Clinical and research application of MRI in diagnosis and monitoring of multiple sclerosis

24-25 February 2016 - Siena, Italy
How to use MRI for diagnosing MS: past, present and future diagnostic criteria

Claudio Gasperini
Centro di Riferimento Regionale per la Sclerosi Multipla
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In the absence of a diagnostic test specific for multiple sclerosis (MS), the neurological community has adopted diagnostic criteria for MS.

It is singular that a morbid state which possesses so distinct and so striking anatomical substratum, and which, in short, is not a rare disease, should have escaped clinical analysis for such a length of time. Yet, nothing is simpler, as I trust to show you, than to diagnose the affection in question, by the bedside of the patient, at least when it has reached a typical period of perfect development (Charcot, Lecture VII, 1868/77).
Diagnosis of MS

- Demonstrate dissemination in space
- Demonstrate dissemination in time
- Ensure that there is no better explanation
**DIAGNOSTIC CRITERIA**

**Diagnostic Criteria:**
- Allison y Millar (1954)
- McAlpine (1965)
- Schumacher (1965)
- Rose (1976)
- Poser (1983)
- McDonald (2001)
- McDonald (2005)
- McDonald (2010)
The Changing Face of Multiple Sclerosis: Diagnosis

New Diagnostic Criteria for Multiple Sclerosis: Guidelines for Research Protocols

W. Ian McDonald, FRCP, 1 Alarico G. A. Kappos, MD, 1 Hans-Peter Hartung, MD, 2 Fred D. Lublin, MD, 3 Chris H. Polman, MD, 4 Stephen C. Reingold, PhD, 5 Brenda Banwell, MD, 6 Michel Clenet, MD, 7 Jeffrey A. Cohen, MD, 8 Massimo Filippi, MD, 6 Kazuo Fujihara, MD, 7

Special Article

Recommended Diagnostic Criteria for Multiple Sclerosis: Guidelines from the International Panel on the Diagnosis of MS

Diagnosing Criteria for Multiple Sclerosis: 2005 Revisions to the “McDonald Criteria”

Chris H. Polman, MD, PhD, 4 Stephen C. Reingold, PhD, 5 Brenda Banwell, MD, 6

Diagnostic Criteria for Multiple Sclerosis: 2010 Revisions to the McDonald Criteria

Chris H. Polman, MD, PhD, 1 Stephen C. Reingold, PhD, 5 Brenda Banwell, MD, 6

MRI criteria for the diagnosis of multiple sclerosis: MAGNIMS consensus guidelines

In patients presenting with a clinically isolated syndrome, MRI can support and substitute clinical information in the diagnosis of multiple sclerosis by showing disease dissemination in space and time and by helping to exclude disorders that can mimic multiple sclerosis. MRI criteria were first included in the diagnostic work-up for multiple sclerosis in 2001, and since then several modifications to the criteria have been proposed in an attempt to simplify lesion-count models for showing disease dissemination in space, change the timing of MRI scanning to show dissemination in time, and increase the value of spinal cord imaging. Since the last update of these criteria, new data on the use of MRI to establish dissemination in space and time have become available, and MRI technology has improved. State-of-the-art MRI findings in these patients were discussed in a MAGNIMS workshop, the goal of which was to provide an evidence-based and expert-opinion consensus on proposed modifications to MRI criteria for the diagnosis of multiple sclerosis.
Diagnostic Criteria for Multiple Sclerosis: 2010 Revisions to the McDonald Criteria

Chris H. Polman, MD, PhD, Stephen C. Reingold, PhD, Brenda Banwell, MD, Michel Clanet, MD, Jeffrey A. Cohen, MD, Massimo Filippi, MD, Kazuo Fujihara, MD, Eva Havrdova, MD, PhD, Michael Hutchinson, MD, Ludwig Kappos, MD, Fred D. Lublin, MD, Xavier Montalban, MD, Paul O’Connor, MD, Magnhild Sandberg-Wollheim, MD, PhD, Alan J. Thompson, MD, Emmanuelle Waubant, MD, PhD, Brian Weinshenker, MD, and Jerry S. Wolinsky, MD

**TABLE 1: 2010 McDonald MRI Criteria for Demonstration of DIS**

DIS Can Be Demonstrated by \( \geq 1 \) 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.

**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; DIS = lesion dissemination in space; CNS = central nervous system.
MRI criteria for MS in patients with clinically isolated syndromes

Figure: New proposed diagnostic algorithm in patients with typical clinically isolated syndromes (CIS)

**DIS**
- ≥1 asymptomatic lesion in each of ≥2 characteristic locations: PV, JC, PF, spinal cord

**DIT**
- (i) Simultaneous presence of asymptomatic Gd enhancing and non-enhancing lesion(s) at any time
- (ii) A new T2 and/or Gd-enhancing lesion on follow up MRI irrespective of timing of baseline scan

X. Montalban, M.D.  
M. Tintoré, M.D.  
J. Swanton, M.D.  
F. Barkhof, M.D.  
F. Fazekas, M.D.  
M. Filippi, M.D.  
J. Frederiksen, M.D.  
L. Kappos, M.D.  
J. Palace, M.D.  
C. Polman, M.D.  
M. Rovaris, M.D.  
N. de Stefano, M.D.  
A. Thompson, M.D.  
T. Yousry, M.D.  
A. Rovira, M.D.  
D.H. Miller, M.D.  

• Allow more rapid diagnosis of MS preserving equivalent specificity and/or sensitivity in comparison with past criteria

• Simplify the diagnostic process with fewer required MRI examinations
The Changing Face of Multiple Sclerosis: diagnosis and patients

- Diagnosis and patients
  - Clinical Threshold
  - Axonal Loss
  - Demyelination
  - Inflammation

- Disease parameter
- First Clinical Attack
- Relapsing–remitting
- Transitional
- Secondary Progressive

- RIS
- CIS

Poser McD 2005
Poser McD 2010
New data on application of MRI to show *dissemination in space* and *time* have become available.

Many improvements in MRI technology have occurred.

New insights into MS disease activity from studies using high-field and ultra-high-field scanners have emerged.
Periventricular lesions
Comparison of MRI criteria at first presentation to predict conversion to clinically definite multiple sclerosis

Frederik Barkhof,1,2 Massimo Filippi,5 David H. Miller,7 Philip Scheltens,1,3 Adriana Campi,6
Chris H. Polman,1,3 Giancarlo Comi,5 Herman J. Adèr,1,4 Nick Losseff9 and Jacob Valk1,2

Table 5 Diagnostic performance of final model compared with Paty’s and Fazekas’ criteria*

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>NPV (%)</th>
<th>PPV (%)</th>
<th>Accuracy (%)</th>
</tr>
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<tr>
<td>Paty’s</td>
<td>88</td>
<td>54</td>
<td>85</td>
<td>60</td>
<td>69</td>
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<td>78</td>
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*Paty et al. (1988) and Fazekas et al. (1988). PPV = positive predictive value; NPV = negative predictive value.

DIS CRITERIA: Relevance of periventricular lesions

Conclusions

• A single lesion was deemed not sufficiently specific

• Three or more periventricular lesions was the most accurate threshold
Cortical lesions
380 subjects were studied: 116 CIS; 163 RRMS; 101 SPMS and 40 HV
Intracortical lesions
Relevance for new MRI diagnostic criteria for multiple sclerosis

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Univariate and multivariate logistic regression analysis results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Variable</td>
<td>Univariate analysis</td>
</tr>
<tr>
<td></td>
<td>OR (95% CI)</td>
</tr>
<tr>
<td>≥1 Gd-enhancing lesion</td>
<td>4.1 (1.0-17.0)</td>
</tr>
<tr>
<td>≥1 spinal cord lesion</td>
<td>2.7 (1.0-7.6)</td>
</tr>
<tr>
<td>≥9 T2 lesions</td>
<td>4.2 (1.6-10.7)</td>
</tr>
<tr>
<td>≥1 infratentorial lesion</td>
<td>3.7 (1.5-9.5)</td>
</tr>
<tr>
<td>≥3 periventricular lesions</td>
<td>7.3 (2.6-20.3)</td>
</tr>
<tr>
<td>≥1 juxtacortical lesion</td>
<td>1.9 (0.8-4.8)</td>
</tr>
<tr>
<td>≥1 ICL</td>
<td>15.3 (4.8-49.0)</td>
</tr>
</tbody>
</table>

Abbreviations: CI = confidence interval; Gd = gadolinium; ICL = intracortical lesion; OR = odds ratio.

* For the variable defined as at least 1 Gd-enhancing lesion or 1 spinal cord lesion.

Conclusions: The accuracy of MRI diagnostic criteria for MS is increased when considering the presence of ICLs on baseline scans from patients at presentation with CIS suggestive of MS. If confirmed by other studies, ICL detection might be considered in future diagnostic algorithms for MS.
DIS & DIT CRITERIA: RELEVANCE OF CLs

CLs / Differential diagnosis

Migraine patients with WMHs

<table>
<thead>
<tr>
<th></th>
<th>Migraine patients (n = 32)</th>
<th>RRMS patients (n = 15)</th>
<th>p values</th>
<th>Bonferroni adjusted p values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean number of WM lesions (SD)</td>
<td>23.3 (31.0)</td>
<td>96.0 (72.4)</td>
<td>&lt;0.0001*</td>
<td>&lt;0.0001*</td>
</tr>
<tr>
<td>Mean WM LV (SD) (ml)</td>
<td>1.52 (2.53)</td>
<td>10.4 (12.0)</td>
<td>&lt;0.0001**</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>≥1 periventricular lesion n (%)</td>
<td>12 (32)</td>
<td>15 (100)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥1 infratentorial lesion n (%)</td>
<td>1 (3)</td>
<td>14 (93)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥1 juxtacortical lesion n (%)</td>
<td>17 (53)</td>
<td>15 (100)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of patients with DIS MRI criteria (%)</td>
<td>11 (34)</td>
<td>15 (100)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

No. (%) of DIS patients with at least:

≥1 periventricular lesion and ≥1 juxtacortical lesion: 10 (29)
≥1 periventricular lesion and ≥1 infratentorial lesion: 1 (3)
≥1 juxtacortical lesion and ≥1 infratentorial lesion: 0 (0)

Mean number of CLs (SD) | 0 | 1.3 (1.3) | 0.0002* | 0.001 |
Mean number of intracortical lesions (SD) | 0 | 0.4 (0.9) | <0.0001* | <0.0001 |
Mean number of mixed GM/WM lesions (SD) | 0 | 0.9 (1.1) | <0.0001** | <0.0001 |
Mean CLs volume (SD) (ml) | 0 | 0.083 (0.09) | 0.005 | 0.03 |

No CLs in NMO

NMO | MS

Absinta et al., J Neurol 2012
Calabrese et al., Neurology 2012
Conclusions

- CL inclusion in MRI diagnostic criteria is promising due to:
  - Identification of CIS patients at risk of evolution to MS
  - Role in differential diagnosis from other neurological conditions
• The likelihood of optic neuritis being a monophasic illness was substantially reduced in the presence of CSF oligoclonal bands or clinically silent brain MRI lesions (with [HR] of 5·1 for patients with one to three lesions and 11·3 for patients with ten or more lesions).

• Presence of even one clinically silent T2-hyperintense brain lesion in children with optic neuritis is highly associated with confirmation of a multiple sclerosis diagnosis.
DIS CRITERIA: Relevance of optic neuritis

Conclusions

• Clinical documentation of optic nerve atrophy or pallor, neurophysiological confirmation of optic nerve dysfunction, or imaging features of clinically silent optic nerve support dissemination in space.
Symptomatic lesions
### Diagnostic criteria 2010

**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:**

<table>
<thead>
<tr>
<th>Area</th>
</tr>
</thead>
<tbody>
<tr>
<td>Periventricular</td>
</tr>
<tr>
<td>Juxtacortical</td>
</tr>
<tr>
<td>Infratentorial</td>
</tr>
<tr>
<td>Spinal cord(^b)</td>
</tr>
</tbody>
</table>

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.
Therefore, it could be considered that CIS patients with one single symptomatic lesion in the brainstem/cerebellum behave as CIS patients with zero brain MRI lesions.

Brainstem/cerebellum syndrome

Therefore: one single symptomatic lesion .....

Courtesy of M Tintore
Therefore: one single symptomatic lesion ..... 

Therefore, it could be considered that CIS patients with one single symptomatic lesion in the spinal cord behave as CIS patients with zero brain MRI lesions.
Objective

To study the risk of developing MS and accumulation of disability of CIS patients presenting with one single symptomatic lesion in the brainstem/cerebellum or spinal cord
Results: study population

Inception cohort
N= 1059

Available MRI data
N= 954

MRI normal*: 0 lesions
N= 290

One single symptomatic lesions N= 35
CIS brainstem + one brainstem lesion N=  20
CIS spinal-cord+ one spinal cord lesion N=15

One single asymptomatic lesions:
CIS optic nerve + one lesion N= 18

MRI**: > 1 lesion
N=611

*MRI normal: 0 brain lesions and 0 spinal cord lesions (when a spinal cord MRI was available n=71), 0 brain lesions (when only the brain MRI was available n=219)

**MRI > 1 lesion brain lesion or spinal cord lesions (when a spinal cord MRI was available n=), 1 brain lesions (when only the brain MRI was available n=)

Courtesy of M Tintore
## KM for CDMS

<table>
<thead>
<tr>
<th>CDMS</th>
<th>aHR</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 lesions</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 single symptomatic lesion</td>
<td>7.2</td>
<td>3.4-15.0</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>1 single asymptomatic lesion</td>
<td>5.7</td>
<td>2.0-16.0</td>
<td>P=0.001</td>
</tr>
<tr>
<td>&gt; 1 lesion</td>
<td>11.8</td>
<td>6.8-20.6</td>
<td>p&lt;0.001</td>
</tr>
</tbody>
</table>

*Courtesy of M Tintore’*
KM for McDonald

<table>
<thead>
<tr>
<th>McDonald MS</th>
<th>aHR</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 lesions</td>
<td>1</td>
<td></td>
<td></td>
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<tr>
<td>1 single symptomatic lesion</td>
<td>7.7</td>
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<td>1 single asymptomatic lesion</td>
<td>5.8</td>
<td>2.3-14.9</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>≥ 1 lesion</td>
<td>14.8</td>
<td>8.9-24.9</td>
<td>p&lt;0.001</td>
</tr>
</tbody>
</table>

Time since first attack (months)

Courtesy of M Tintore’
Conclusions DIS

- Patients with single symptomatic lesion behave similar than patients with one asymptomatic lesion

It is robust enough for a revision of the MR diagnostic criteria

Yes
Dissemination in time (MRI)

McDonald 2001/2005

3 months

MRI(1st): Gad enhancing lesion topography # relapse

1 month

MR

MRI-2 New T2 lesion
A Single, Early Magnetic Resonance Imaging Study in the Diagnosis of Multiple Sclerosis

Alex Rovira, MD; Josephine Swanton, MD; Mar Tintore, MD; Elena Huerga, RT; Fredrick Barkhof, MD; Massimo Filippi, MD; Jette L. Frederiksen, MD; Annika Langkilde, MD; Katherine Miszkiel, MD; Chris Polman, MD; Marco Rovaris, MD; Jaume Sastre-Garriga, MD; David Miller, MD; Xavier Montalban, MD

CIS

MRI (> 3months)

First (0-3 months)

¾ Barkhof criteria + ≥1 gad lesion

¾ Barkhof criteria + ≥1 gad lesion

MS
Diagnostic properties of MRI in two different time points

MAGNIMS group

First MRI
- Sensitivity: 47%
- Specificity: 88%
- Accuracy: 76.5%

Second MRI
- Sensitivity: 43%
- Specificity: 87%
- Accuracy: 75%

Courtesy of M Tintore
MRI criteria for MS in patients with clinically isolated syndromes

Neurology® 2010;74:427-434

CONTEMPORARY ISSUES IN NEUROLOGIC PRACTICE

CIS

MRI at any time without DIS

New MRI: DIS + DIT

MRI at any time with DIS

New MRI: DIT

MRI at any time with DIS + Gd

MS

DIS

≥1 T2 lesion in ≥2 topographies

DIT

New T2 or Gd at any time

MAGNIMS group; Montalban et al, Neurology 2010.
DIT: 2010 McDonald criteria:

A new T2 on follow-up MRI, with reference to a baseline scan, irrespective of the timing of the baseline MRI

Simultaneous presence of asymptomatic gadolinium-enhancing and nonenhancing lesions at any time
Application and a proposed modification of the 2010 McDonald criteria for the diagnosis of multiple sclerosis in a Canadian cohort of patients with clinically isolated syndromes

Kang H et al. MSJ 2014

<table>
<thead>
<tr>
<th></th>
<th>Met</th>
<th>Not met</th>
<th>Total</th>
</tr>
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<tbody>
<tr>
<td><strong>2010 McDonald DIS criteria</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2010 McDonald DIT Criteria</td>
<td>33</td>
<td>06</td>
<td>37 (33.9%)</td>
</tr>
<tr>
<td>Met</td>
<td>03</td>
<td>04</td>
<td>07 (66.1%)</td>
</tr>
<tr>
<td>Not met</td>
<td>29</td>
<td>22</td>
<td>51 (46.0%)</td>
</tr>
<tr>
<td>Total</td>
<td>07</td>
<td>00</td>
<td>10 (9.1%)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>76 (69.7%)</td>
<td>33 (30.3%)</td>
<td>N = 109</td>
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**2010 Modified McDonald DIT criteria**

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<tr>
<td>Met</td>
<td>36</td>
<td>04</td>
<td>40 (36.7%)</td>
</tr>
<tr>
<td>Not met</td>
<td>29</td>
<td>04</td>
<td>33 (30.3%)</td>
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DIS: dissemination in space; DIT: dissemination in time. *Simultaneous presence of any (asymptomatic AND symptomatic) gadolinium enhancing-lesions and nonenhancing lesions.

Conclusion: Using 2010 McDonald criteria, 30% of the CIS patients could be diagnosed with MS using a single MRI scan. Inclusion of symptomatic lesions in the DIT criteria further increases this proportion to 33%.
Conclusions DIT

• Excluding the symptomatic lesion decrease sensitivity

• No rational for excluding the symptomatic lesion when dealing with the concept of DIT.

It is robust enough for a revision of the MR diagnostic criteria
Yes
TABLE 1: 2010 McDonald MRI Criteria for Demonstration of DIS

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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.

Panel 2: Recommended 2016 MAGNIMS MRI criteria to establish disease dissemination in space in multiple sclerosis

Dissemination in space can be shown by involvement* of at least two of five areas of the CNS as follows:

- Three or more periventricular lesions
- One or more infratentorial lesion
- One or more spinal cord lesion
- **One or more optic nerve lesion**
- **One or more cortical or juxtacortical lesion**$^f$

*If a patient has a brainstem or spinal cord syndrome, or optic neuritis, the symptomatic lesion (or lesions) are not excluded from the criteria and contribute to the lesion count. $^f$This combined terminology indicates the involvement of the white matter next to the cortex, the involvement of the cortex, or both, thereby expanding the term juxtacortical lesion.
**Dissemination in space**

**PERIVENTRICULAR LESIONS**
- A single lesion was deemed not sufficiently specific
- **Three or more periventricular** lesions was the most accurate threshold

**OPTIC NERVE LESIONS**
- Clinical documentation of optic nerve atrophy or pallor, neurophysiological confirmation of optic nerve dysfunction, or imaging features of clinically silent optic nerve support dissemination in space.

**CORTICAL LESIONS**
- Since intracortical, leukocortical, and juxtacortical lesions cannot be distinguished reliably and consistently on conventional MRI scans, these lesions should be combined in a single term (cortical/juxtacortical lesions) that indicates involvement of the white matter next to the cortex, the cortex, or both.

---

Barkhof F et al, Brain 1997
Dissemination in time

The criteria for dissemination in time should therefore remain unchanged, the presence of non-enhancing black holes should not be considered as a potential alternative criterion to show dissemination in time in adult patients with MS, but might be useful to identify MS in paediatric patients.

Symptomatic lesions

No distinction needs to be made between symptomatic and asymptomatic MRI lesions to establish dissemination in both space and time.

Spinal cord imaging

SC imaging is recommended in patients with clinical features suggestive of spinal cord involvement to exclude alternative cord pathology and in those with non-spinal CIS that do not fulfil brain MRI criteria for DIS.
MRI criteria for DIT and DIS identical to those applied in adults should be used in children aged 11 years or older who have non-ADEM presentation.

2010 McDonald criteria apply well irrespective of world region, and, therefore, MRI criteria for DIT and DIS apply equally well to patients from Asia and Latin America as to patients from Europe and North America.

People should not be diagnosed with MS on the basis of MRI findings alone, and at least one clinical event consistent with acute demyelination remains a cornerstone for MS diagnosis.
Thank you for your kind attention !!!
Use of high-field and ultra-high field scanners

1.5 T 3.0 T 7.0 T

scan enables detection of a significantly higher number of lesions in patients with CIS with improved recognition of lesions involving the cortical, infratentorial, and periventricular regions.

BUT this influence does not lead to an earlier diagnosis of lesion dissemination in time and therefore definite MS.


Use of high-field or ultra-high-field scanners is not likely to result in an earlier diagnosis. However, lesion features distinctive MS could emerge from use of these scanners and might eventually enhance differentiation of multiple sclerosis from other diseases.
Comparison of MRI criteria at first presentation to predict conversion to clinically definite multiple sclerosis

Frederik Barkhof,1,2 Massimo Filippi,5 David H. Miller,7 Philip Scheltens,1,3 Adriana Campi,6 Chris H. Polman,1,3 Giancarlo Comi,5 Herman J. Adér,1,4 Nick Losseff7 and Jacob Valk1,2

Table 5  Diagnostic performance of final model compared with Paty's and Fazekas' criteria*

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