Dalla chiarezza diagnostica all'efficacia terapeutica

Monza, 2 febbraio 2012

IMAGING AL SERVIZIO DI DIAGNOSI E TERAPIA

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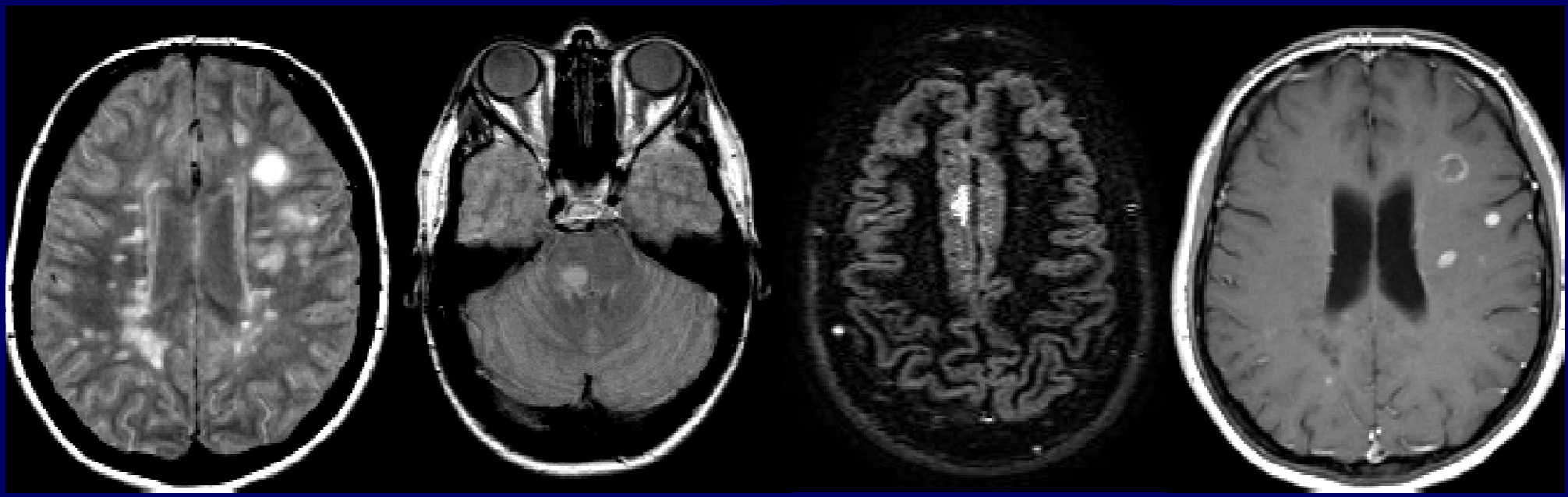
RM E DIAGNOSI DI SM

- Sensibilità nell'identificazione delle lesioni
- Sviluppo tecnologico e fattibilità
- Sicurezza
- Riproducibilità
- Diagnosi precoce
- Diagnosi differenziale

RM E DIAGNOSI DI SM

Caratteristiche delle lesioni visibili - Encefalo



Sede:
- Periventricolare
- Infratentoriale
- Corpo calloso
- Juxtacorticale (fibre ad U)
- Intracorticale (RM DIR)

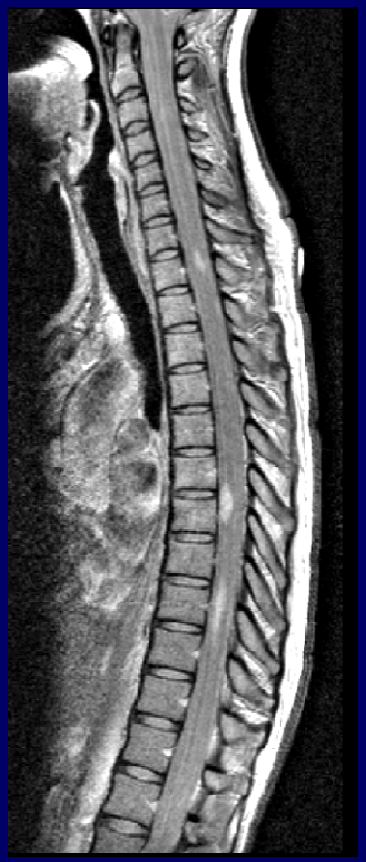
Morfologia:
- Irregolare
- Ovoidale
- “Dita di Dawson”

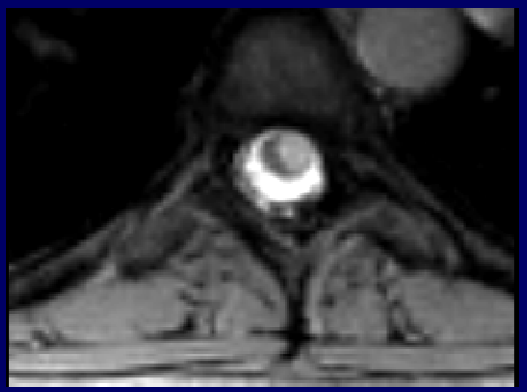
Distribuzione:
- Asimmetrica

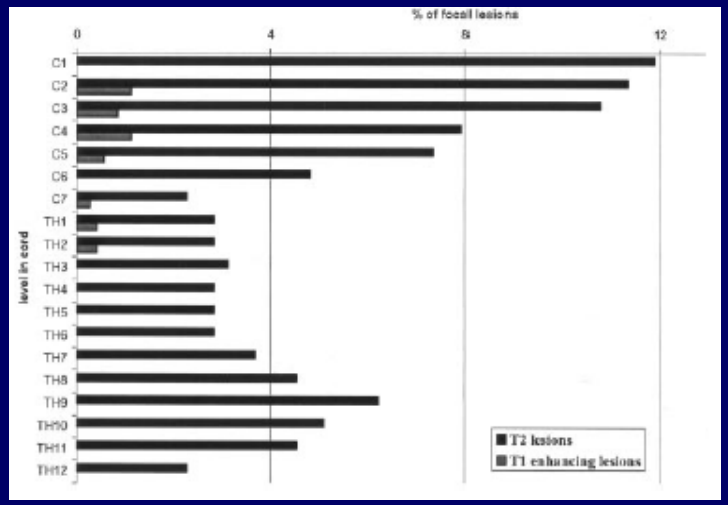
Captazione:
- Variabile

RM E DIAGNOSI DI SM

Caratteristiche delle lesioni visibili - Midollo spinale







- Dimensioni:
  - <2 segmenti vertebrali
  - <50% della sezione midollare trasversa
- Sede:
  - soprattutto cervicale
  - cordoni laterali e posteriori
  - SG centrale non risparmiata
- Morfologia: ovoidale
- Caratteristiche del segnale RM:
  - infrequente captazione
  - rara ipointensità in T1
- Effetti sul midollo:
  - edema di lieve entità (fase acuta)
  - atrofia locale (fase cronica)

Bot et al., Neurology 2004

Lycklama et al., Lancet Neurol 2003

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

W. Ian McDonald, FRCP,[1] Alistair Compston, FRCP,[2] Gilles Edan, MD,[3] Donald Goodkin,[4] Hans-Peter Hartung, MD,[5] Fred D. Lublin, MD,[6] Henry F. McFarland, MD,[7] Donald W. Paty, MD,[8] Chris H. Polman, MD,[9] Stephen C. Reingold, PhD,[10] Magnhild Sandberg-Wollheim, MD,[11] William Sibley, MD,[12] Alan Thompson, MD,[13] Stanley van den Noort, MD,[14] Brian Y. Weinshenker, MD,[15] and Jerry S. Wolinsky, MD[16]

The International Panel on MS Diagnosis presents revised diagnostic criteria for multiple sclerosis (MS). The focus remains on the objective demonstration of dissemination of lesions in both time and space. Magnetic resonance imaging is integrated with clinical and other paraclinical diagnostic methods. The revised criteria facilitate the diagnosis of MS in patients with a variety of presentations, including "monosymptomatic" disease suggestive of MS, disease with a typical relapsing-remitting course, and disease with insidious progression, without clear attacks and remissions. Previously used terms such as "clinically definite" and "probable MS" are no longer recommended. The outcome of a diagnostic evaluation is either MS, "possible MS" (for those at risk for MS, but for whom diagnostic evaluation is equivocal), or "not MS."

Ann Neurol 2001;50:121–127

Diagnostic Criteria for Multiple Sclerosis: 2005 Revisions to the "McDonald Criteria"

Chris H. Polman, MD, PhD,[1] Stephen C. Reingold, PhD,[2] Gilles Edan, MD,[3] Massimo Filippi, MD,[4] Hans-Peter Hartung, MD,[5] Ludwig Kappos, MD,[6] Fred D. Lublin, MD,[7] Luanne M. Metz, MD,[8] Henry F. McFarland, MD,[9] Paul W. O'Connor, MD,[10] Magnhild Sandberg-Wollheim, MD,[11] Alan J. Thompson, MD,[12] Brian G. Weinshenker, MD,[13] and Jerry S. Wolinsky, MD[14]

New diagnostic criteria for multiple sclerosis integrating magnetic resonance image assessment with clinical and other paraclinical methods were introduced in 2001. The "McDonald Criteria" have been extensively assessed and used since 2001. New evidence and consensus now strengthen the role of these criteria in the multiple sclerosis diagnostic workup to demonstrate dissemination of lesions in time, to clarify the use of spinal cord lesions, and to simplify diagnosis of primary progressive disease. The 2005 Revisions to the McDonald Diagnostic Criteria for MS should simplify and speed diagnosis, whereas maintaining adequate sensitivity and specificity.

Ann Neurol 2005;58:840–846

RM E DIAGNOSI DI SM
Criteri di disseminazione spaziale

Presenza di almeno 3 delle seguenti condizioni:

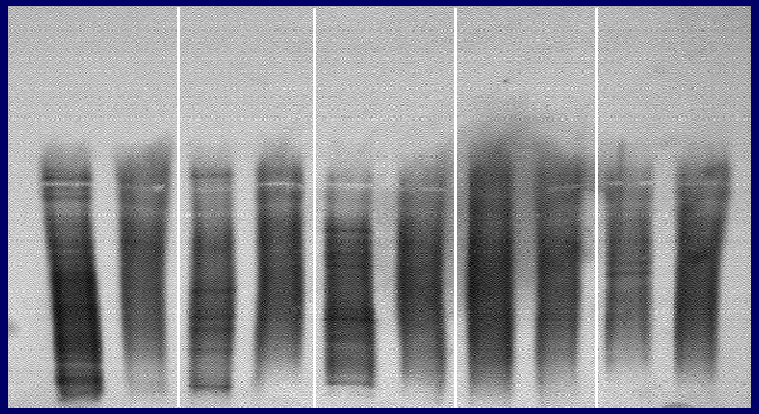
- **1 lesione captante il Gd (encefalica o midollare) o 9 o più lesioni in totale (encefaliche o midollari)**
- **1 o più lesioni infratentoriali o midollari**
- **1 o più lesioni juxtacorticali**
- **3 o più lesioni periventricolari**

Polman et al., Ann Neurol 2005

RM E DIAGNOSI DI SM

Criteri di disseminazione spaziale

Bande oligoclonali liquorali



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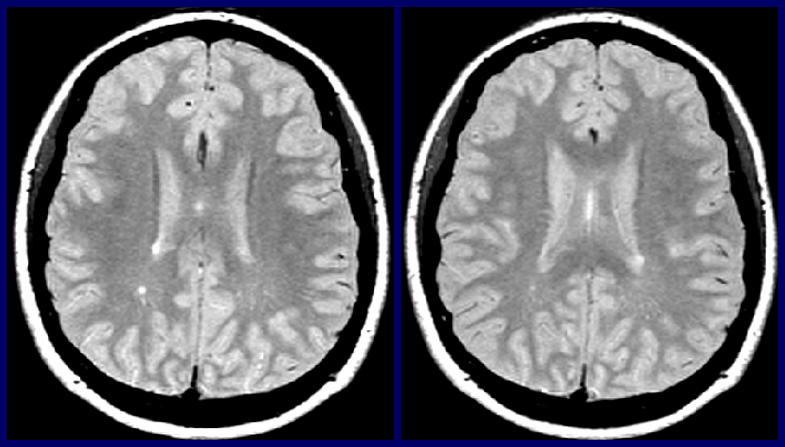
2 o più lesioni T2 subcliniche



Polman et al., Ann Neurol 2005

RM E DIAGNOSI DI SM
Criteri di disseminazione temporale

- **Presenza di una lesione captante Gd almeno 3 mesi dopo l'esordio clinico, purchè non nella sede dell'evento stesso**

- **Presenza di una nuova lesione T2 rispetto ad un esame "basale"eseguito almeno 30 giorni dopo l'insorgenza dell'attacco clinico (criterio valido per ogni esame successivo al basale di riferimento)**

Polman et al., Ann Neurol 2005

RM E DIAGNOSI DI SM
DIS e DIT – Verso una semplificazione?

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

Chris H. Polman, MD, PhD,[1] Stephen C. Reingold, PhD,[2] Brenda Banwell, MD,[3]
Michel Clanet, MD,[4] Jeffrey A. Cohen, MD,[5] Massimo Filippi, MD,[6] Kazuo Fujihara, MD,[7]
Eva Havrdova, MD, PhD,[8] Michael Hutchinson, MD,[9] Ludwig Kappos, MD,[10]
Fred D. Lublin, MD,[11] Xavier Montalban, MD,[12] Paul O'Connor, MD,[13]
Magnhild Sandberg-Wollheim, MD, PhD,[14] Alan J. Thompson, MD,[15]
Emmanuelle Waubant, MD, PhD,[16] Brian Weinshenker, MD,[17] and Jerry S. Wolinsky, MD[18]

New evidence and consensus has led to further revision of the McDonald Criteria for diagnosis of multiple sclerosis. The use of imaging for demonstration of dissemination of central nervous system lesions in space and time has been simplified, and in some circumstances dissemination in space and time can be established by a single scan. These revisions simplify the Criteria, preserve their diagnostic sensitivity and specificity, address their applicability across populations, and may allow earlier diagnosis and more uniform and widespread use.

ANN NEUROL 2011;69:292–302

RM E DIAGNOSI DI SM

Criteri di disseminazione spaziale e temporale

Disseminazione spaziale:

- **Presenza di ≥1 lesione in T2 in almeno 2 di queste 4 sedi: periventricolare, sottotentoriale, juxtacorticale, midollare (escluse le lesioni sintomatiche)**

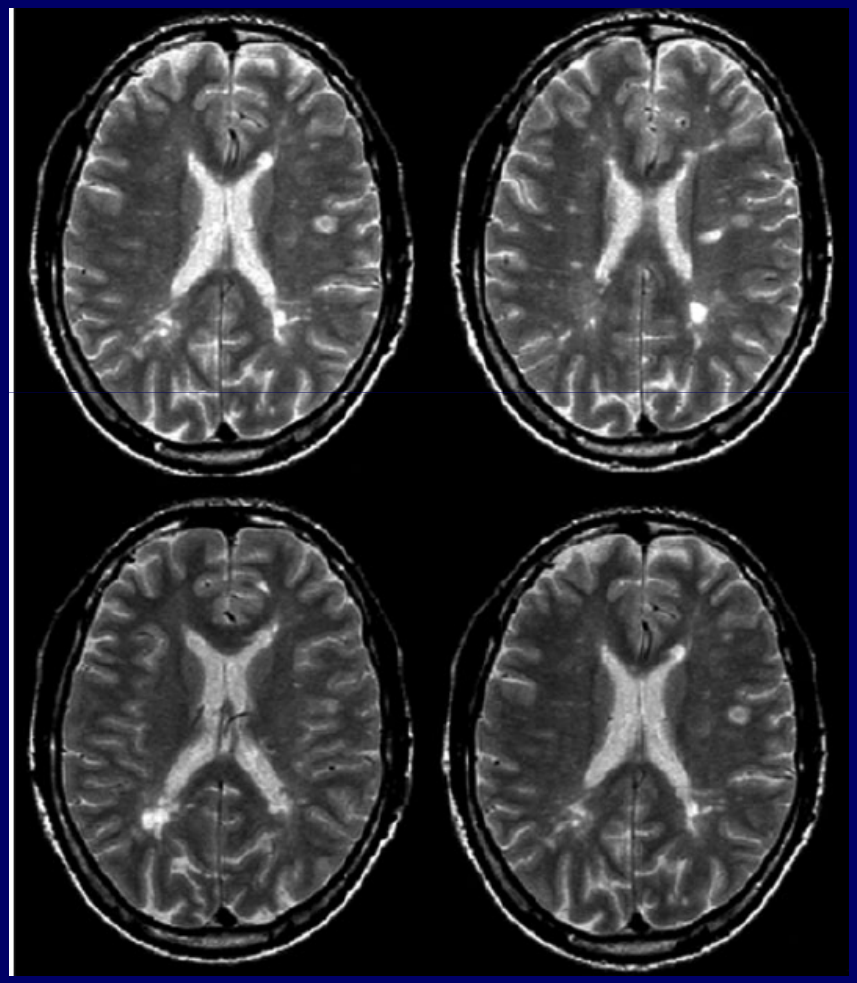
Disseminazione temporale:

- **Presenza di una nuova lesione T2 o captante Gd rispetto ad un esame basale**
- **Presenza contemporanea di lesioni captanti e non captanti Gd**

Polman et al., Ann Neurol 2011

RM E DIAGNOSI DI SM

Riscontri RM “incidentali” – Forme fruste



Soggetto fSM

152 parenti sani I grado SM sporadica (sSM)
88 parenti sani I grado SM familiare (fSM)
56 controlli sani (CS)

Alterazioni RM:
- 31 sSM (20%)
- 28 fSM (32%)
- 9 CS (16%)

Criteri di Fazekas:
- 7 sSM (5%)
- 10 fSM (11%)

Criteri di Barkhof:
- 6 sSM (4%)
- 9 fSM (10%)

Nessuna differenza tra gruppi per volume cerebrale e MTR lesioni/SBAN

De Stefano et al., Ann Neurol 2006

RM E DIAGNOSI DI SM

Riscontri RM “incidentali” - Dalla CIS alla RIS?

30 pazienti sottoposti a RM per cefalea, traumi, dismenorrea, sintomi “atipici”
(17%: depressione, epilessia, disturbi cognitivi)
RM di controllo dopo 6 (3-30) mesi
Follow-up clinico: 5 anni

Caratteristiche RM basale:
9 o più lesioni in T2: 21 pazienti
1 o più lesioni Gd+: 9 pazienti
1 o più lesioni infratentoriali: 10 pazienti

Esame liquor positivo: 10 pazienti

Disseminazione spaziale e temporale alla RM: 23 pazienti (77%)
Manifestazioni compatibili con CIS: 11 pazienti (37%)
Mediana di evoluzione: 2.3 anni
Pregressa DIS/DIT RM: 8, esame LCR positivo: 6

Lebrun et al., JNNP 2008

RM E DIAGNOSI DI SM

Diagnosi differenziale – Studio del midollo

	SM (n=25)	LES (n=13)	UCTD (n=18)	Sarcoidosi (n=5)
RM encefalo alterata	**100%**	**38%**	**72%**	**40%**
Paty +	**100%**	**23%**	**56%**	**40%**
Fazekas +	**92%**	**0%**	**22%**	**20%**
Barkhof +	**76%**	**0%**	**11%**	**0%**
RM midollo alterata	**92%**	**8%**	**6%**	**0%**

Bot et al., Radiology 2002

RM E DIAGNOSI DI SM

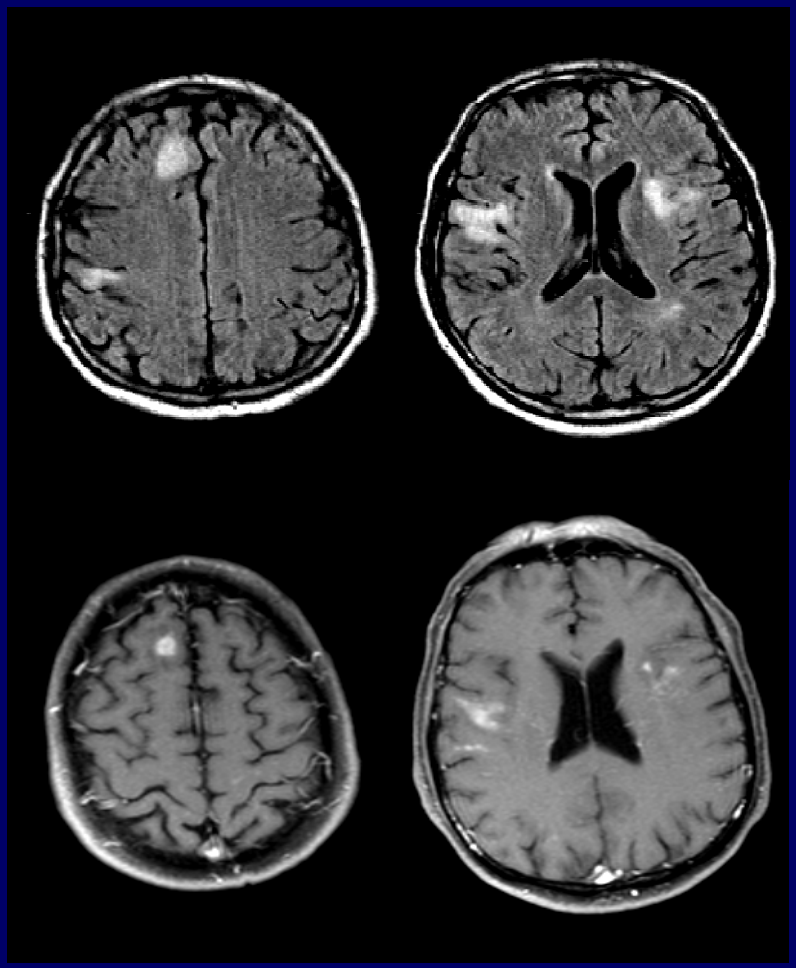
"No better explanation" – "Red flags" di RM

	Disease
Brain white matter	
Normal	NMO (absent or few lesions), ATM
Large lesions	AMS (sometimes confluent and perilesional oedema), BCS (concentric whorls of alternating rings of enhancement), PACNS (with mass effect)
Symmetrically distributed lesions	ADEM, AFL
Poorly defined lesion margins	ADEM
Absent or rare Dawson fingers, corpus callosum and periventricular lesions	ADEM
Absent MRI activity at follow-up	ADEM
T2-hyperintensity of the temporal pole, U-fibres at the vertex, external capsule and insular regions	CADASIL
Multiple bilateral microhaemorrhagic foci	CADASIL, SVD
Frequent sparing of corpus callosum and cerebellum	CADASIL, SVD
Lesions in the centre of corpus callosum, sparing the periphery	Susac's syndrome
Haemorrhages	PACNS
Simultaneous enhancement of all lesions	ADEM, PACNS, sarcoidosis
Infarcts	SID, PACNS, SVD
Punctiform parenchymal enhancement	PACNS, sarcoidosis, NBD
Predominance of lesions at the cortical/subcortical junction	SID
Diffuse WM involvement	NBD, encephalitis (HIVE), SVD, CADASIL
Cerebral venous sinus thrombosis	NBD
Large and infiltrating brainstem lesions	NBD
Anterior temporal and inferior frontal lobe involvement, associated with enhancement or mass effect	Encephalitis (HSE)
Isolated lesions with ring enhancement (often complete)	Abscesses
Mass effect	Abscesses
Multifocal, asymmetrical lesions starting in a juxtacortical location and progressively enlarging	PML
Large lesions with absent or rare mass effect	PML
Extensive and bilateral periventricular abnormalities in isolation	B12D, ACD
Cortical grey matter	
Cortical/subcortical lesions crossing vascular territories	MELAS
Prevalent involvement versus white matter	Encephalitis
Infiltrating lesions that do not remain in grey or white matter boundaries	Abscesses
Deep grey matter	
Bilateral lesions	ADEM (at the grey–white-matter junction), CADASIL
Lacunar infarcts	CADASIL, SVD
T1-hyperintensity of the pulvinar	FD
Multiple discrete lesions in the basal ganglia and thalamus	Susac's syndrome
Large and infiltrating basal ganglia lesions	NBD
Infiltrating lesions without respecting grey-matter or white-matter boundaries	Abscesses
T2-hyperintense lesions in the dentate nuclei	AFL (CTX)
Spinal cord	
Large and swelling lesions	NMO (with corresponding T1 hypointensity), ADEM, ATM, Sjögren's syndrome
Diffuse abnormalities in the posterior columns	B12D, ACD
Other	
No "occult" changes in the NAWM	NMO, Lyme disease, SID (except in NSLE)
Pontine lacunar infarcts	CADASIL, SVD
Dilation of Virchow-Robin spaces	HHC, PACNS
Diffuse lactate increase on brain MRS	MELAS
Meningeal enhancement	Susac's syndrome, PACNS, NBD, meningitis, Lyme disease, sarcoidosis
Hydrocephalus	Sarcoidosis
Absence of optic-nerve lesions	PML
Regional atrophy	HHC (hippocampus and amygdala), NBD (brainstem)

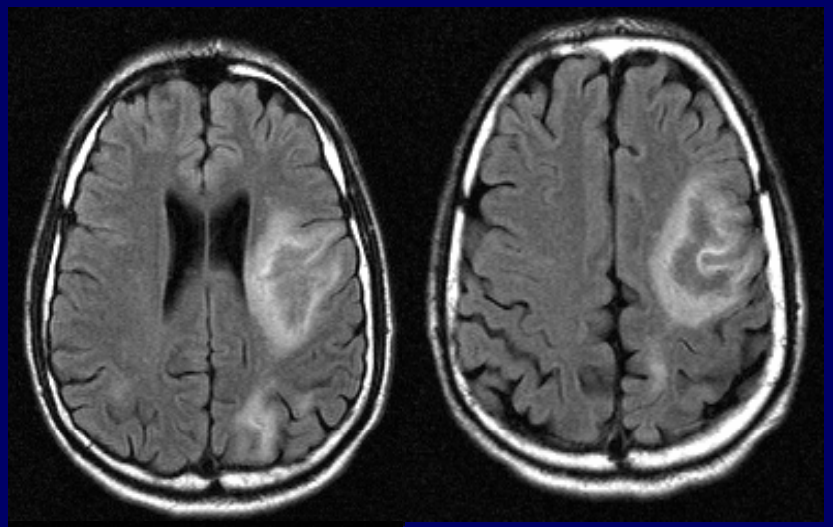
Charil et al., Lanc Neurol 2006

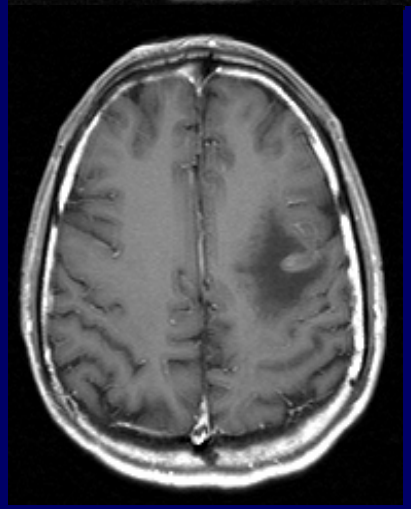
RM E DIAGNOSI DI SM

"Red flags" di RM – Captazione di Gd



Vasculite primitiva del SNC





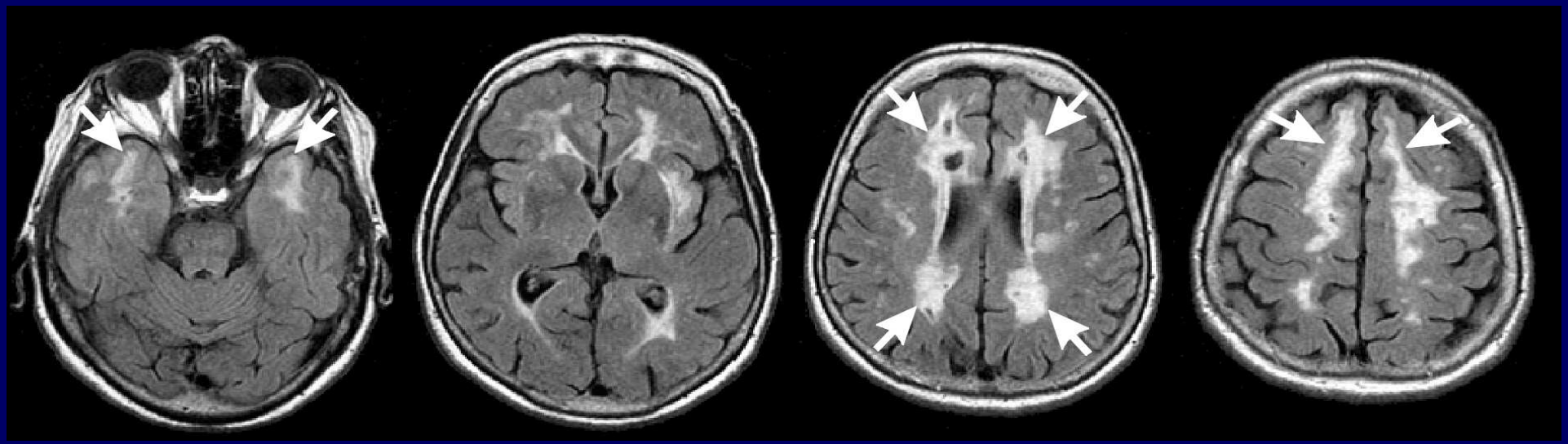
Leucoencefalopatia multifocale progressiva (PML)

Charil et al., Lancet Neurol 2006

RM E DIAGNOSI DI SM

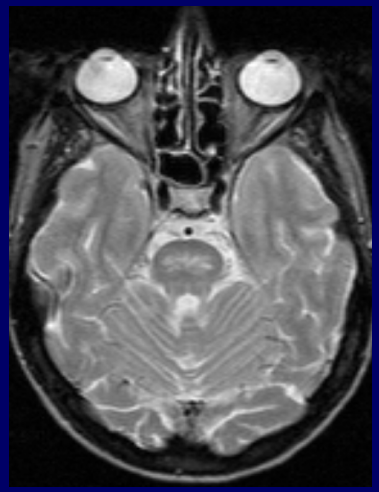
"Red flags"– Sede delle lesioni

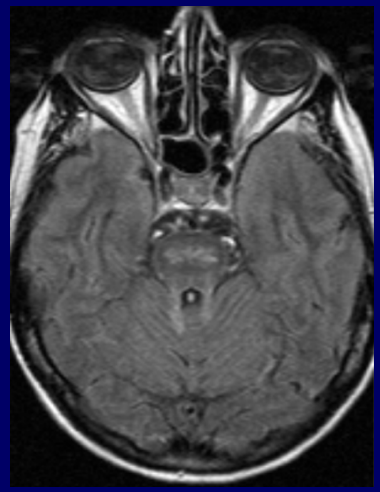
CADASIL



Auer et al., Radiology 2001

Encefalopatia ischemica

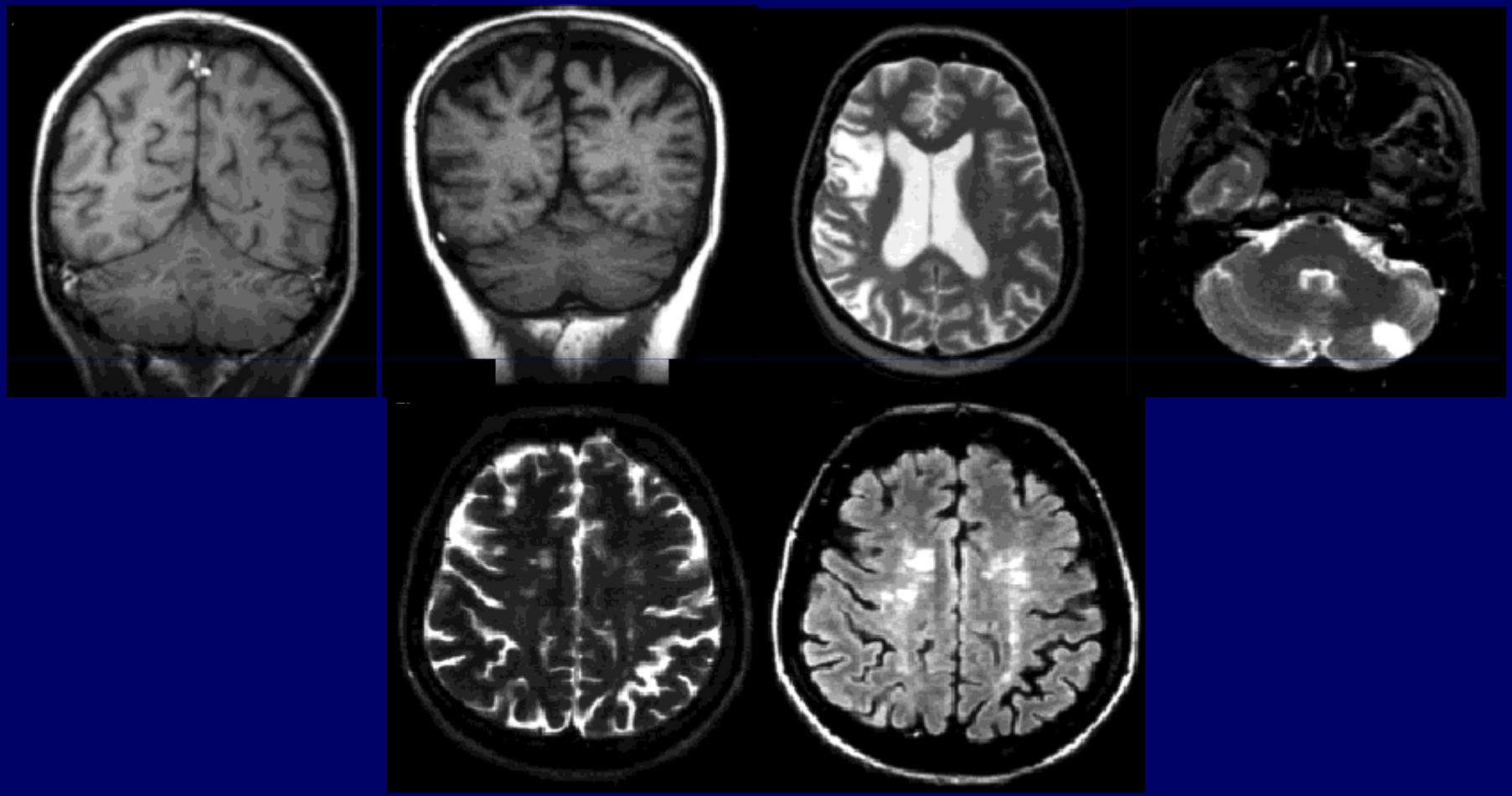




Charil et al., Lancet Neurol 2006

RM E DIAGNOSI DI SM

“Red flags”– Tipologia delle lesioni



NeuroLES

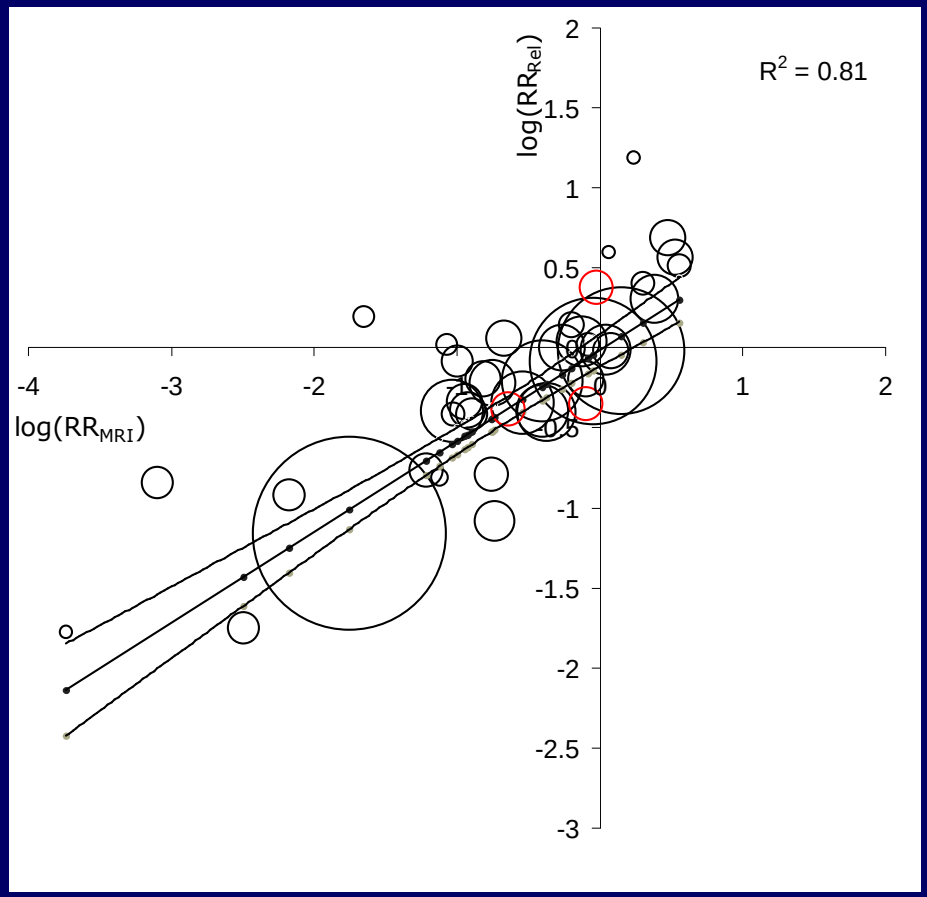
Csepany et al., J Neurol 2003

RM E MONITORAGGIO DELLE TERAPIE

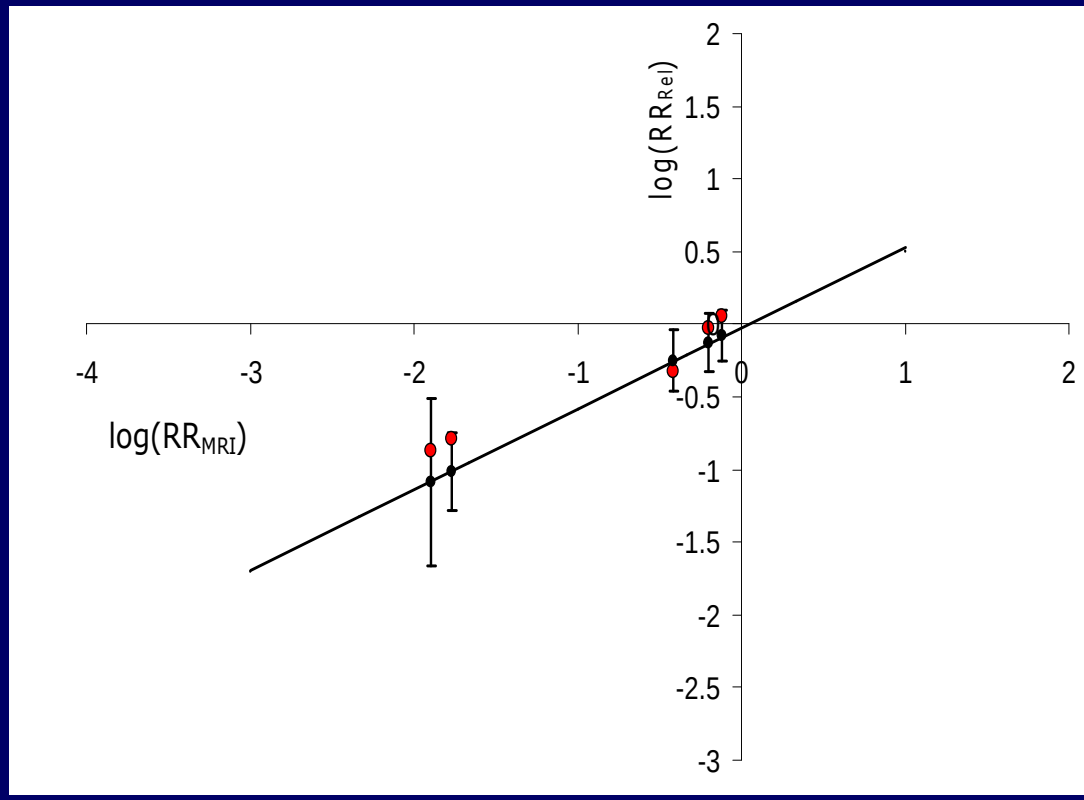
- Marcatore sensibile, oggettivo e riproducibile di attività di malattia
- Correlazione clinica “subottimale”
- Mancanza di “reali” alternative
- Utilizzo in studi di gruppo (trial)
- Utilizzo in singoli pazienti (risposta alla terapia)

RM E MONITORAGGIO DELLE TERAPIE

RM come surrogato delle ricadute



"Working dataset"



"Validation dataset"

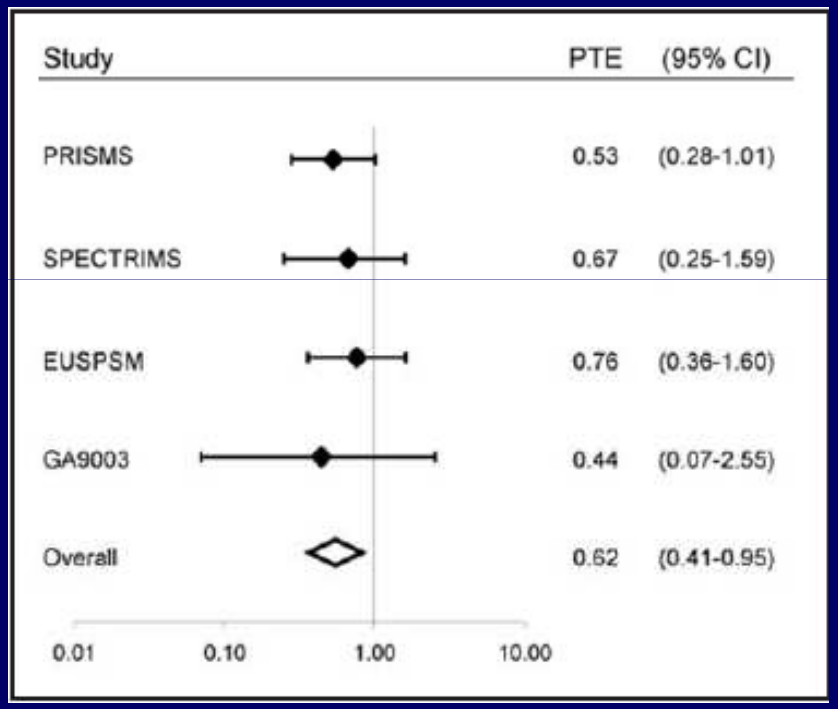
Sormani et al., Ann Neurol 2009

RM E MONITORAGGIO DELLE TERAPIE
RM come surrogato delle ricadute – Livello individuale

Analisi studi PRISMS e SPECTRIMS (986 casi)

Criteri di Prentice soddisfatti da conta nuove lesioni in T2

PTE nuove lesioni a 1 anno per numero ricadute anno successivo pari al 70%

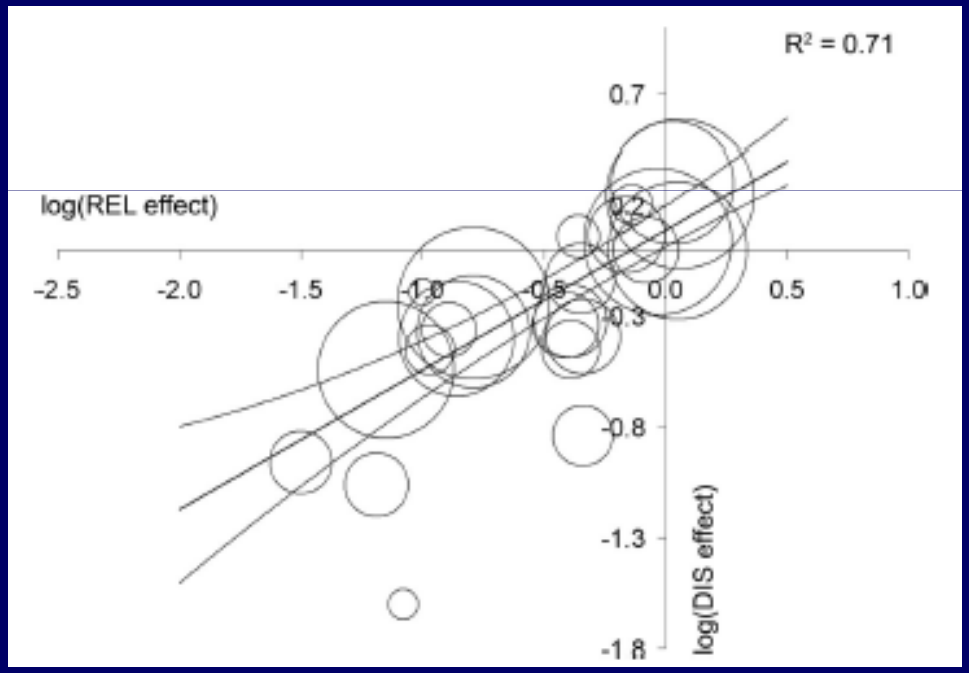


Sormani et al., Mult Scler 2011

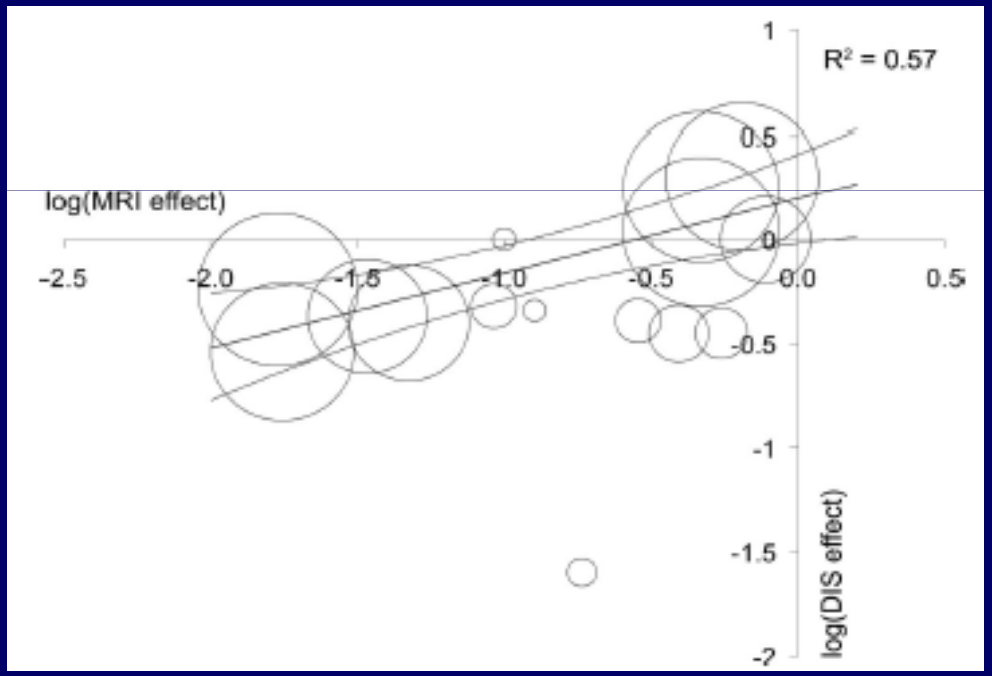
RM E MONITORAGGIO DELLE TERAPIE

RM come surrogato della progressione

Efficacia della terapia:
EDSS *vs.* frequenza ricadute



Efficacia della terapia:
EDSS *vs.* attività RM



Sormani et al., Neurology 2010

RM E MONITORAGGIO DELLE TERAPIE
Criteri di risposta individuale – SM RR

172 pazienti SM RR

Studio di 2 anni, RC in DC *vs.* placebo, con IFN beta-1a (30 mcg IM la settimana)

Criteri di risposta alla terapia (analisi ROC):

- Ricadute nei 2 anni di studio
- Nuove lesioni T2 (RM II anno *vs.* basale)
- Lesioni captanti (RM I anno + II anno)

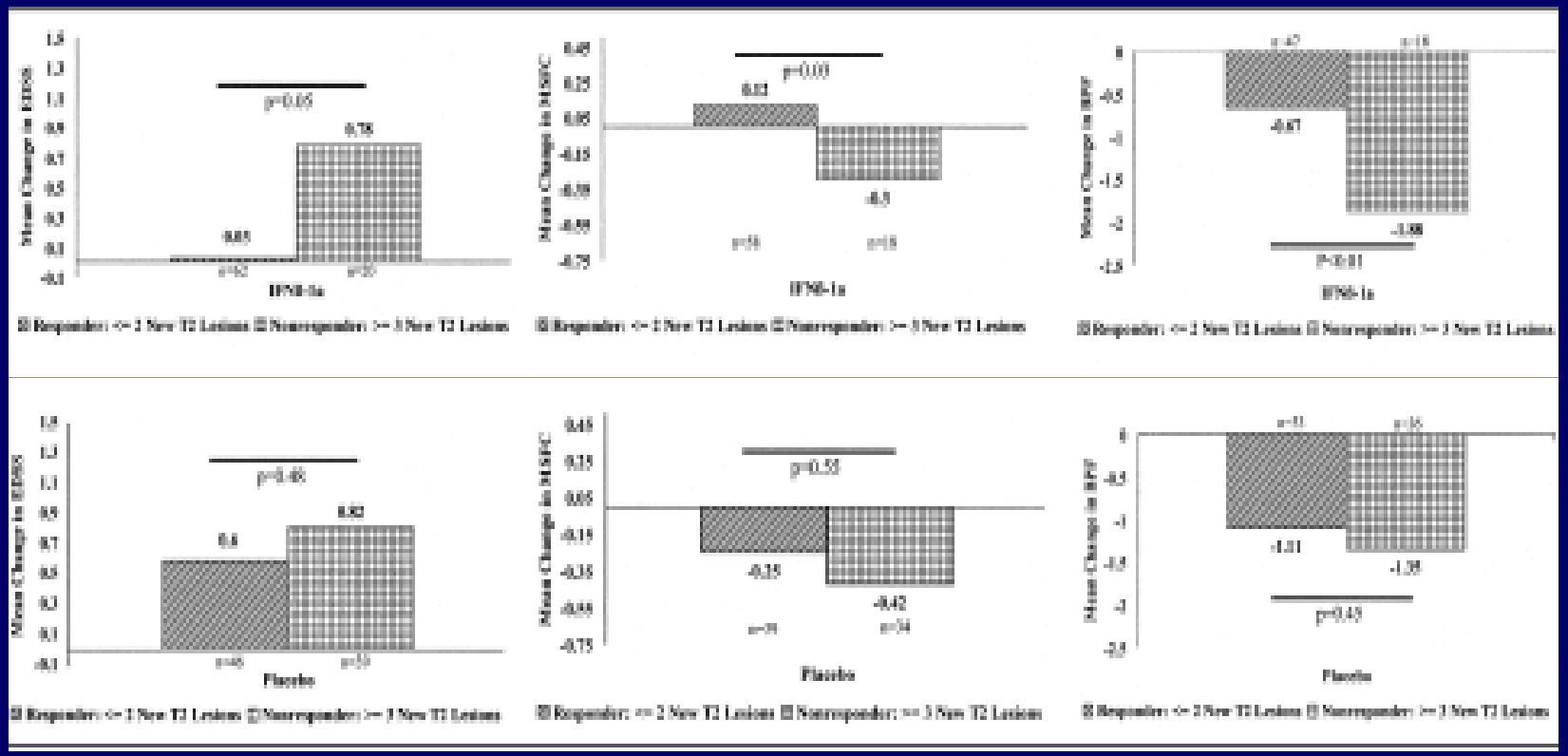
Outcome:

- Disabilità (cambiamenti EDSS e MSFC al II anno)
- Atrofia (BPF RM II anno *vs.* basale)

Rudick et al., Ann Neurol 2004

RM E MONITORAGGIO DELLE TERAPIE

Outcome – Criterio: nuove lesioni T2



- Δ EDSS
- Δ MSFC
- Δ BPF

Rudick et al., Ann Neurol 2004

RM E MONITORAGGIO DELLE TERAPIE
Criteri di risposta individuale – SM RR

152 pazienti SM RR in terapia con IFN (follow-up: 2 anni)
Valutazione RM basale e a 12 mesi
Definizione di non risposta:
aumento di ≥1 punto dell'EDSS confermato dopo 6 mesi
Pazienti "non-responder": 24 (16%)

Correlazione tra presenza di lesioni captanti a 1 anno e successive ricadute (OR 3.7, p=0.003)

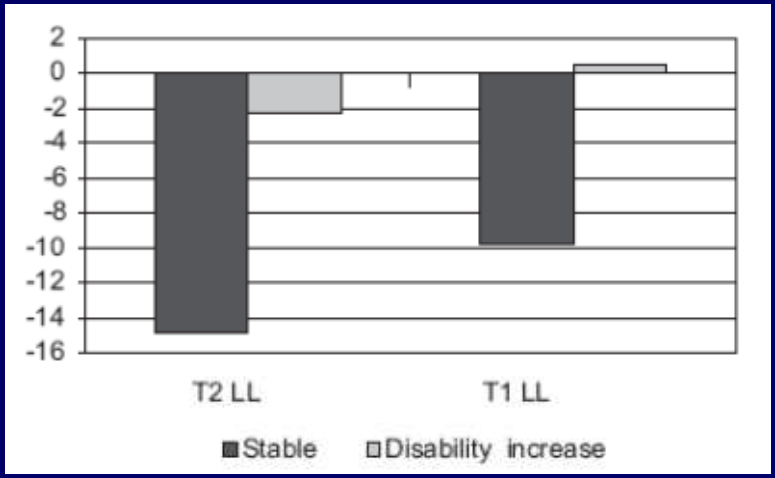


Table 3 MRI variables associated with increase of disability during treatment with IFN-β

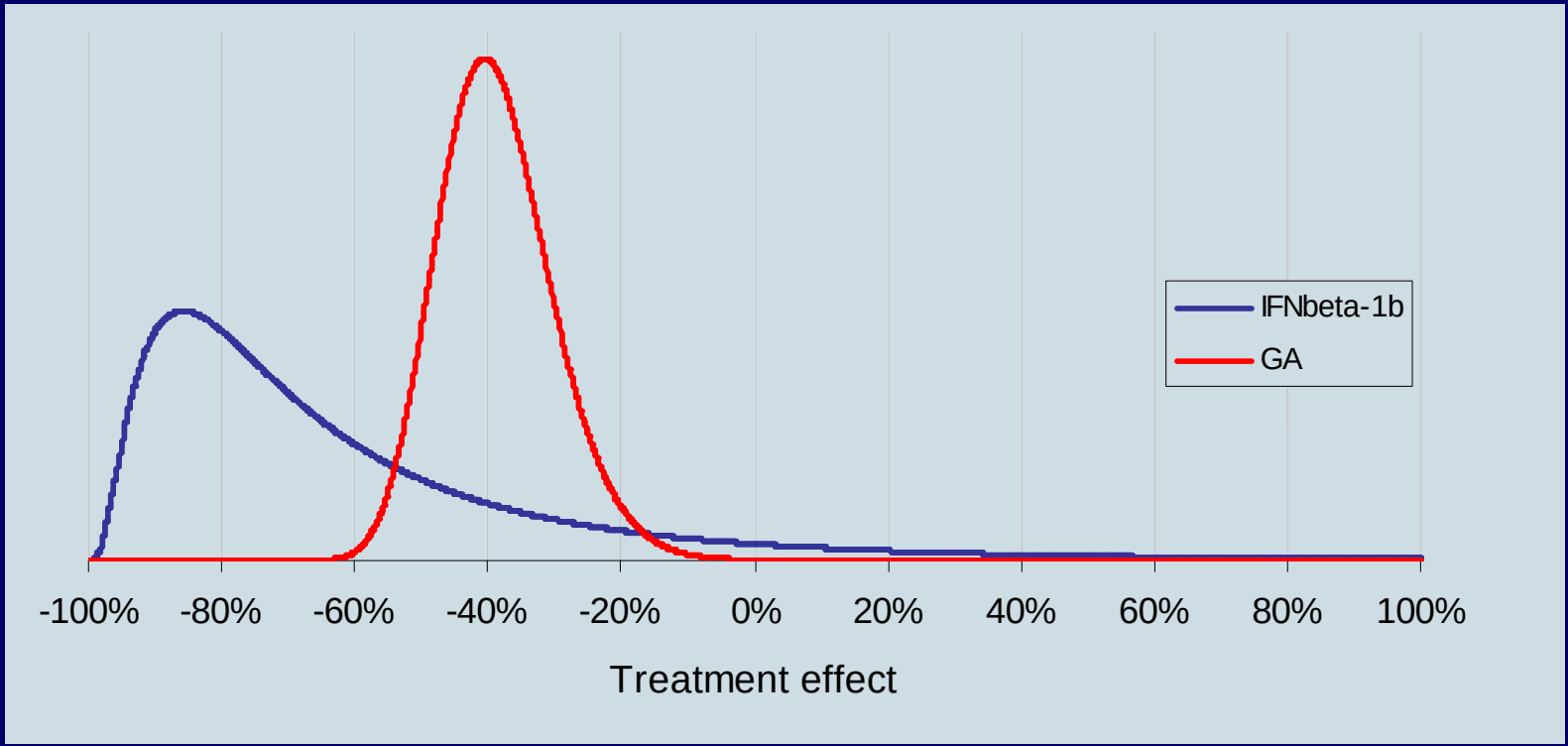
Active lesions at 1 year	OR	95% CI	*p*-value
≤ 2	1.0		
> 2	8.3	3.1–21.9	$p < 0.0001$

Sensibilità 77%, NPV 93%, PPV 37%, accuratezza 76%

Rio et al., MSJ 2008

RM E MONITORAGGIO DELLE TERAPIE

Caratteristiche della risposta RM alla terapia

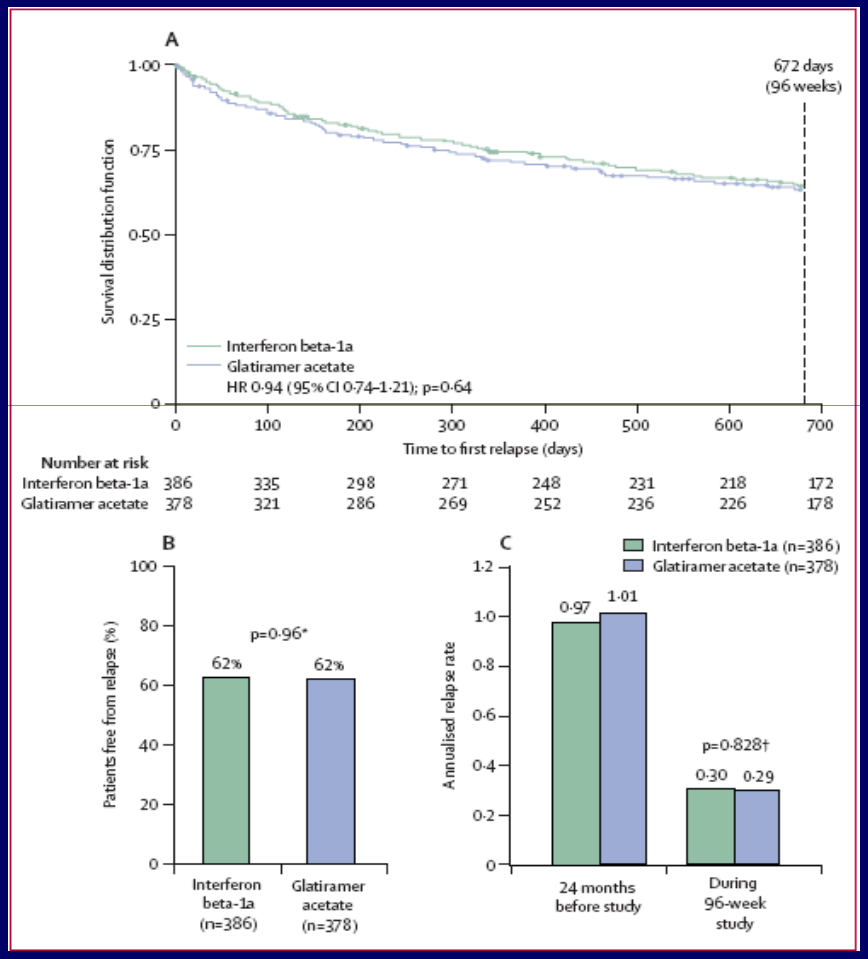


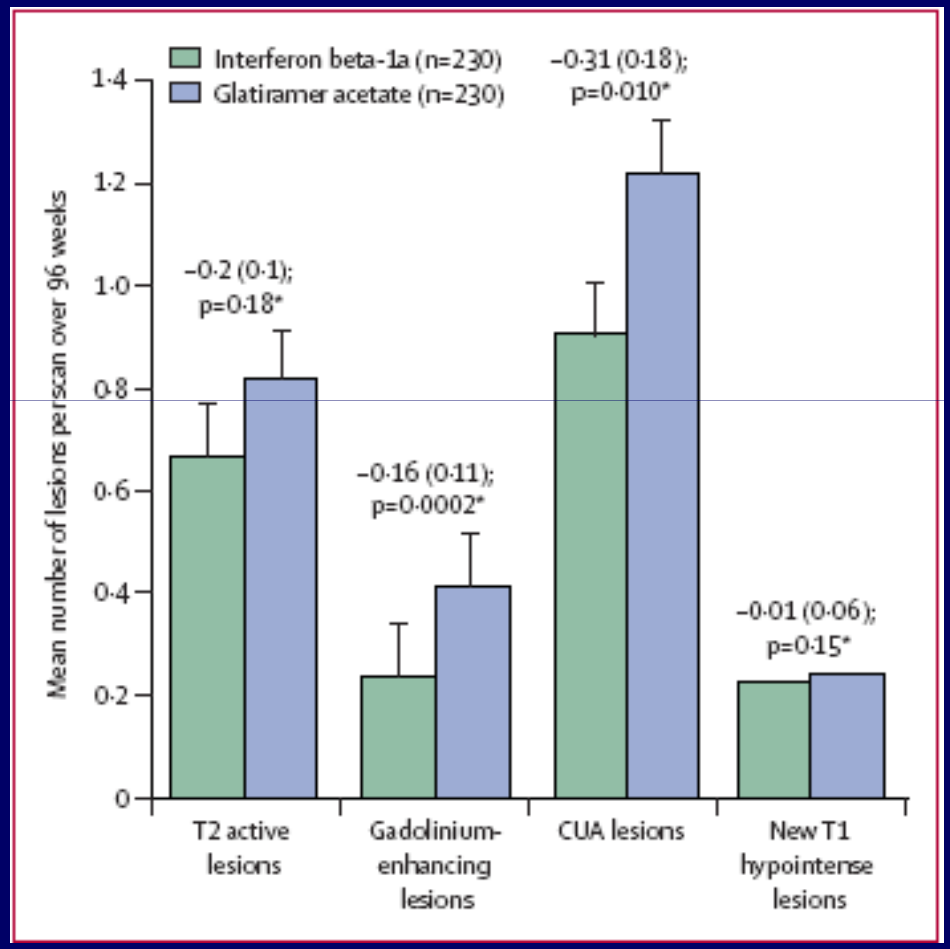
GA/SMRR: riduzione del -20/-54% delle nuove lesioni Gd+ nel 95% dei pazienti

IFNβ-1b/SMSP: riduzione ≥ 60% delle lesioni T2 attive in >65% dei pazienti
Stabilità o aumento nel 7% dei pazienti

Sormani et al., MSJ - J Neurol 2005

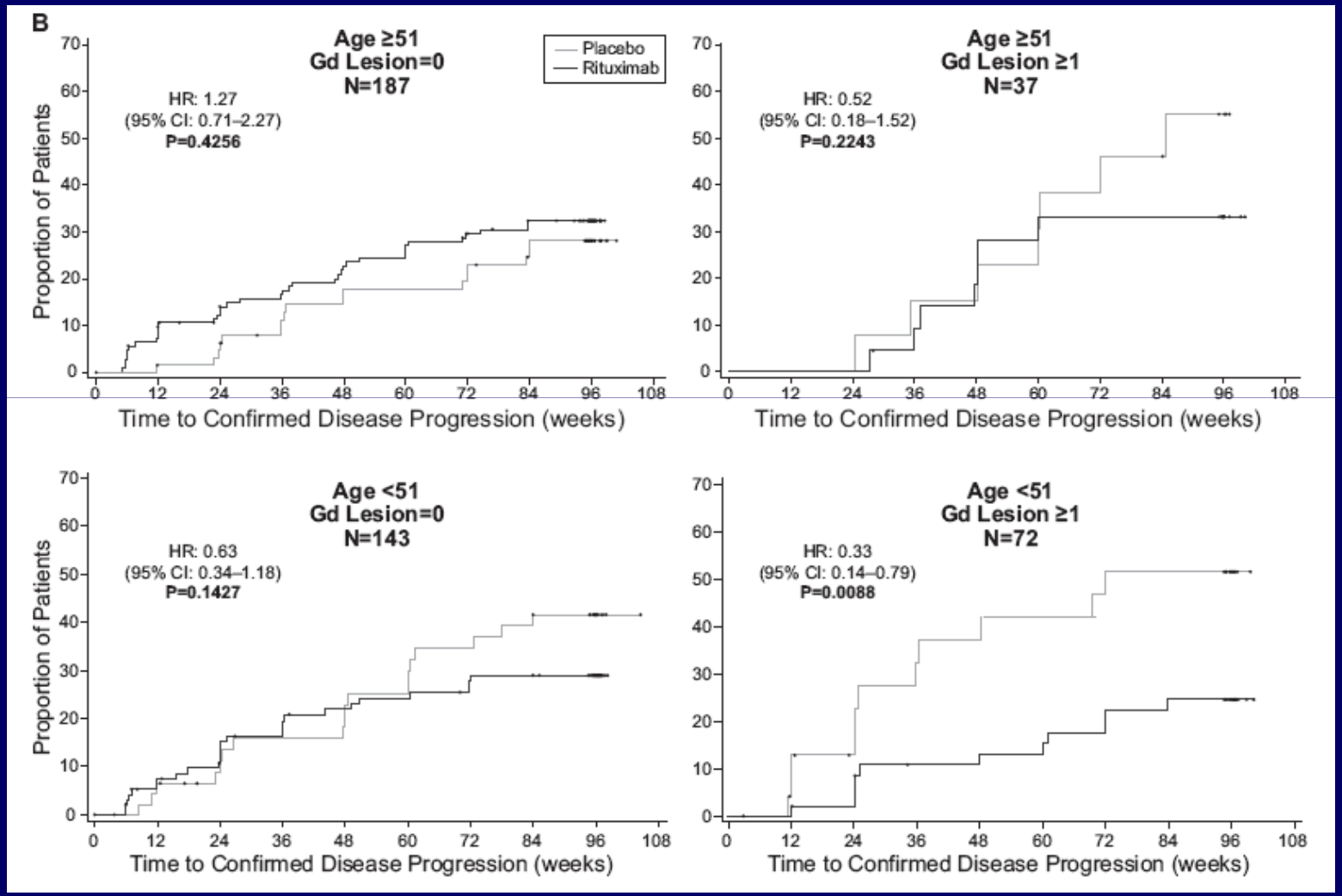
RM E MONITORAGGIO DELLE TERAPIE
Caratteristiche della risposta RM alla terapia





Mikol et al., Lanc Neurol 2008

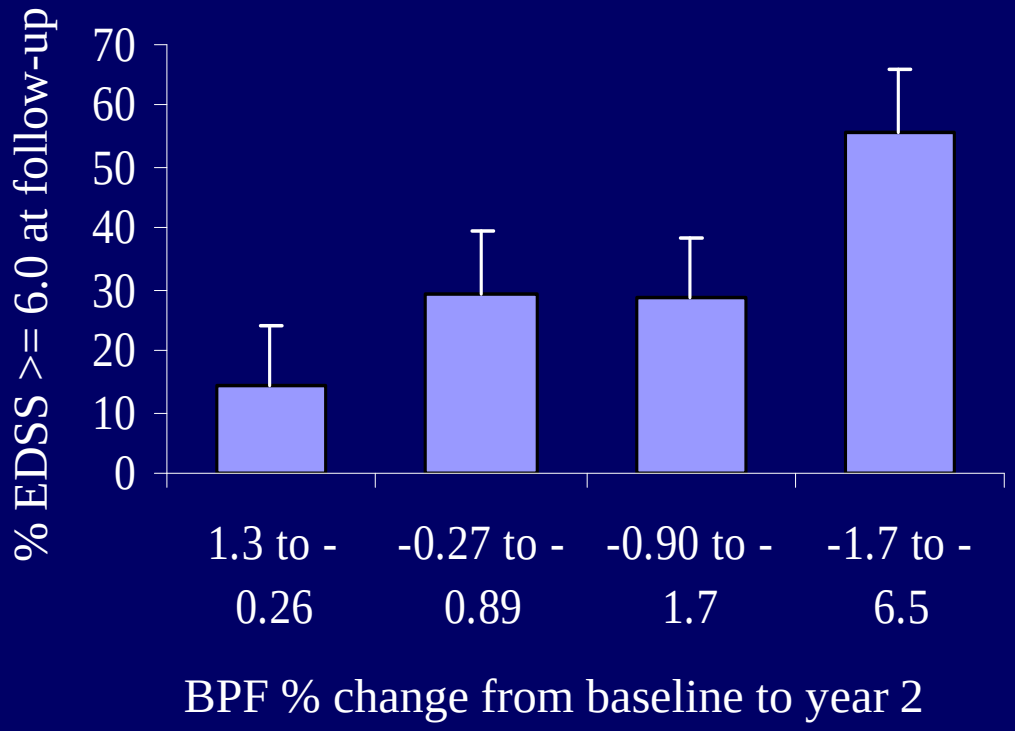
RM E MONITORAGGIO DELLE TERAPIE
Predizione di efficacia – SM PP



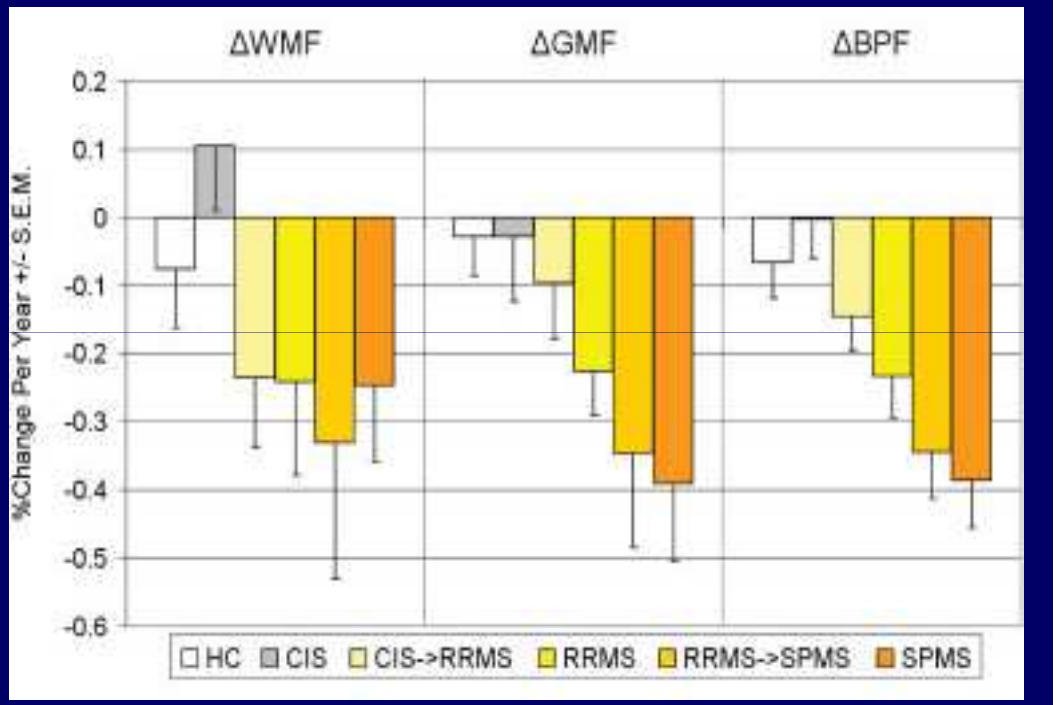
Hawker et al., Ann Neurol 2009

RM E MONITORAGGIO DELLE TERAPIE

Atrofia ed efficacia terapeutica



Fisher et al., Neurology 2002



Fisher et al., Ann Neurol 2008

RM E MONITORAGGIO DELLE TERAPIE
Atrofia ed efficacia terapeutica

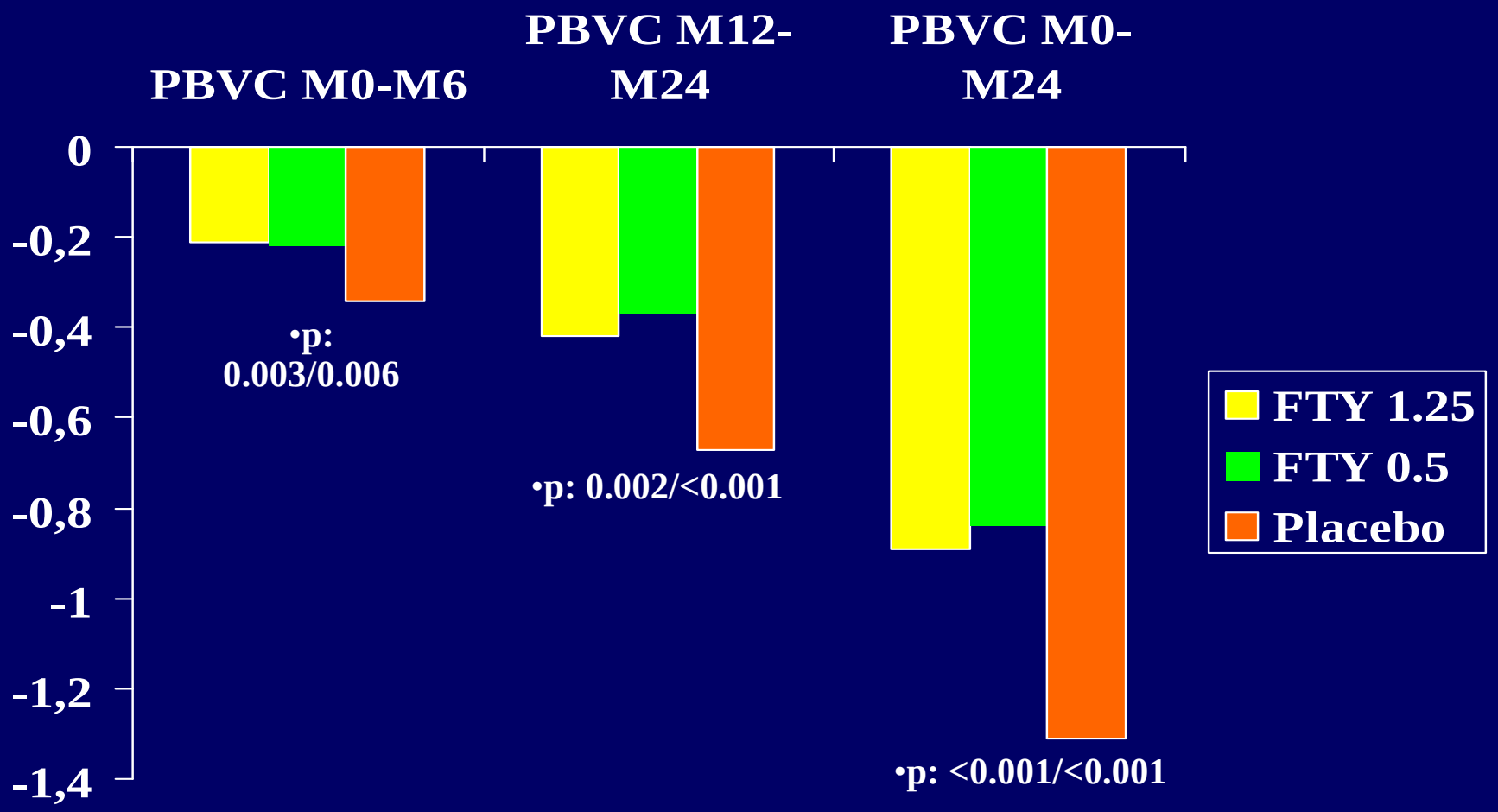
Treatment	Trial design	Duration, mo (no. of patients)	Disease type	Treatment effect on BV
IM IFN-β-1a (30 μg weekly)[14]	PLC	24 (140)	RRMS	S (12–24 mo)
IM IFN-β-1a (30 μg vs 60 μg weekly)[20]	DB, PG	36 (386)	RRMS	S (12–24 mo), S (24–36 mo)
IM IFN-β-1a (30 μg weekly vs no treatment)[25]	OLC	36 (54)	RRMS	S (0–36 mo)
SC IFN-β-1a (66 μg or 132 μg weekly)[18]	PLC	24 (519)	RRMS	NS
SC IFN-β-1a (66 μg or 132 μg weekly)[24]	PLC, OLC (baseline vs FU)	84–96 (382)	RRMS	NS
GA (20 mg daily)[31]	PLC in the 0–9 mo; OLC in the 9–18 mo	18 (239)	RRMS	NS
GA (20 mg daily)[13]	PLC in the 0–9 mo; OLC in the 9–18 mo	18 (194)	RRMS	S (9–18 mo), S (0–18 mo)
GA (20 mg daily)[33]	PLC	24 (27)	RRMS	S (0–24 mo)
GA (20 mg daily)[33]	OLC (baseline vs FU)	80.4 (135)	RRMS	S (0–80.4 mo)
IVMP (1 g daily for 5 d)[17]	OLC	60 (81)	RRMS	S (0–60 mo)
Natalizumab[15]	PLC	24 (942)	RRMS	S (12–24 mo)
IVIg[40]	PLC	12 (127)	RRMS	S (0–12 mo)
SC IFN-β-1a (22 μg weekly)[28]	PLC	24 (163)	CIS	S (0–24 mo)
IVIg[41]	PLC	24 (318)	SPMS	S (0–24 mo)
SC IFN-β-1b (875 μg weekly)[19]	PLC	36 (95)	SPMS	NS
Cladribine (0.7 or 2.1 mg/kg)[42]	PLC	12 (159)	SPMS, PPMS	NS
IM IFN-β-1a (60 μg weekly)[27]	PLC	24 (50)	PPMS	NS

Possibili cause di discrepanza tra l'efficacia sulla attività lesionale e l'inefficacia sull'atrofia:

Meccanismi d'azione delle terapie (antiinfiammatorie *vs.* neuroprotettive)
Pseudo-atrofia (risoluzione di edema e infiammazione)
Modifiche non legate alla SM
Aspetti metodologici (riproducibilità e varianza delle misure, numerosità dei campioni)

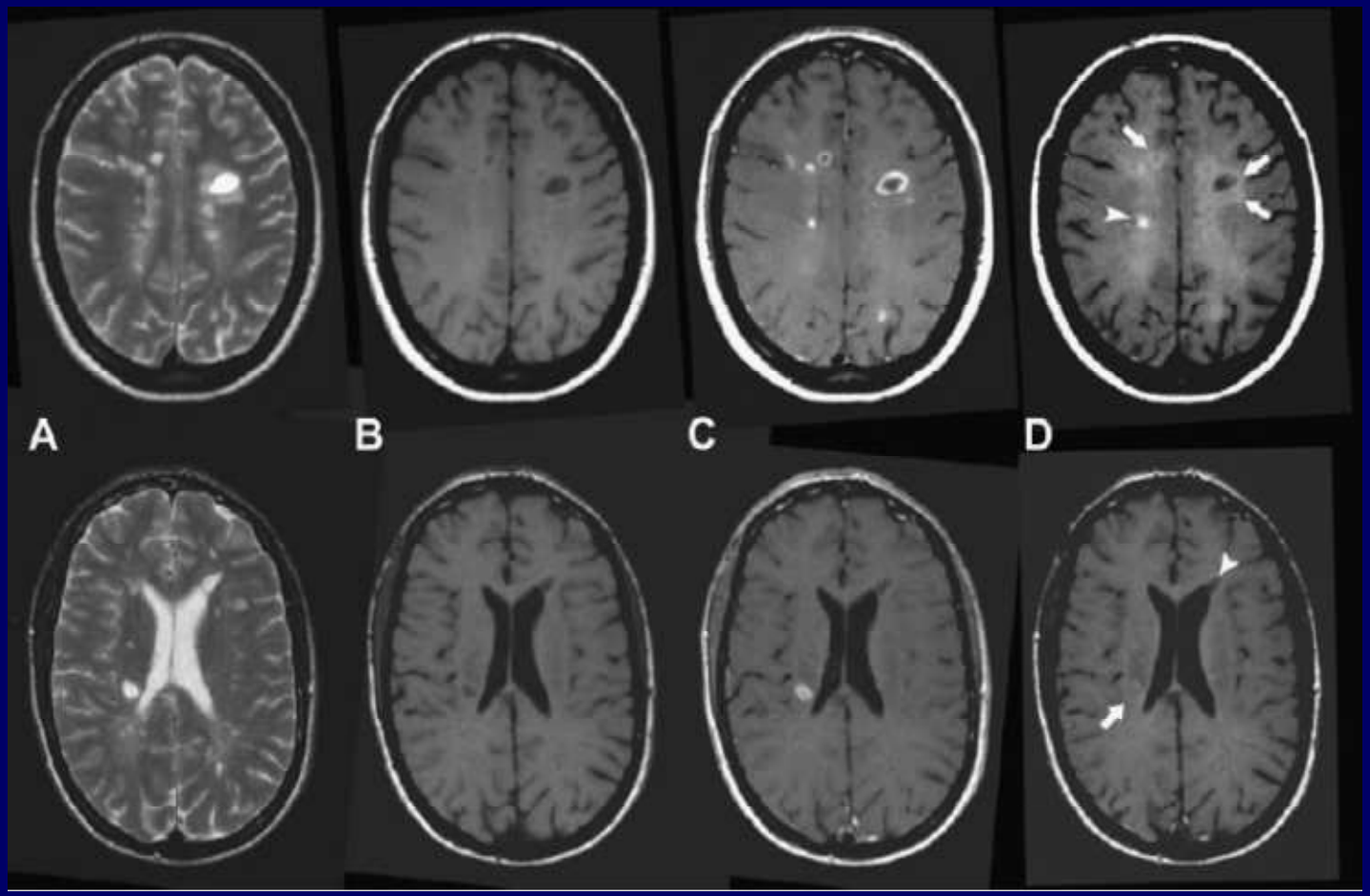
Zivadinov et al., Neurology 2008

RM E MONITORAGGIO DELLE TERAPIE
Atrofia ed efficacia terapeutica – Studio FREEDOMS



Kappos et al., NEJM 2010

RM E MONITORAGGIO DELLE TERAPIE
Nuove strategie - USPIO



19 pazienti SM RR

Studio longitudinale con RM mensili (3 mesi + FU)

USPIO + e Gd- in 144/188 lesioni

Gd+ e USPIO- in 15/59 lesioni

USPIO+ prima che Gd+ in 4% delle lesioni

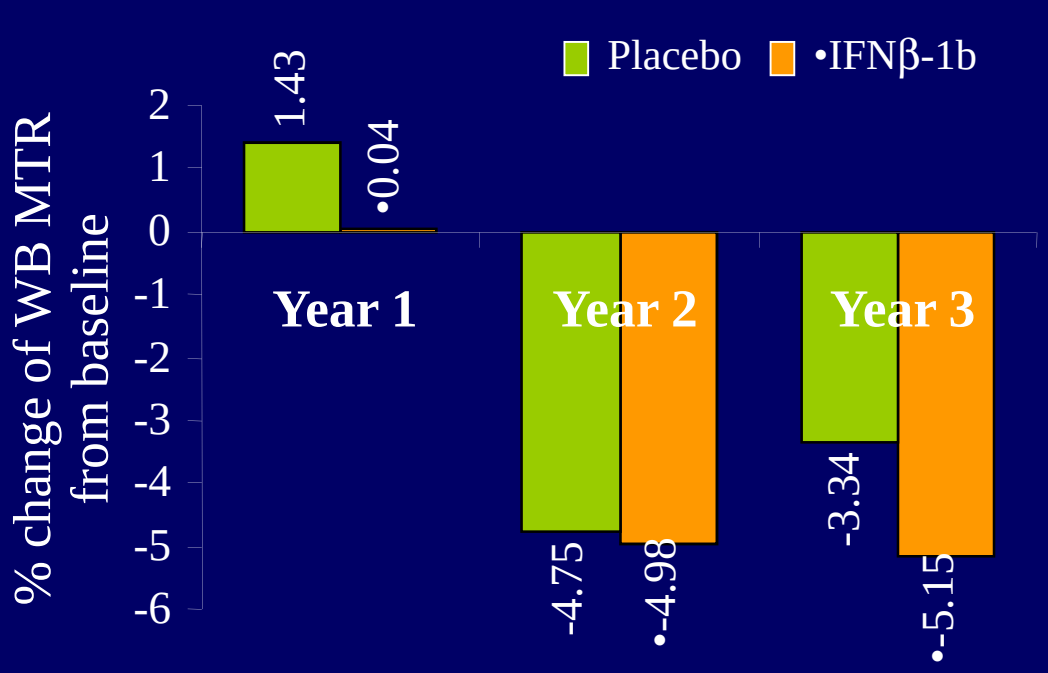
USPIO+ “ring-like”: minore probabilità di evolvere a “buchi neri”

Vellinga et al., Brain 2008

RM E MONITORAGGIO DELLE TERAPIE

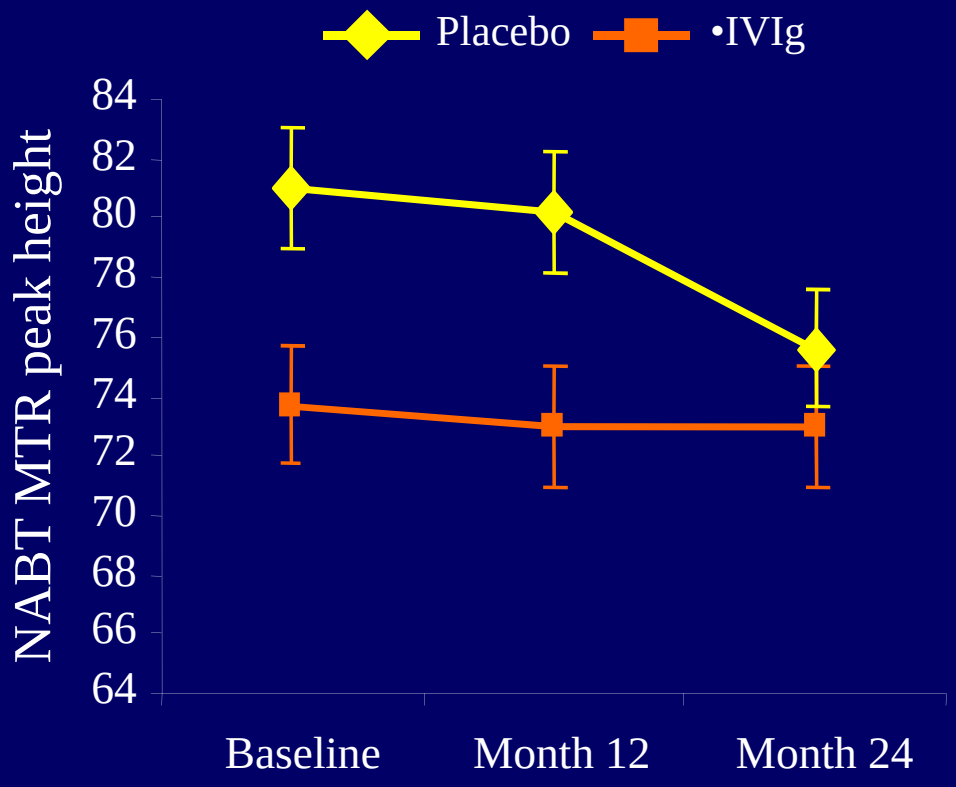
Nuove strategie – RM MT

IFNβ-1b/SPMS



Inglese et al., Neurology 2003

IVIg/SPMS

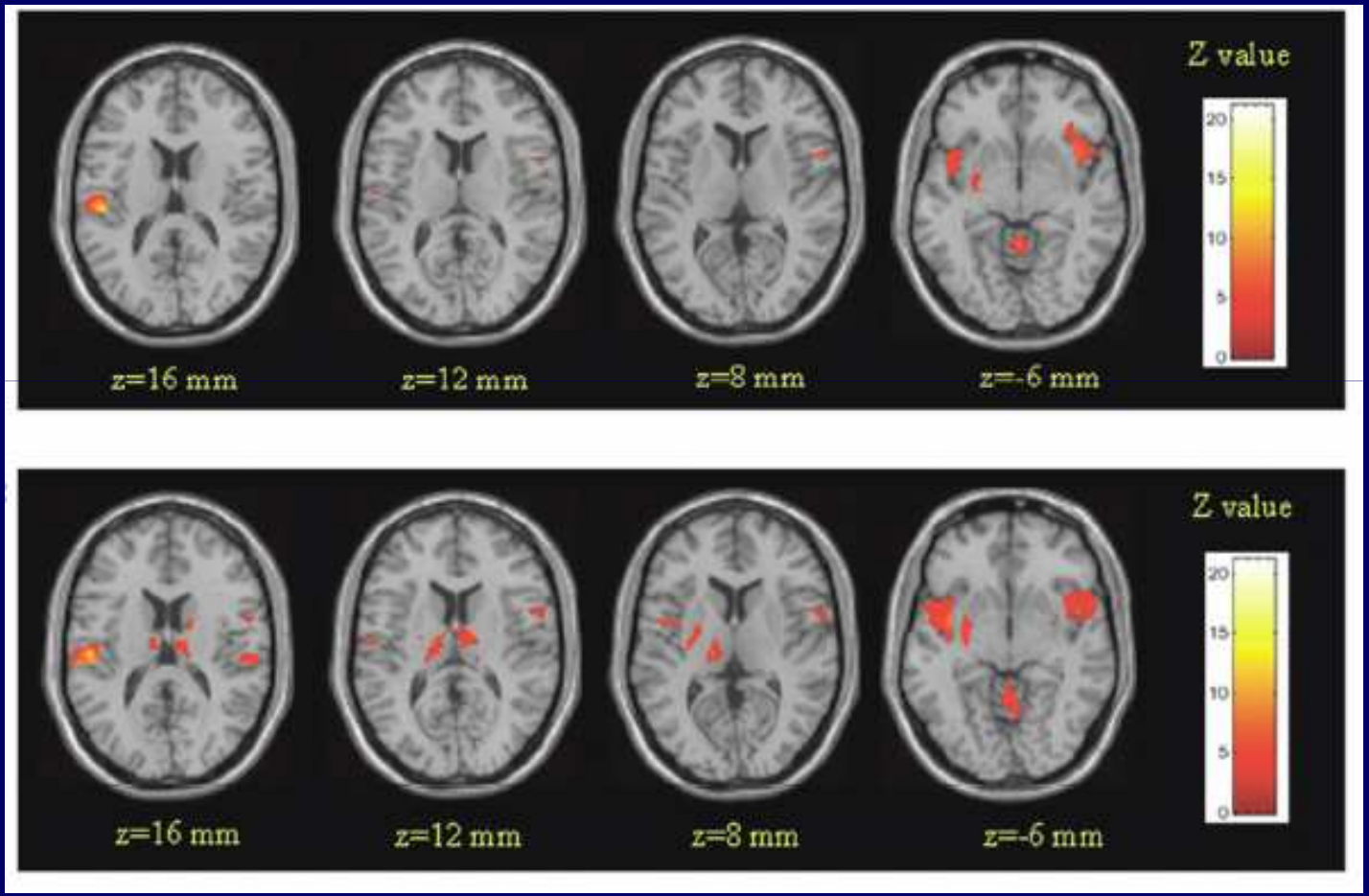


Filippi et al., Arch Neurol 2004

RM E MONITORAGGIO DELLE TERAPIE
Nuove strategie – RM funzionale

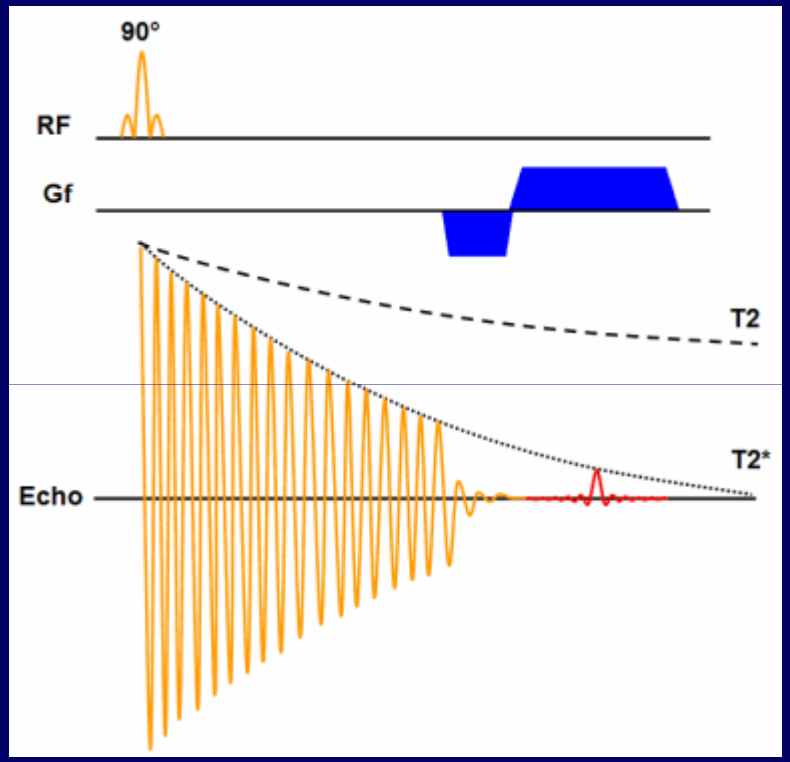
Placebo

3,4 DAP

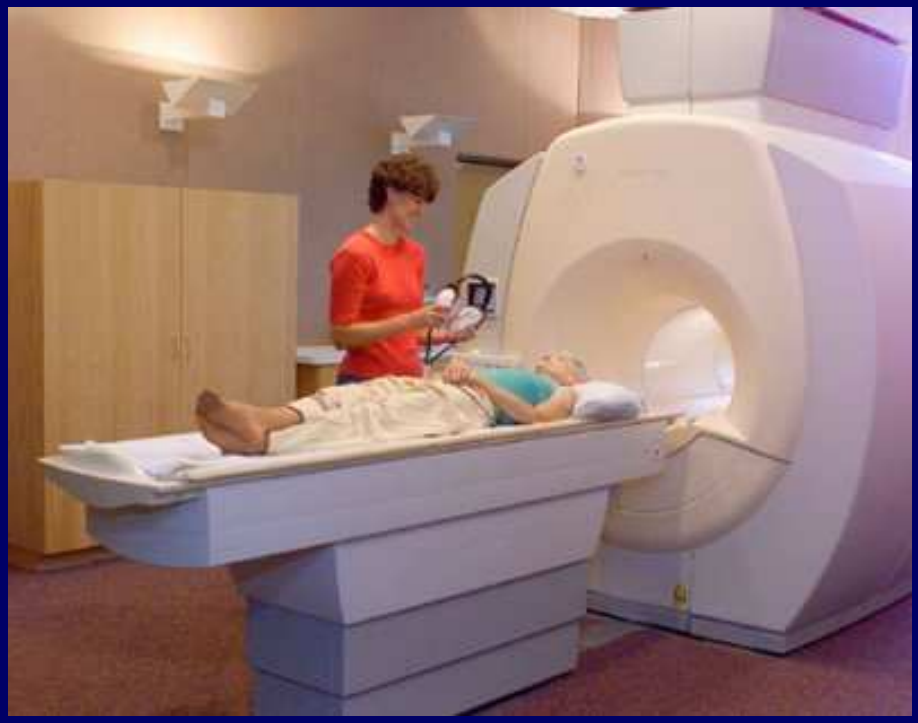


Mainero et al., Neurology 2004

RM E MONITORAGGIO DELLE TERAPIE
Dalla ricerca alla pratica clinica



Variabilità degli schemi di acquisizione



Problemi di artefatti (posizionamento, scarsa compliance)

RM E MONITORAGGIO DELLE TERAPIE
Linee guida?

REVIEW ARTICLE

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MR Imaging in Multiple Sclerosis: Review and Recommendations for Current Practice

SUMMARY: MR imaging is widely used for the diagnosis and monitoring of patients with MS. Applications and protocols for MR imaging continue to evolve, prompting a need for continual reassessments of the optimal use of this technique in clinical practice. This article provides updated recommendations on the use of MR imaging in MS, based on a review of the trial evidence and personal experiences shared at a recent expert meeting of radiologists and neurologists.

ABBREVIATIONS: BBB = blood-brain barrier; CIS = clinically isolated syndrome; CNS = central nervous system; DTI = diffusion tensor imaging; DWI = diffusion-weighting imaging; FLAIR = fluid-attenuated inversion recovery; Gd = gadolinium; IFNB = interferon β; MS = multiple sclerosis; NSF = nephrogenic systemic fibrosis

Consensus Statement. MR imaging has utility for monitoring the effects of therapies in clinical trials. Further evidence is needed to support a role for MR imaging in monitoring therapeutic response in routine clinical practice.

Consensus Statement. Early initiation of treatment offers benefits in most patients, and these benefits appear to persist for the long-term. MR imaging contributes to the early initiation of treatment by facilitating early diagnosis.

AJNR 2010

CONCLUSIONI

- Indubbio valore nella diagnosi differenziale di SM in pazienti con forme all'esordio di malattia, purchè inserita in un contesto di valutazioni cliniche e paracliniche complementari
- Strumento principale per giungere ad una diagnosi più precoce di SM, con notevoli ripercussioni sulle scelte terapeutiche
- Criteri di diagnosi con indubbio valore prognostico e classificativo, ma non pensati per fornire evidenze a supporto della diagnosi differenziale di SM

- Metodica paraclinica più semplice da utilizzare in trial clinici e per l'identificazione del paziente non-responder
- Reperti sempre e comunque da interpretare alla luce dell'andamento clinico
- Utile per fornire alcune indicazioni sulla scelta di un trattamento, ma effettivo valore da definire e comunque complementare ad altri elementi di valutazione