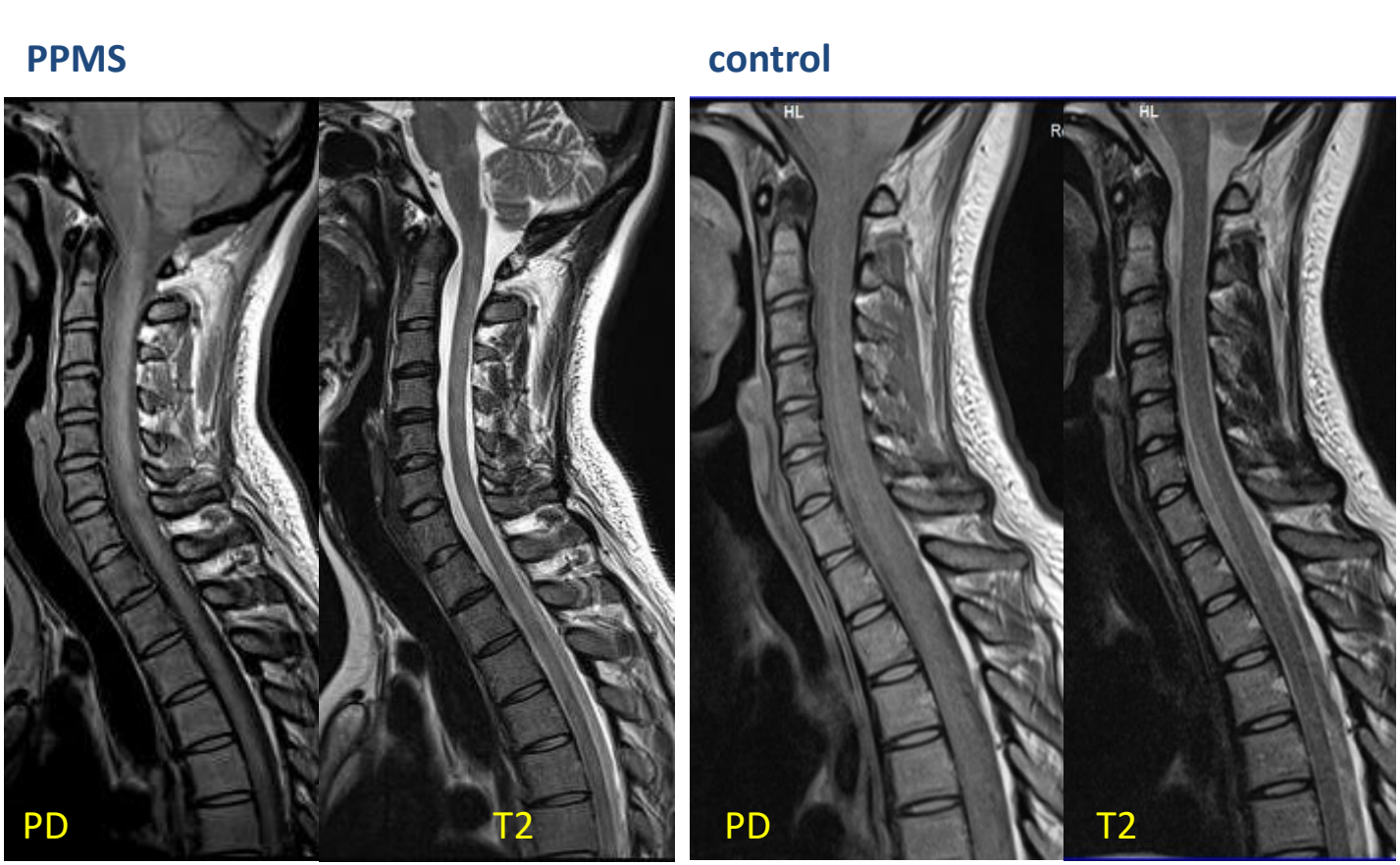
Tumefactive MS lesions

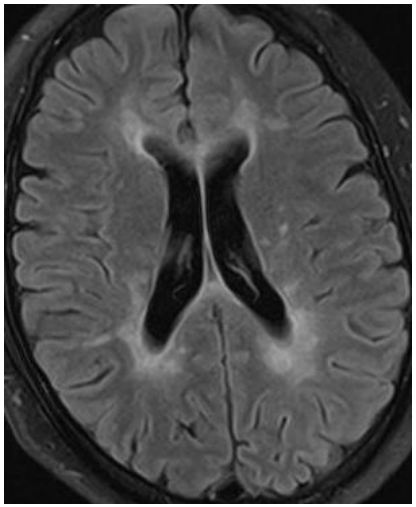


Diffuse pattern

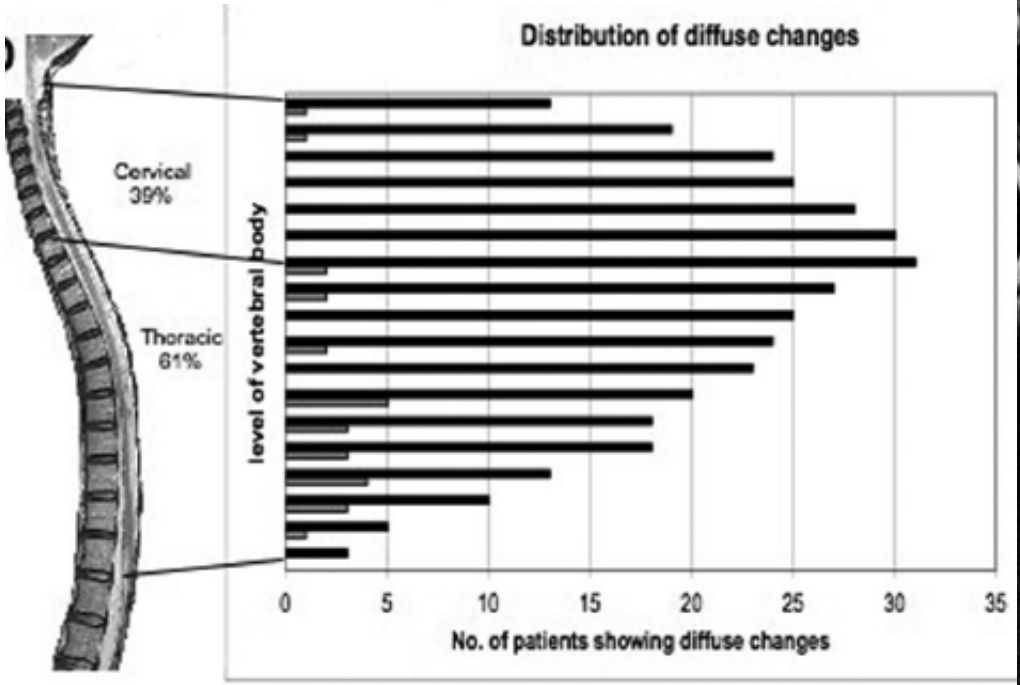
Diffuse abnormality in brain and spinal cord, but no focal lesions

Zwemmer et al. Mult Scler J 2008

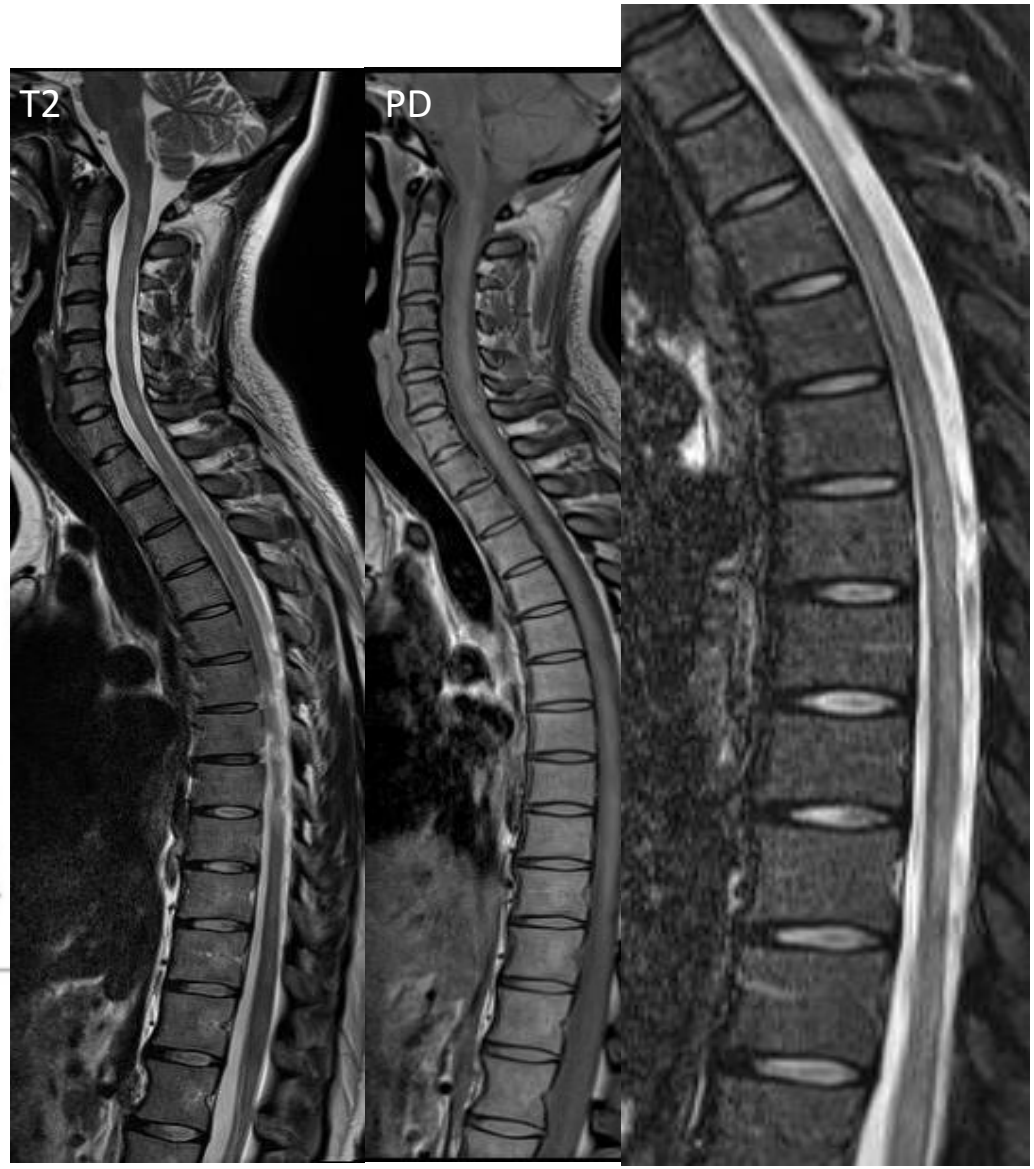




Distribution of diffuse lesions in the spinal cord

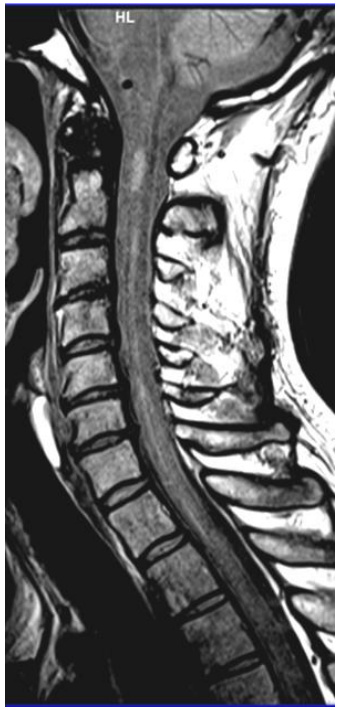


Diffuse signal changes seen in 15% of patients and extended along 4–17 vertebral segments (mean=10.2 segments)



Weier et al. Mult Scler 2012

Prevalence of spinal cord lesions in Multiple Sclerosis



- Spinal cord lesions in 30% of subjects with RIS
  - *84% progressed to CIS or PPMS (median time 1.6 years)*
  - *OR of clinical progression: 75.3*
- Subclinical lesions in 27-53% of patients with CIS
- Spinal cord lesions 83% of patients with early relapsing MS
- Spinal cord lesions in 74-92% of patients with MS and in 6% of patients with non-MS white matter diseases

O'Riordan et al. J Neurol Neurosurg Psychiatry. 1998;64:353-7; Dalton et al. J Neurol Neurosurg Psychiatry. 2003;74:1577-80;
Nijeholt et al. Brain 1998;121:687-97; Bot et al. Neurology 2004;62:226-33; Okuda et al. Neurology 2011;76:686-92

Indications of spinal cord MRI in Multiple Sclerosis

Situation	Objective
Clinically isolated syndrome with spinal cord symptoms	Detect symptomatic lesion Rule out alternative diagnosis
Clinically isolated syndrome with/without spinal cord symptoms	Predict risk of conversion to MS Predict disability
Clinically isolated syndrome with inconclusive / non specific brain MRI findings	Increase specificity of diagnosis
Negative brain scan, but strong clinical suspicion of MS	Increase sensitivity of diagnosis
Primary progressive MS	Required for diagnosis (McDonald criteria for dissemination in space) Rule out alternative diagnosis
Radiologically isolated syndrome	Predict risk of conversion to MS
Monitoring MS (If clinical activity or disease progression cannot be explained by brain MRI findings)	Detect disease activity

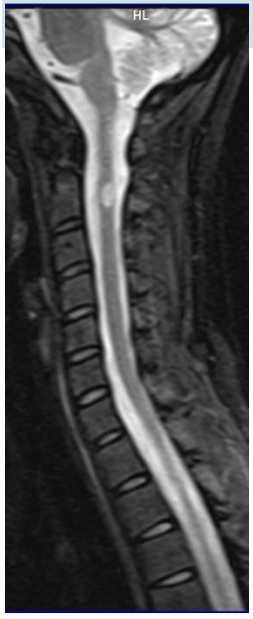
Rovira A, De Stefano N. Curr Op Neurol 2016 in press

Clinically isolated syndrome: Barcelona cohort
First symptoms of MS (85-90% od cases)

BASELINE CHARACTERISTICS

Demographic characteristics	N=1015
Females: N (%)	686 (67.6)
Age at onset (mean, SD)	31.1 (8.2)

CIS topography N (%)	N=1015
ON	373 (36.7)
BS	271 (26.7)
SC	261 (25.7)
Other	110 (10.8)

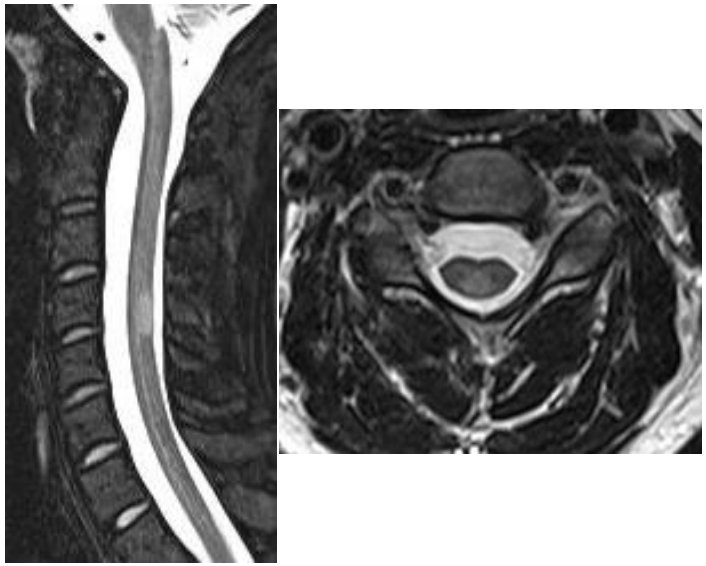


Tintore M, Rovira A, et al. Brain 2015

Indications of spinal cord MRI in Multiple Sclerosis

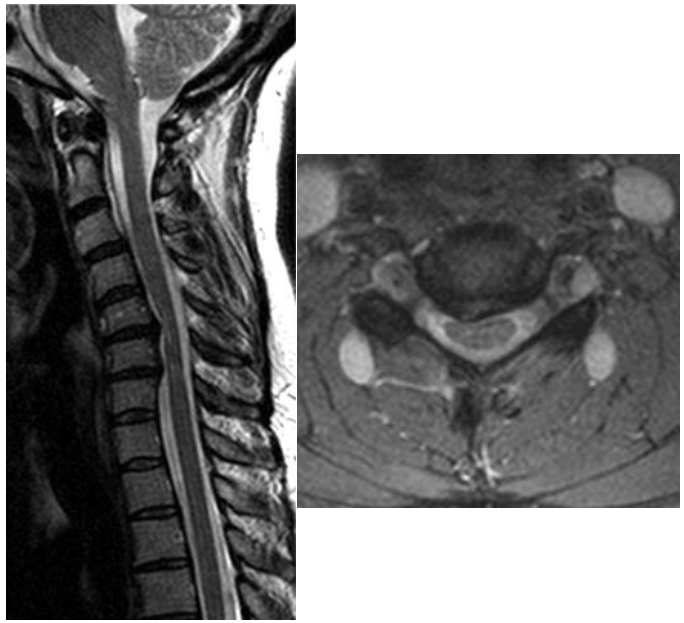
In patients with spinal cord syndrome

Identify the demyelinating lesion that cause the clinical symptoms



Typical demyelinating cervical cord lesion involving the posterior columns

Rule out non-demyelinating lesions responsible for the clinical symptoms



Microcystic spinal cord degeneration secondary to cervical disk herniation

Added value of spinal cord MRI in the diagnosis of MS

32 year old woman
Unilateral optic neuritis

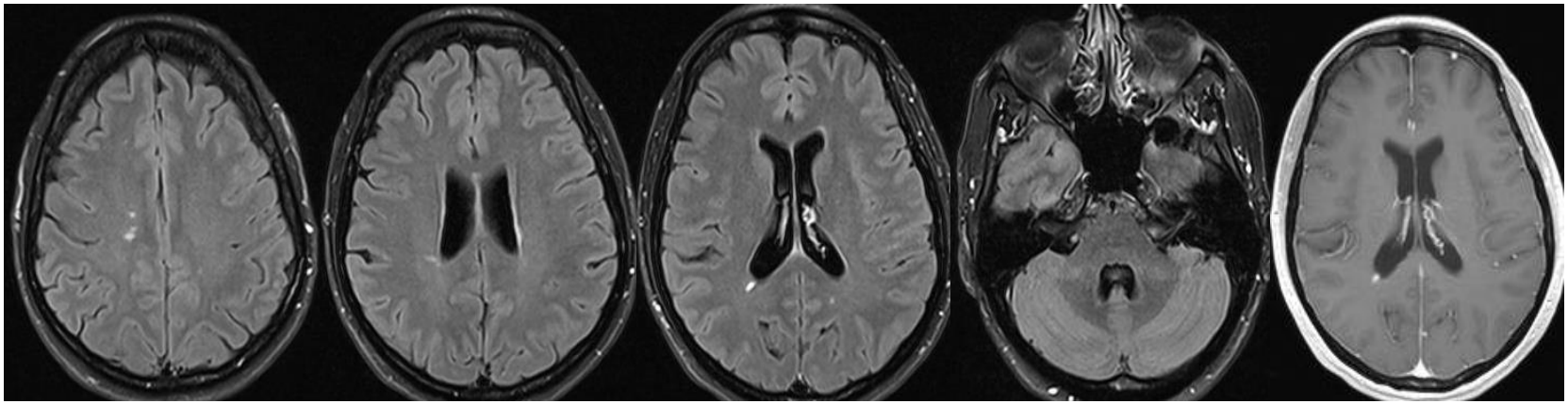


TABLE 1: 2010 McDonald MRI Criteria for Demonstration of DIS

DIS Can Be Demonstrated by ≥1 T2 Lesion[a] in at Least 2 of 4 Areas of the CNS:	
Periventricular	✓
Juxtacortical	✗
Infratentorial	✗
Spinal cord[b]	✗

Based on Swanton et al 2006, 2007.[22,27]
[a]Gadolinium enhancement of lesions is not required for DIS.
[b]If a subject has a brainstem or spinal cord syndrome, the symptomatic lesions are excluded from the Criteria and do not contribute to lesion count.
MRI = magnetic resonance imaging; DIS = lesion dissemination in space; CNS = central nervous system.

TABLE 2: 2010 McDonald MRI Criteria for Demonstration of DIT

DIT Can Be Demonstrated by:	
1. A new T2 and/or gadolinium-enhancing lesion(s) on follow-up MRI, with reference to a baseline scan, irrespective of the timing of the baseline MRI	✗
2. Simultaneous presence of asymptomatic gadolinium-enhancing and nonenhancing lesions at any time	✓

Based on Montalban et al 2010.[24]
MRI = magnetic resonance imaging; DIT = lesion dissemination in time.

Added value of spinal cord MRI in the diagnosis of MS

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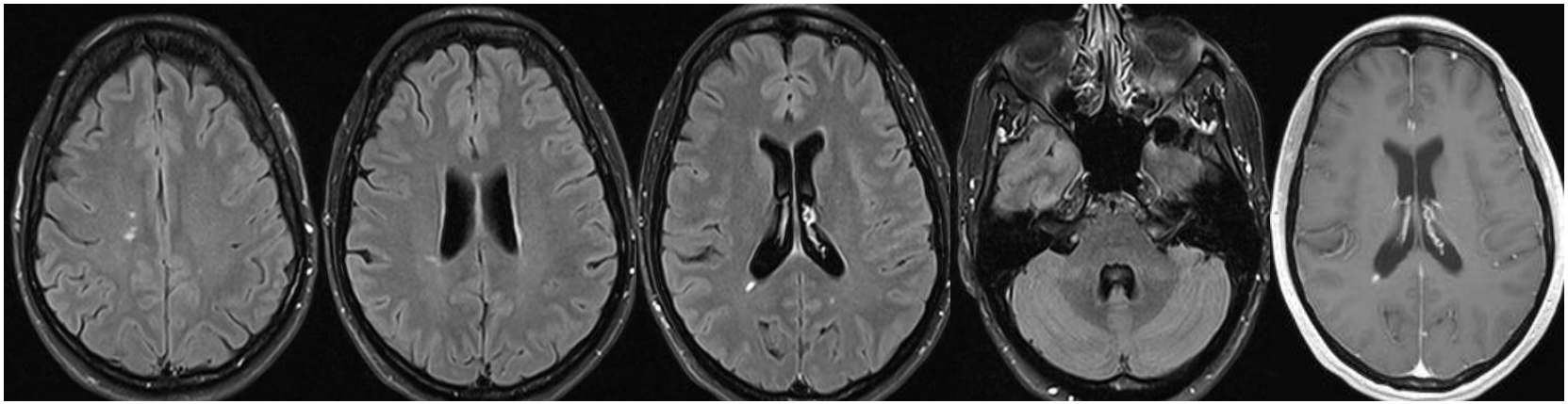

Two asymptor

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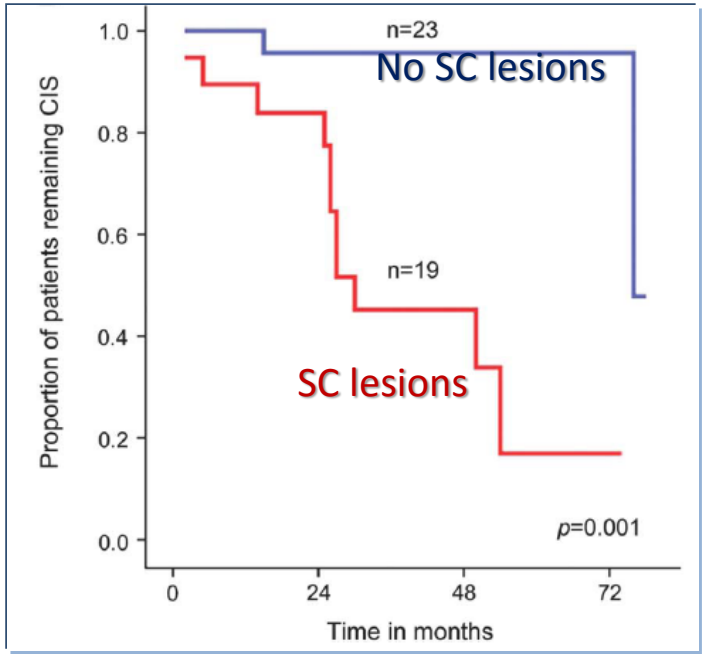
MRI = magnetic resonance imaging; DIT = lesion dissemination in time.

Prognostic value of spinal cord MRI in CIS
Amsterdam cohort

	No. of patients	No. of patients with SC lesions	No. of patients without SC lesions	OR for patients with SC lesions to develop CDMS vs patients without SC lesions (95% CI)	Hazard ratio for time to develop CDMS, using Cox regression[b] (95% CI)
1. Spinal CIS fulfilling McDonald brain MRI criteria	20	18	2	NA[c]	0.69 (0.14-3.36), $p = 0.65$
2. Spinal CIS *not* fulfilling McDonald brain MRI criteria	43	33	10	1.33 (0.29-6.14)	1.08 (0.29-4.06), $p = 0.92$
3. Nonspinal CIS fulfilling McDonald brain MRI criteria	16	12	4	1.67 (0.11-25.4)	0.89 (0.21-3.71), $p = 0.87$
4. Nonspinal CIS *not* fulfilling McDonald brain MRI criteria	42	19	23	14.4 (2.60-80.03)	51.38 (5.54-476.33), $p = 0.001$

Non spinal CIS not fullfilling McDonald brain MRI criteria

- 7 MRI scans needed to diagnose 1 more patient
- Prognostic value: identifies a subgroup that has a very low risk of developing MS



Spinal cord MRI in CIS:

- All patients with SC presentation
- Non SC patients who do not meet McDonald criteria on brain MRI

Sombekke et al. Neurology 2013

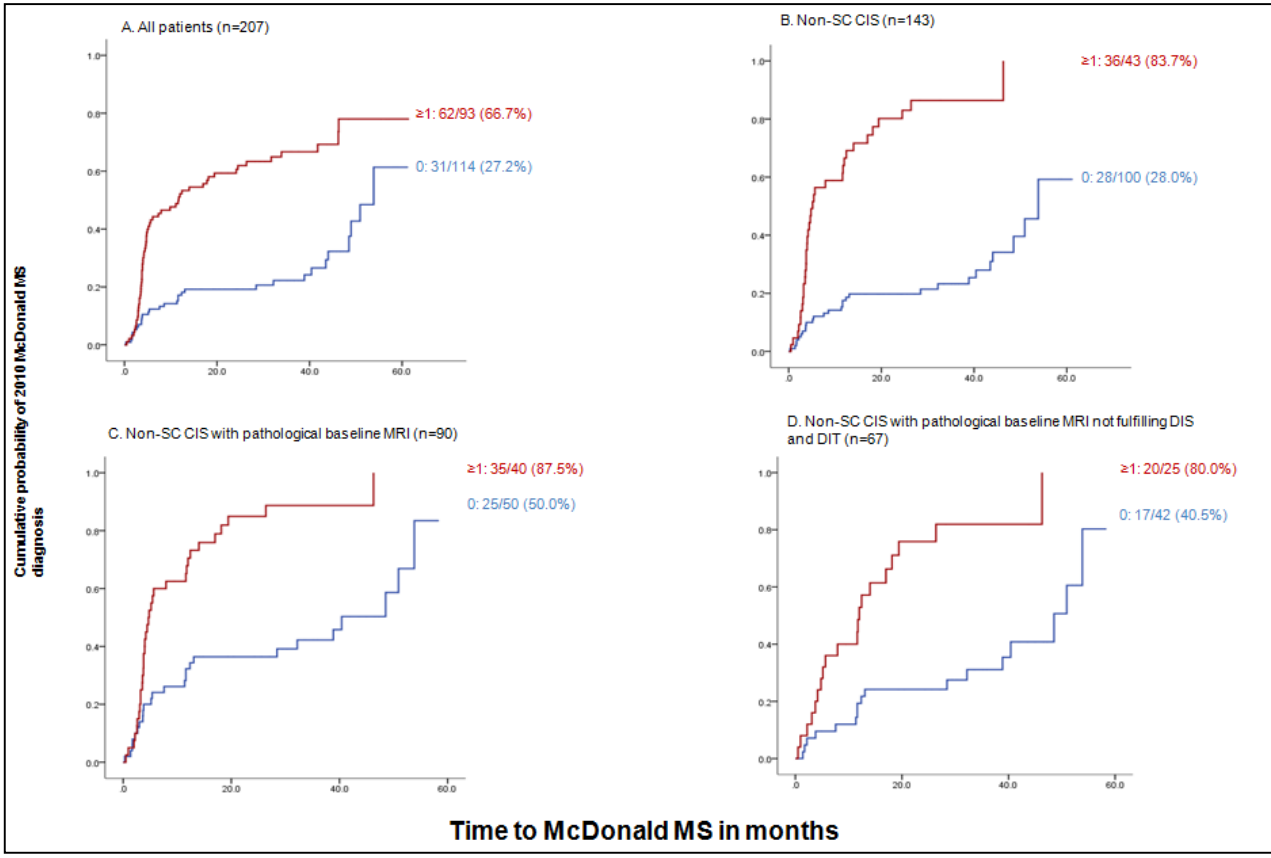
Prognostic value of spinal cord MRI in CIS
The Barcelona inception cohort

- Study design: single-center, observational
- Sample size: 207 CIS patients (31% with a spinal cord syndrome)
- Follow-up: mean 35.7 (15.8) months.
- Outcomes: conversion to MS (CDMS, McDonald)

Presence of SC lesions is an independent risk factor for evolving to MS

Covariables considered:

- Brain T2 lesion number
- OCB in CSF
- Age
- Gender
- CIS topography
- Treatment with DMT



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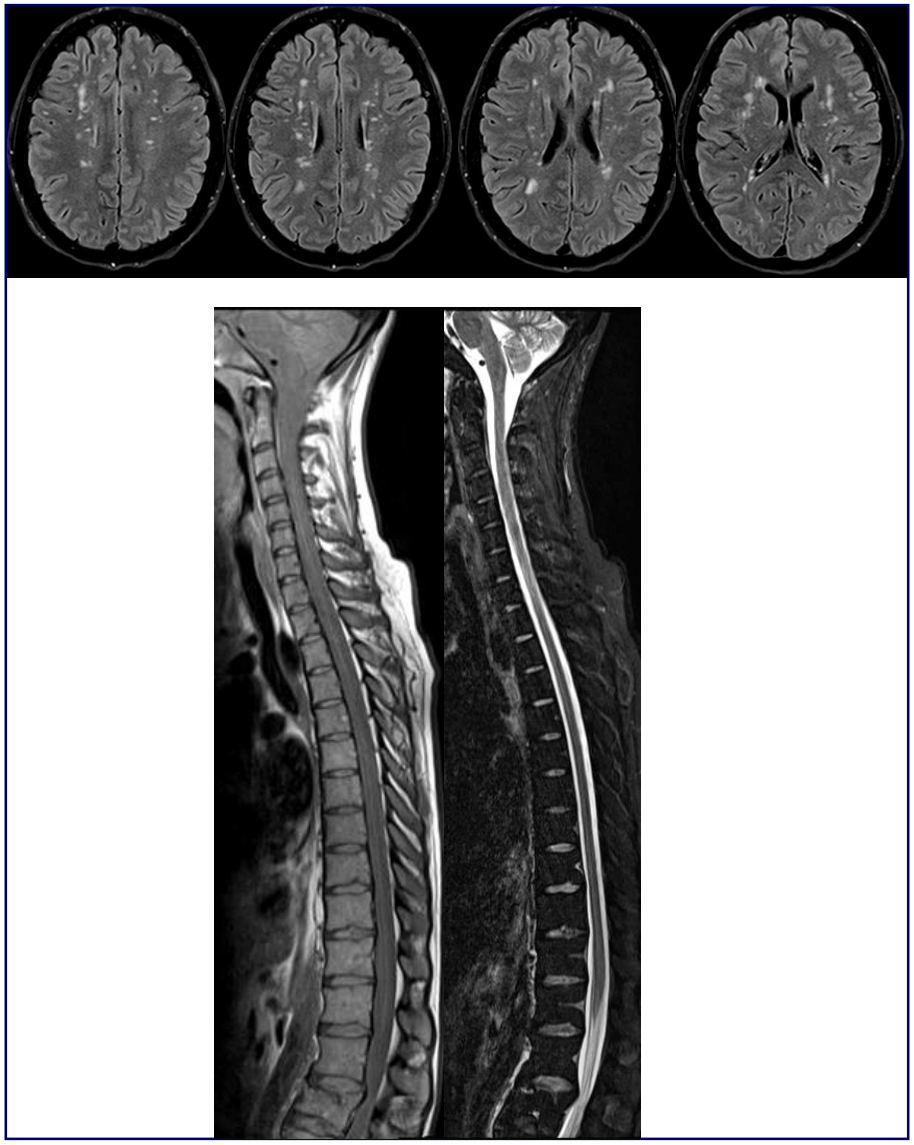
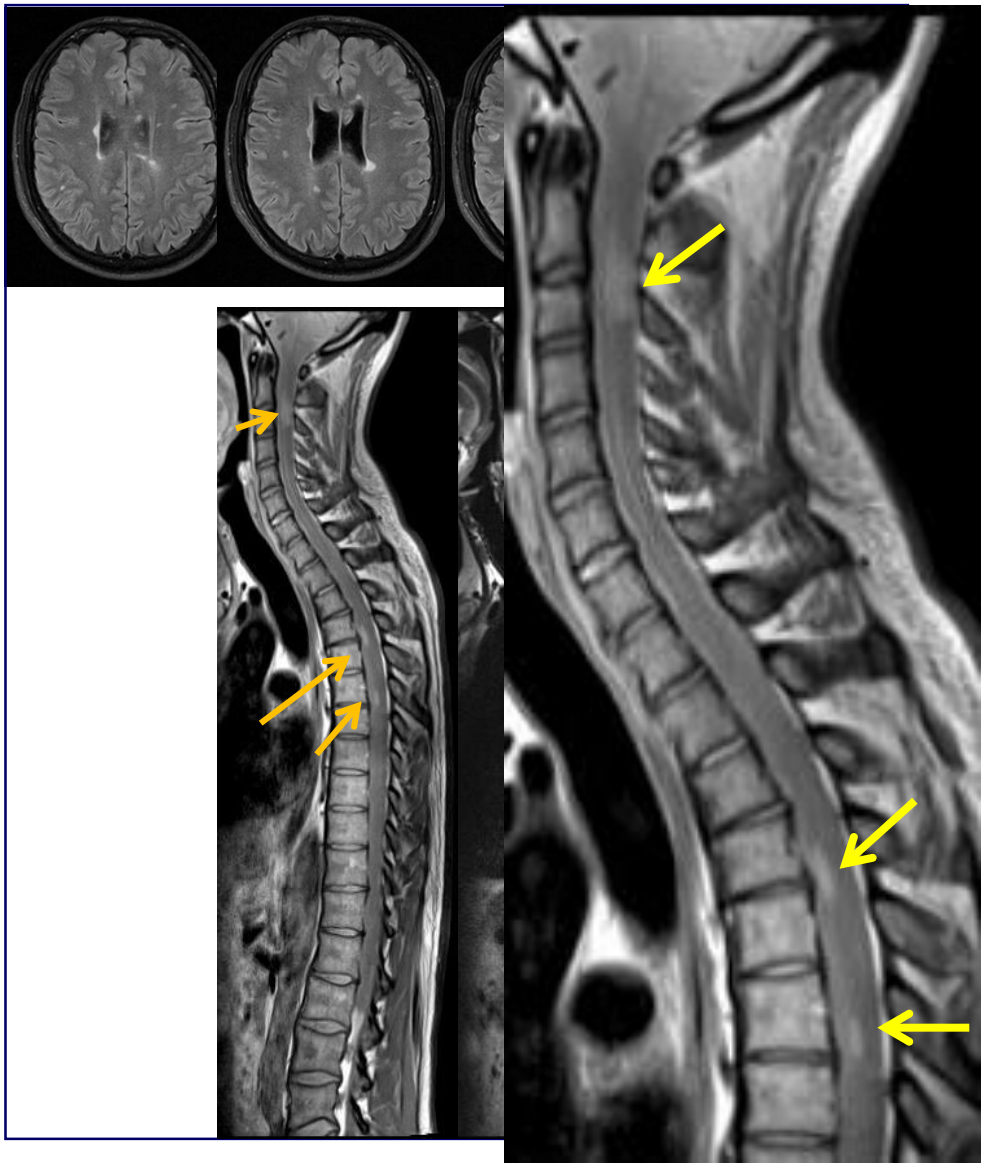
Arrambide G et al. Poster presentation (P996) ECTRIMS 2015

Brain MRI with equivocal findings

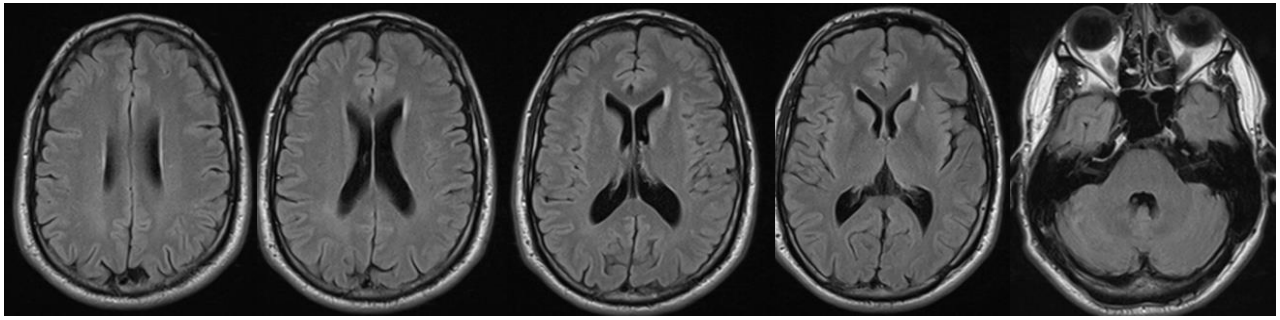




Rovira et al. Nat Rev Neurol 2015;11:471-82.

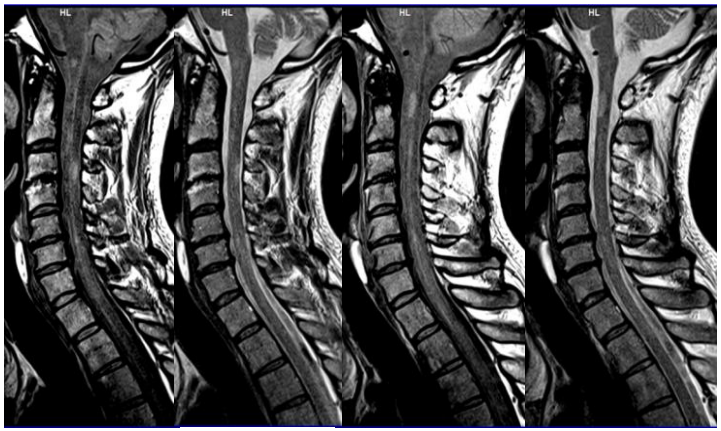
Negative brain scan, but strong clinical suspicion of MS

- One year disease progression
- Normal brain MRI
- Positive CSF analysis



Primary progressive MS

OB in CSF

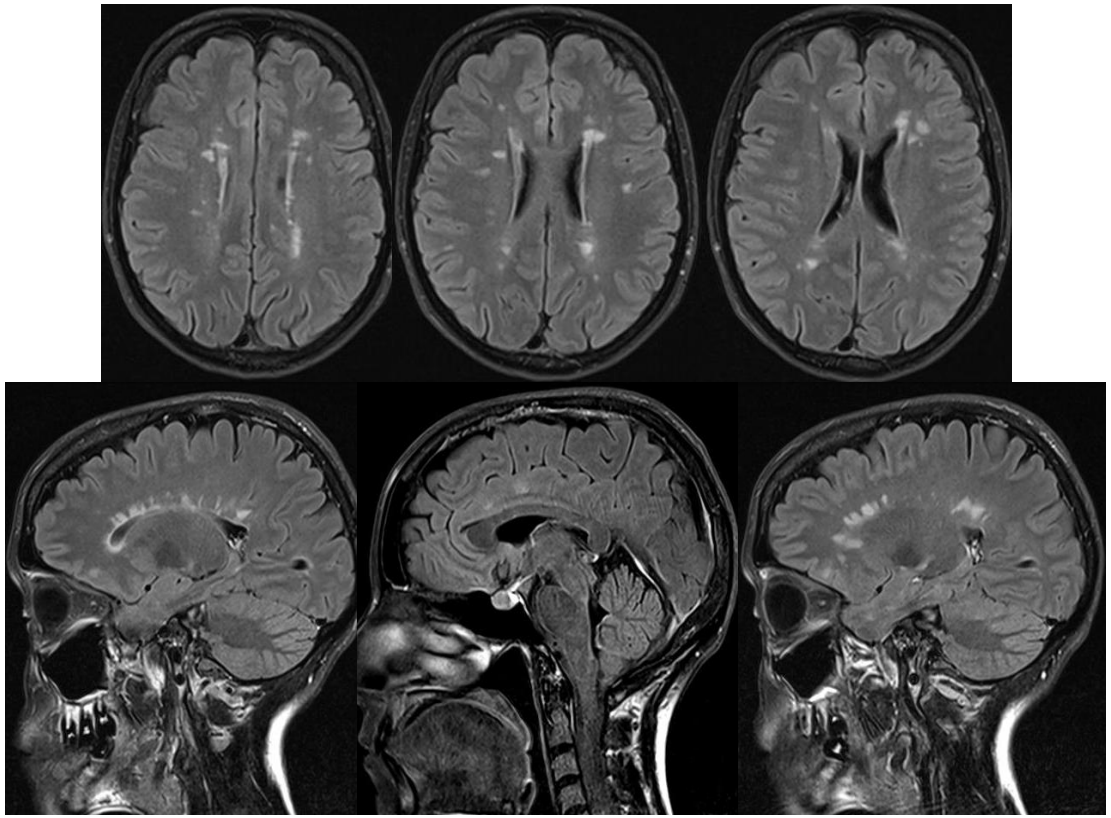


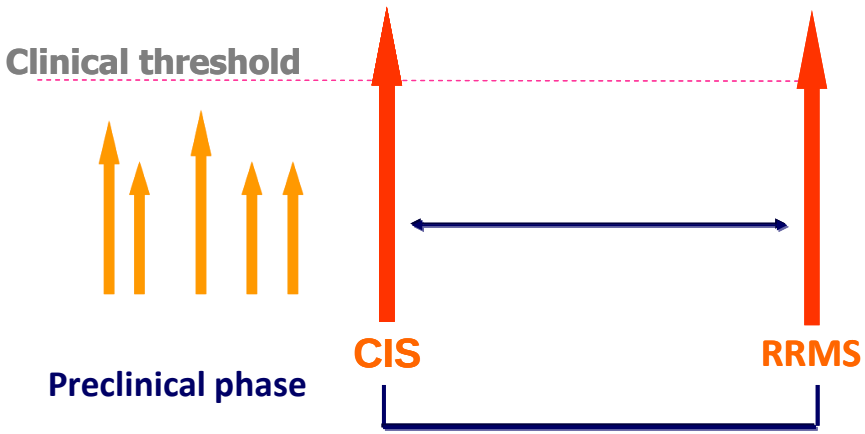
Normal brain in MRI in MS patients: 1-3%, 50% are PPMS. Most have an abnormal SC MRI

Thorpe et al. Brain 1996

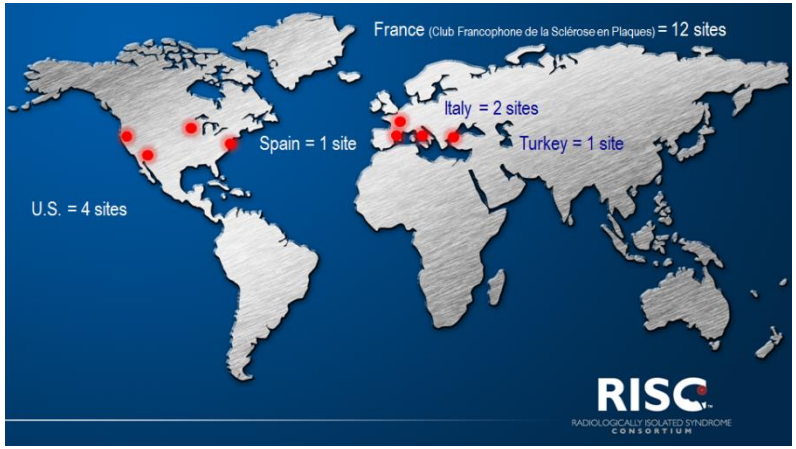
Radiologically Isolated Syndrome (RIS)

- First proposed in 2009 (Okuda et al. Neurology 2009)
- Incidental MRI anomalies within the CNS suggestive of multiple sclerosis

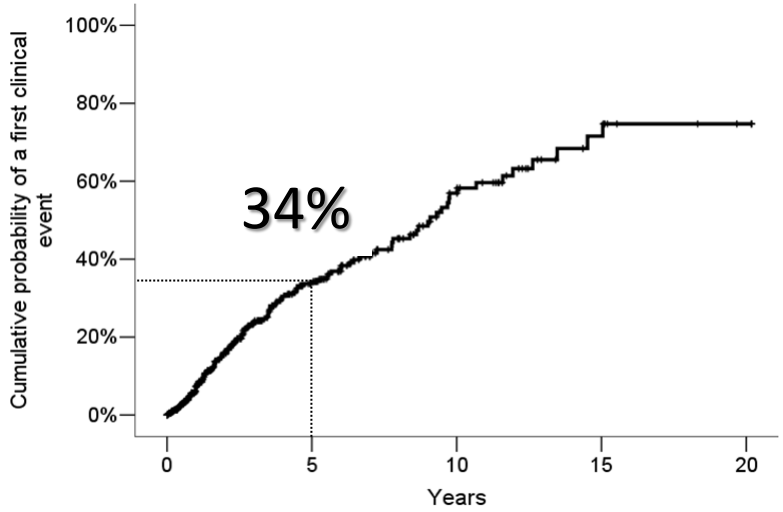




Radiologically Isolated Syndrome (RIS)

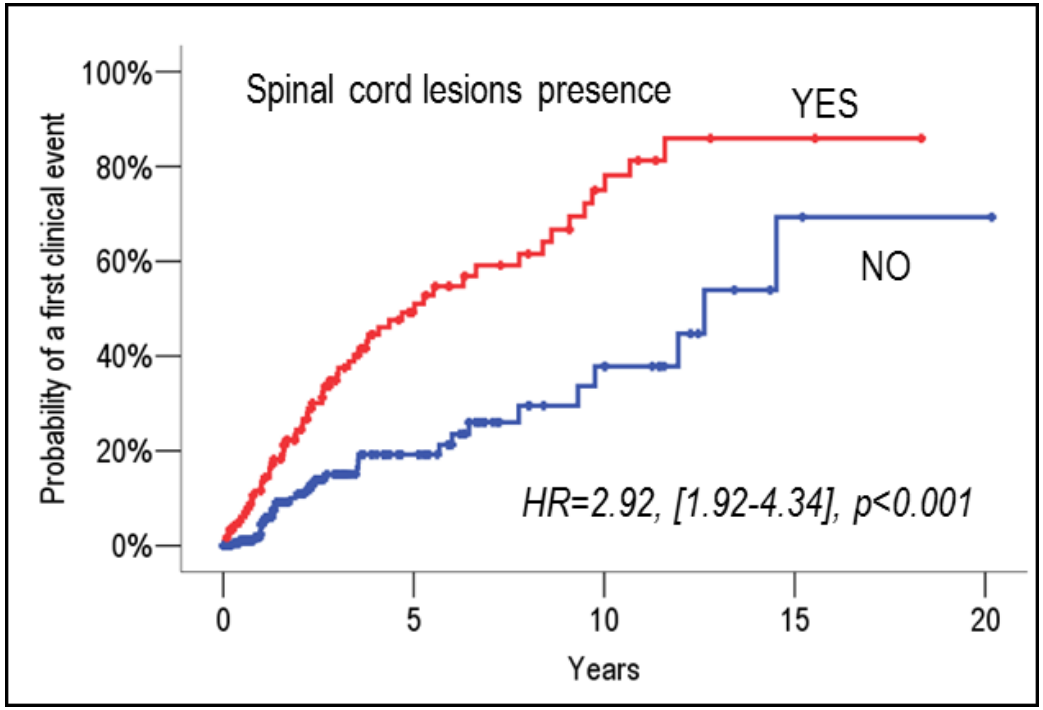


RIS Cases = 451 (20 databases, 5 countries)



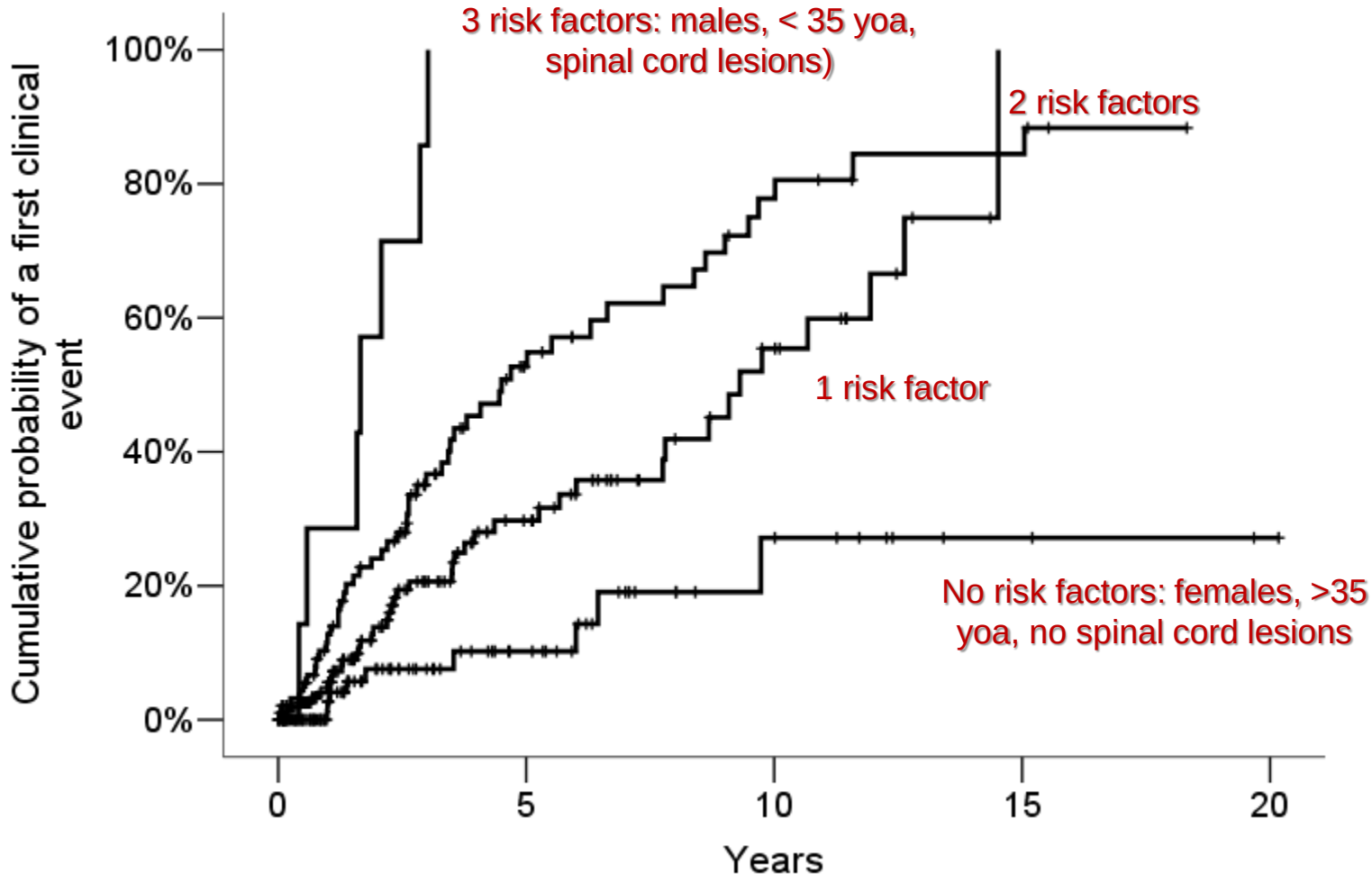
Kaplan-Meier survival analysis with the endpoint of time to the first acute or progressive event at 5-years for the entire RIS cohort.

Kaplan-Meier survival analysis with the endpoint of time to a first clinical event by the presence of spinal cord lesions



Okuda et al. Plos One 2014

Radiologically Isolated Syndrome (RIS)



0 : 116 subjects, 5-year probability of a first clinical event = 10%

1: 163 subjects, 5-year probability of a first clinical event = 34%

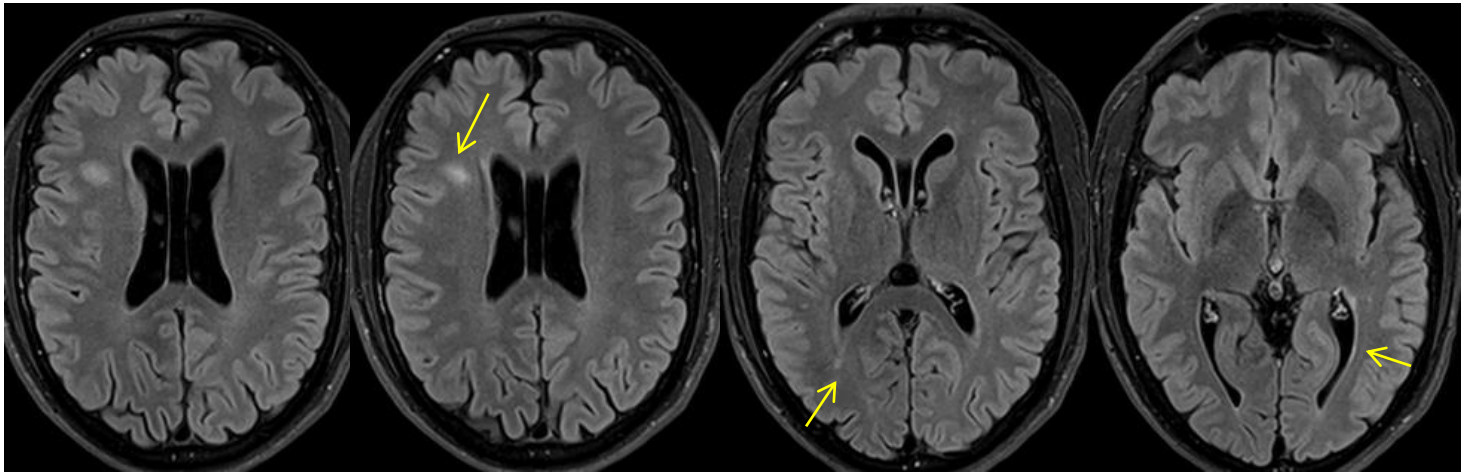
2: 96 subjects, 5-year probability of a first clinical event = 53%

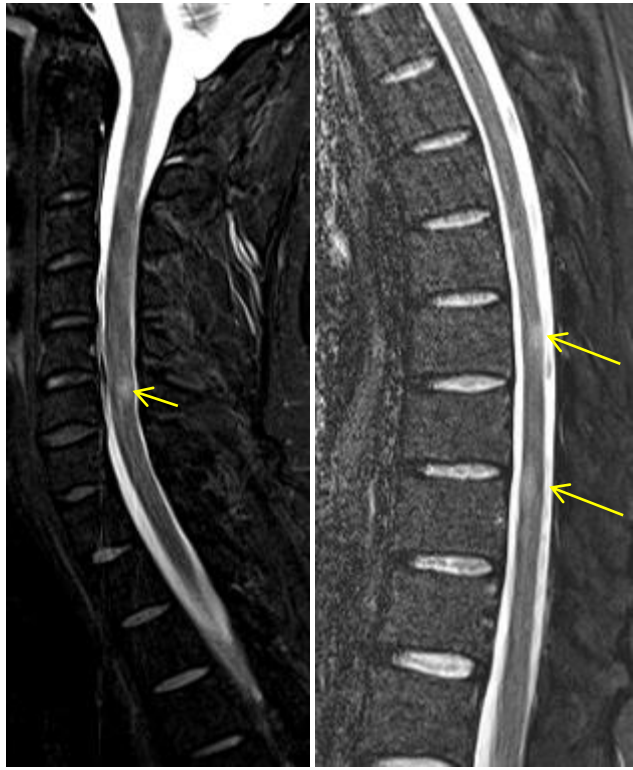
3: 8 subjects, 5-year probability of a first clinical event = 100%

Okuda et al. Plos One 2014

Radiologically Isolated Syndrome (RIS)

Male, 43 years





5-year probability of a first clinical event = 53%

Prognostic value of spinal cord MRI in CIS
The Barcelona inception cohort

- Study design: single-center, observational
- Sample size: 207 CIS patients (31% with a spinal cord syndrome)
- Follow-up: mean 35.7 (15.8) months.
- Outcomes: reach significant disability EDSS ≥ 3.0

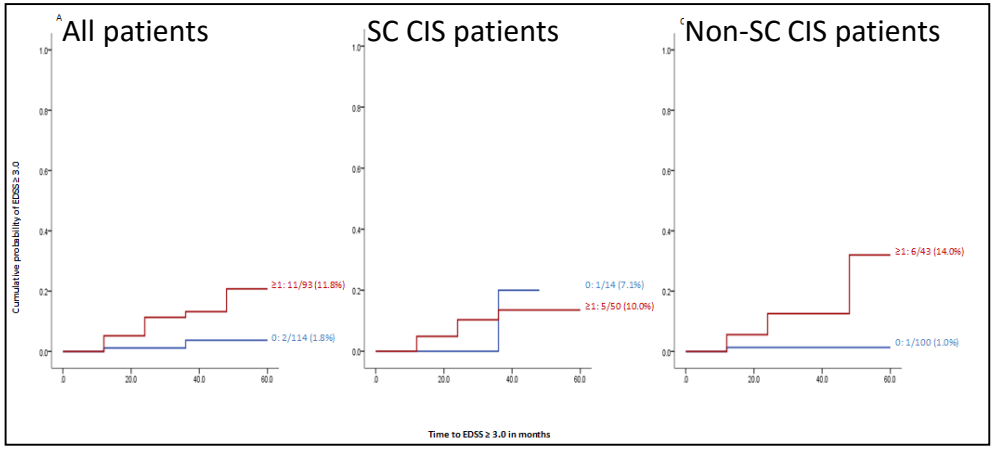
Proportion of patients with SC lesions and EDSS ≥3.0.

	All CIS n=207	SC CIS n=64	Non-SC CIS n=143	p
Presence of SC lesions: n (%)	93 (44.9)	50 (78.1)	43 (30.1)	<0.0001
EDSS ≥3.0: n (%)	13 (6.3)	6 (9.4)	7 (4.8)	0.171

Presence of at least one SC lesion was associated with an EDSS ≥ 3.0: 11.8% (vs 1.8%) p=0.003

	n	aHR	95% CI	p
All				
No SC lesions	114	1		
SC lesions	93	5.7	0.9-36.0	0.067
SC CIS				
No SC lesions	14	1		
SC lesions	15	0.5	0.04-7.9	0.647
Non-SC CIS				
No SC lesions	100	1		
SC lesions	43	36.2	1.5-880.4	0.028

aHR for reaching an EDSS >=3.0.



Prognostic value of SC lesions on reaching an EDSS ≥3.0. A: All patients (n=207). B: SC CIS (n=64). C: Non-SC CIS (n=143).

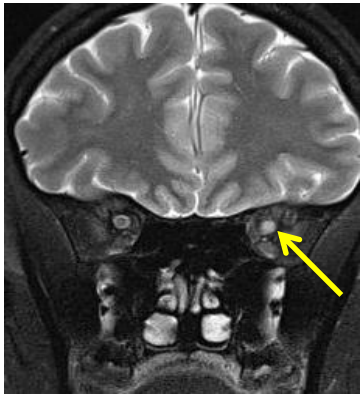
The presence of at least one SC lesion at the time of the CIS is associated with short-term disability and further contributes to estimate the risk of disability accumulation, particularly in non-SC CIS.

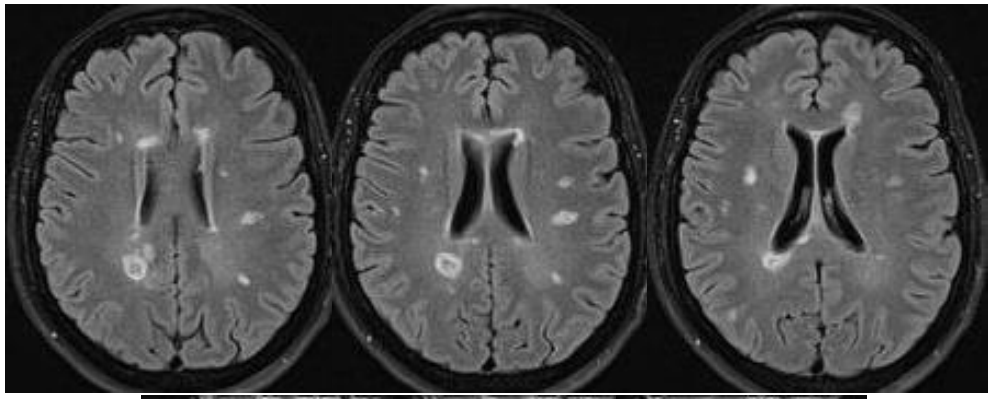
Arrambide G et al. Poster presentation (P996) ECTRIMS 2015

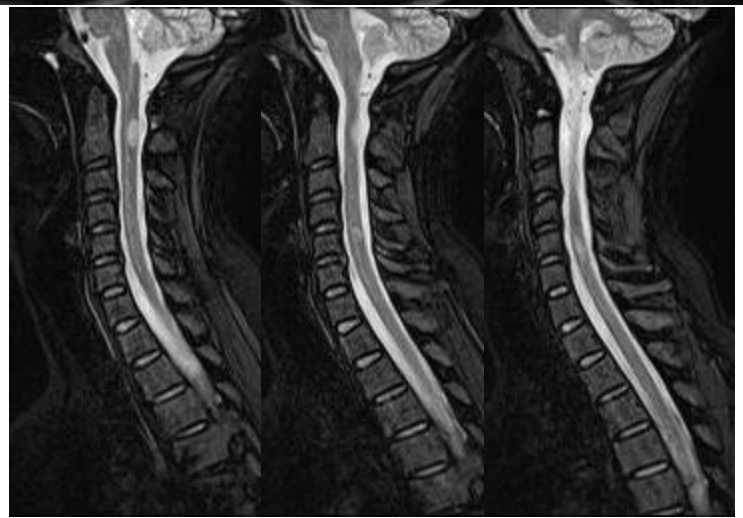
Spinal cord MRI in CIS
Diagnostic and prognostic value

- It is recommended performing a SC MRI in non-SC CIS who do not fulfill the McDonald criteria with brain MRI alone for diagnostic purposes

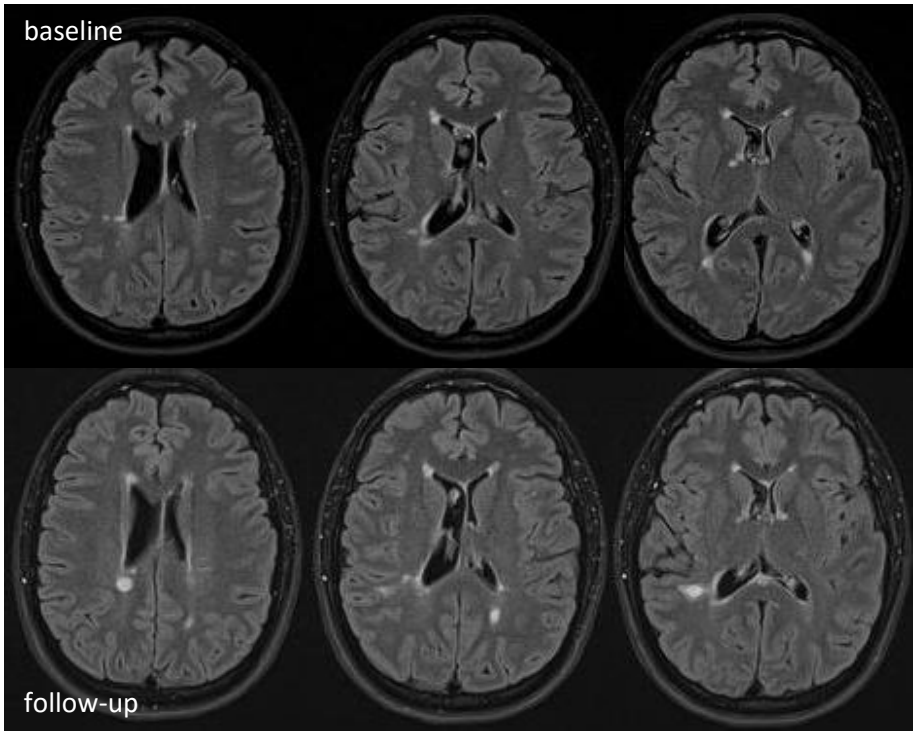
- However, acquiring a baseline SC MRI in all CIS patients is useful to estimate their prognosis.

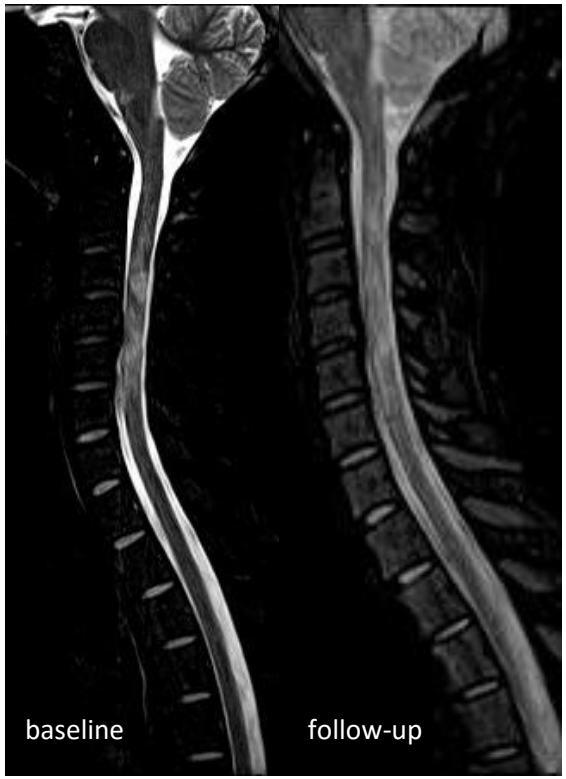






Spinal cord MRI in monitoring MS





- Serial spinal MRI shows considerably fewer new lesions than serial brain MRI
- Most are symptomatic
- Difficult to detect
- A relationship exists between development of new lesions in the brain and the development of new lesions in the spinal cord

Vall d'Hebron Hospital

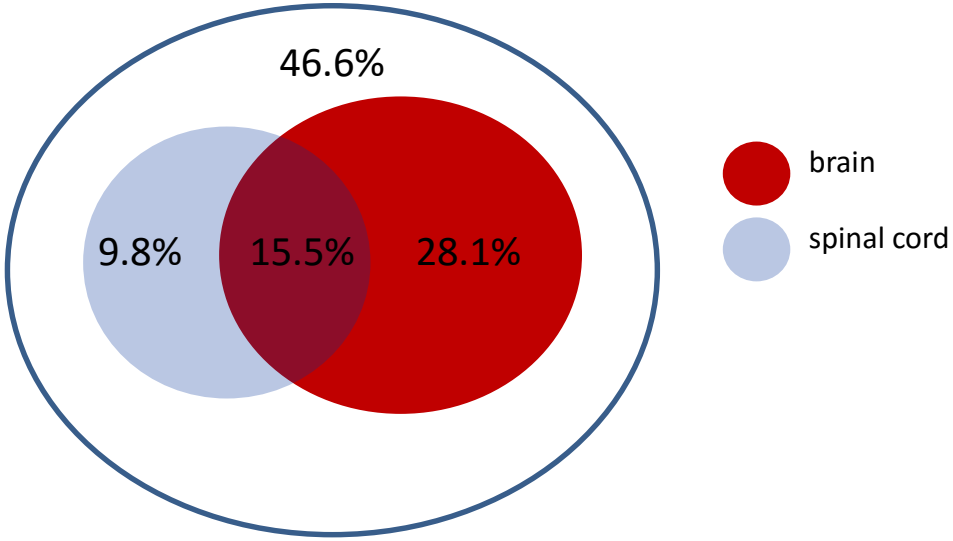
Thorpe et al. Neurology 1996

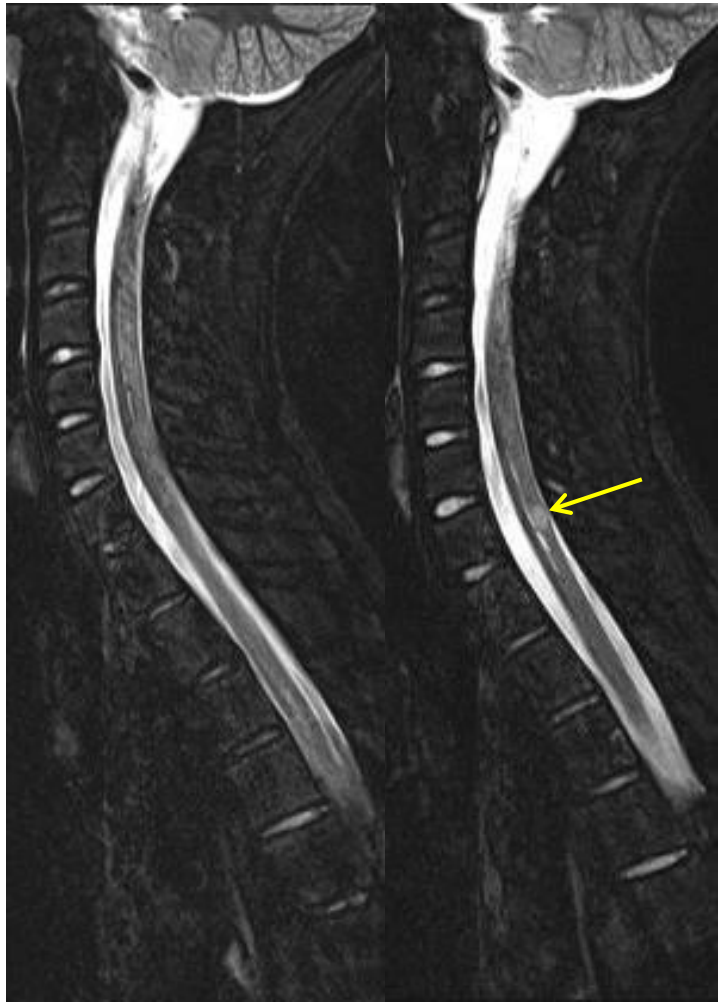
Spinal cord MRI in monitoring MS

103 RRMS patients: clinically stable
Median interval between scans: 17 months

New asymptomatic lesions

- 43.7% brain
- 25.2% spinal cord
- **9.8% only asymptomatic SC lesions**





A significant proportion of disease activity only in the SC, a fact that could have important implications in assessing and predicting treatment response

Zecca et al. Mult Scler J 2015

A lesion topography-based approach

To predict treatment response to IFNB

- Study design: Independent, single-centre, post-marketing analysis
- Sample size: 390 RRMS patients starting IFNB and reassessed one year after
- Follow-up: 1-4 years after treatment start
- Outcomes: relapses, sustained disability progression

…clinical relapses (n=160, 41%)

Independent Predictor	HR (95% CIs)	p
Age (each year)	0.98 (0.96-0.99)	**0.03**
Relapses 1Y	1.7 (1.1-2.6)	**0.01**
New T2 lesion count 1Y		
0	Ref.	-
1	1.4 (0.7-2.7)	0.29
2	1.7 (1.0-2.8)	0.06
3+	2.6 (1.5-4.5)	**<0.001**

Lesion location did not contribute to fit the model

…sustained disability worsening (n=65, 16%)

Independent Predictor	HR (95% CIs)	p
Male gender	1.9 (1.1-3.3)	**0.02**
EDSS score (each step)	2.1 (1.6-2.8)	**<0.001**
Relapses 1Y	2.9 (1.6-5.2)	**0.001**
New infratentorial lesions 1Y	2.6 (1.2-5.6)	**0.01**
New spinal cord lesions 1Y	2.3 (1.1-4.8)	**0.02**

Lesion count did not contribute to fit the model

Galassi et al. Mult Scler 2015;23 (11 Suppl):307 (abs P634)

Spinal cord MRI in Multiple Sclerosis

•MR imaging of the spinal cord is more challenging than imaging of the brain in MS patients, and a meticulous standardized MR technique is essential to enable acquisition of high-quality images.

•Spinal cord MR imaging provides additional useful information to brain MR imaging to establish a prompt and accurate diagnosis of MS, to provide valuable prognostic information, and in certain cases for monitoring the disease course and treatment response.

•Quantitative MR-based measures, in particular spinal cord atrophy measurements, have proven valuable for assessing the type and degree of spinal cord damage, although their assessment is technically challenging and cannot still be currently incorporated into the daily clinical setting.

Rovira À, De Stefano N. Curr Op Neurol 2016 (in press)

Neuroimmunology Unit **NeuroRx Unit**

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