

**Educational Session 1 (MAGNIMS)**  
International 2020 MAGNIMS-CMSC-NAIMS consensus guidelines on the  
use of MRI in multiple sclerosis

**“MRI activity: gadolinium lesions or new T2 lesions?”**

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# Disclosures

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**A. Rovira** serves on scientific advisory boards for Novartis, Sanofi-Genzyme, Biogen IDEC, OLEA Medical, and Synthetic MR, and has received speaker honoraria from Sanofi-Genzyme, Merck-Serono, Teva Pharmaceutical Industries Ltd, Novartis, Roche and Biogen Idec.

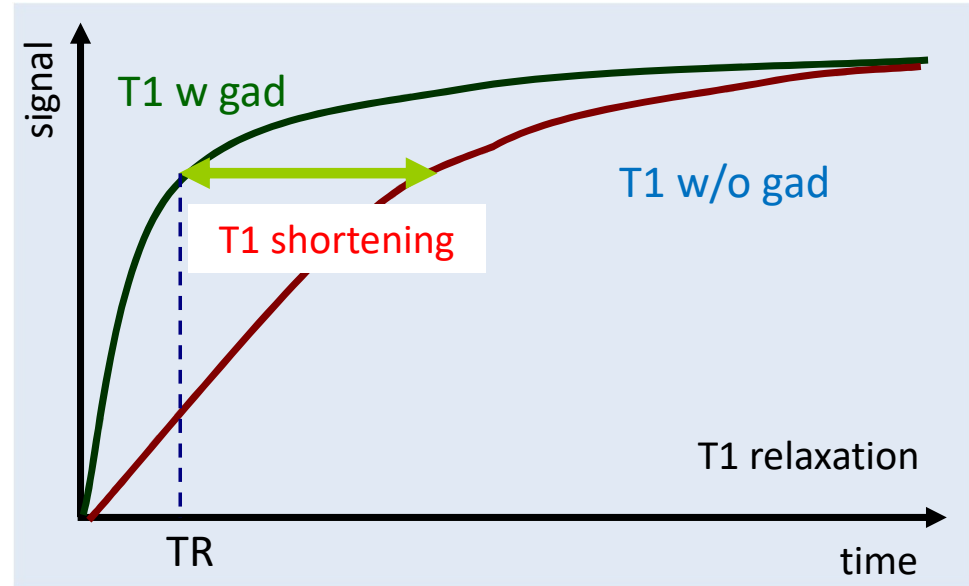
# Use of gadolinium-based contrast agents (GBCAs)

- First time used 1988 ( + 30 years)
- Used annually in approximately 30-40 million procedures, with more than 300-400 million procedures performed to date
- Used in approximately 1/3 of all MRI examinations
- Excellent safety profile
  - ✓ Rates of adverse reactions very low: between **0.03% and 2.4%** (most transient and mild)
  - ✓ Life-threatening and fatal reactions very rare: **40 deaths per 51 million**
  - ✓ **NSF** in patients with severe renal dysfunction (linear GBCAs)
  - ✓ Gadolinium **deposition in CNS** (mainly with linear agents)

Mallio, Rovira et al. Neuroradiology 2020

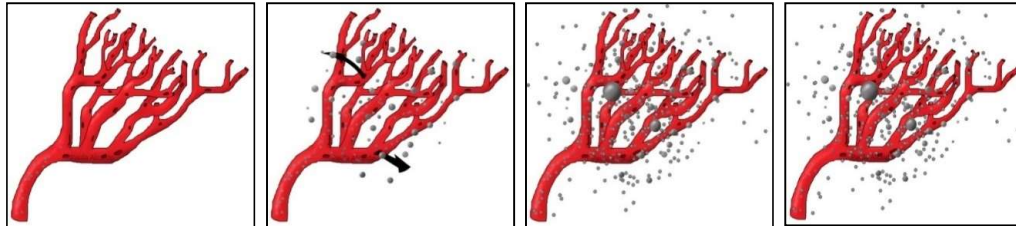
# Gadolinium-based contrast agents: Relaxivity

- Rare-earth lanthanide metal, with strong paramagnetic effects

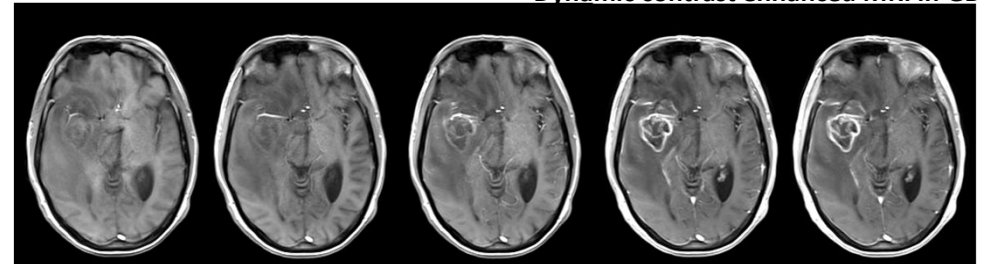


For a certain TR, the shorter the T1, the higher the signal

- Markedly decreases the T1 (T2) relaxation times of adjacent mobile water protons
- Local increase signal on T1WI from CNS tissues w/o or compromised BBB



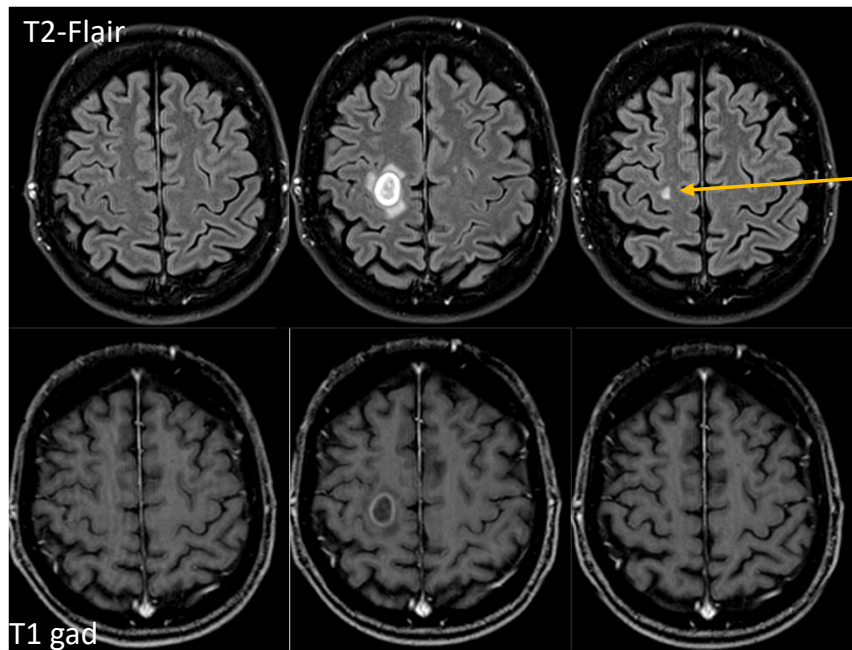
Dynamic contrast enhanced MRI in GB



## GBCAs in Multiple Sclerosis

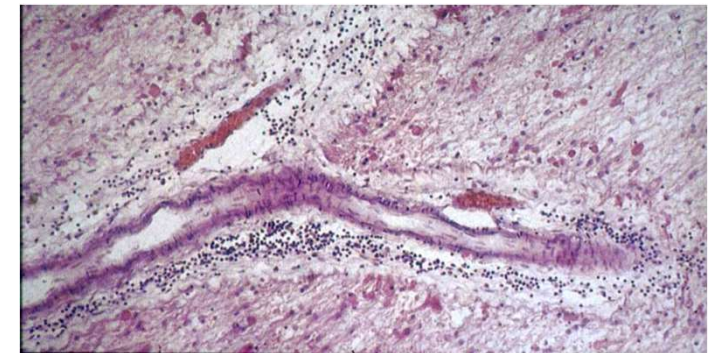
- Marker of acute focal inflammation (disease activity)
- Enhancement correlated with an altered BBB permeability
- Almost constant in new T2 lesions (relapsing forms)
- Lasts from few days to weeks (average duration of enhancement: 3.1 weeks)

Cotton et al. Neurology. 2003



T2 lesions: permanent footprint of a prior focal inflammatory event

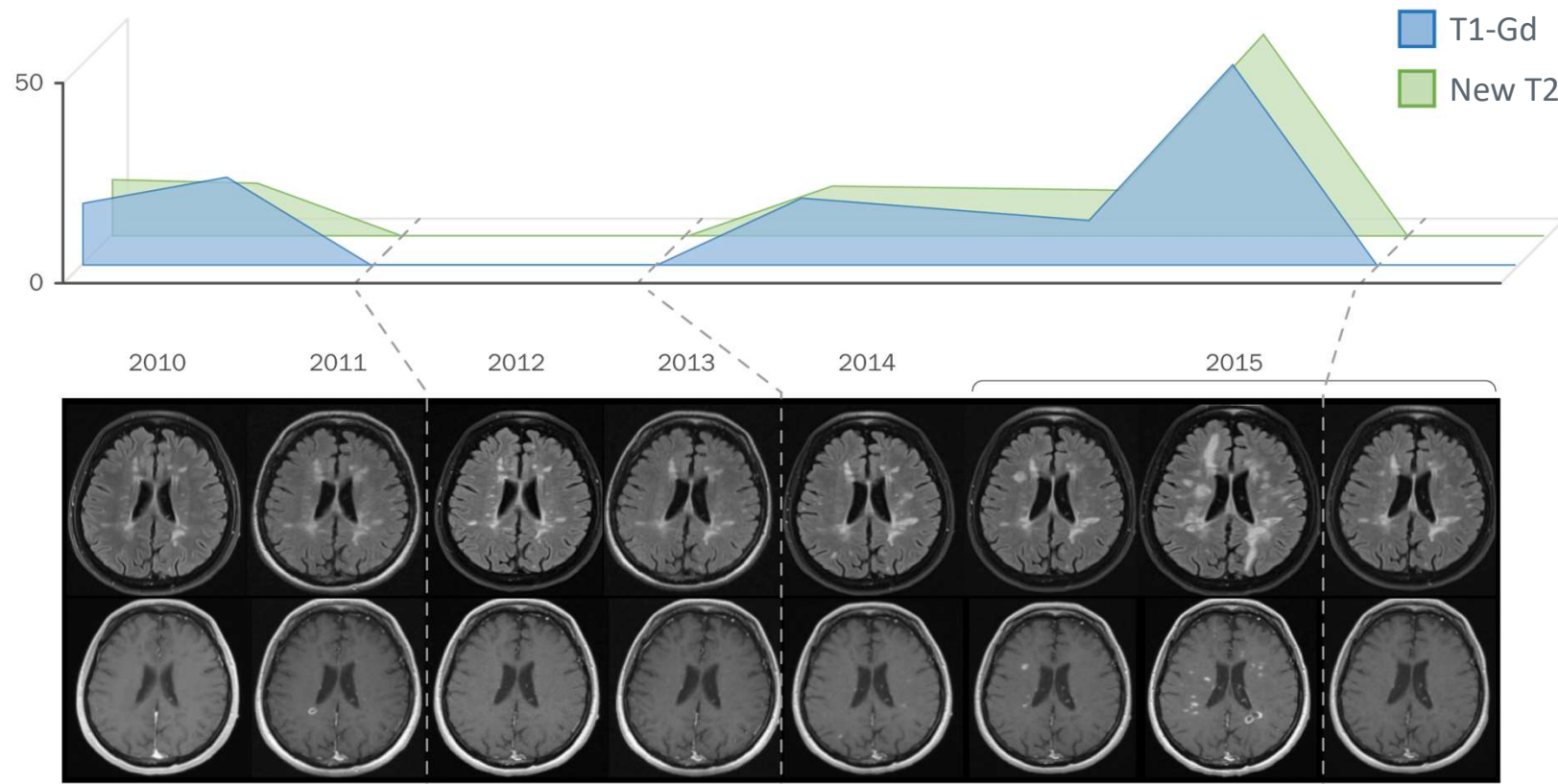
Kirk et al. J Pathol 2003



Acute perivascular inflammation

Serial monthly MRIs in a patient with relapsing MS: A new frontal T2 lesion showing contrast uptake

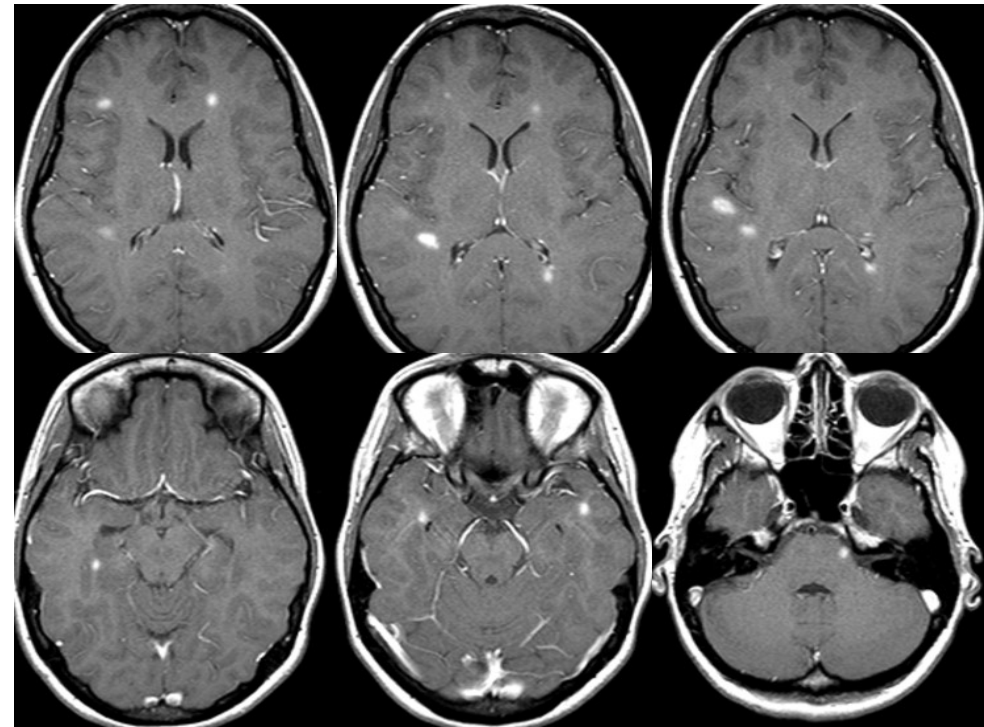
# MRI markers of disease activity: new T2 /Gad lesions



# Advantages of using GBCAs for assessing disease activity

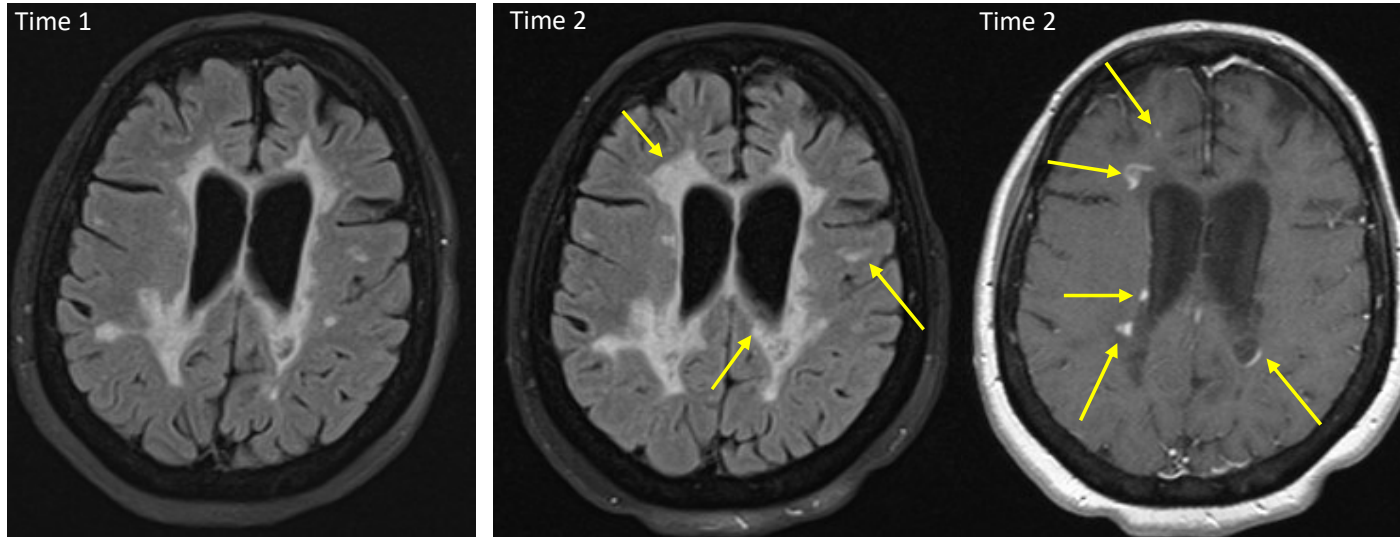
(in comparison with new/enlarged T2 lesions)

- **Identifies acute (recent) inflammatory activity (3-4 weeks)**
- **Increase sensitivity for detecting active lesions**
  - Small new T2 lesions
  - Large/ confluent chronic T2 lesion
- **Higher reproducibility**
- **No reference scans required**



# Assessing T2 active lesions in patients with confluent chronic lesions

Relapsing MS patient



New/enlarged T2 lesions: 3

Gad enhancing lesions: 5

**Active lesions: 7**

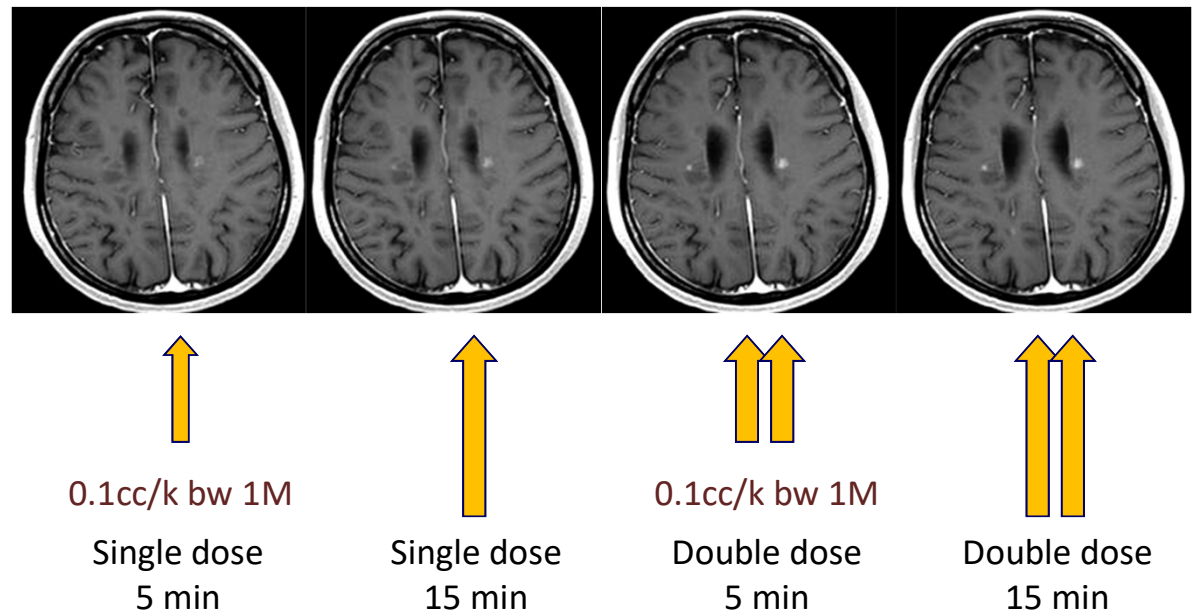
Some new T2 lesions can only be visually detected after being identified as gadolinium-enhancing lesions, owing to their small size or their location in areas with chronic confluent lesions



# Disadvantages of using GBCAs for assessing disease activity

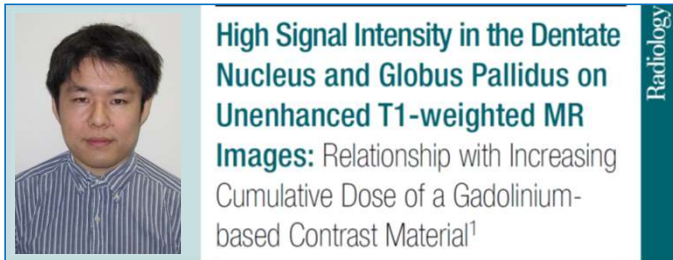
- Ignore less recent disease activity (and certain forms of inflammation)
- Cost /time
- Depends on imaging strategy
  - Type of T1w sequence
  - Field strength
  - Dose
  - Relaxivity of GBCA
  - Delay after injection
- Safety
  - Allergic reactions
  - NSF (severe renal impairment)
  - CNS deposition

Rovira et al. Am J Neuroradiol 2018



# Gad deposition in CNS

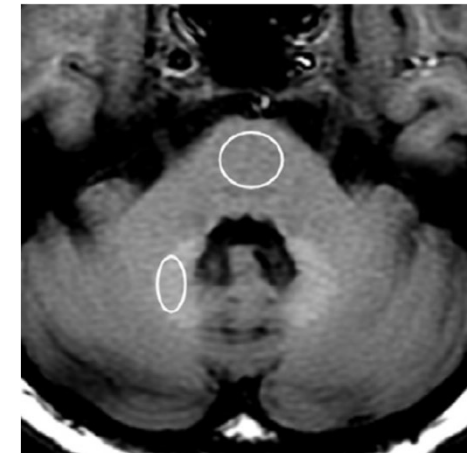
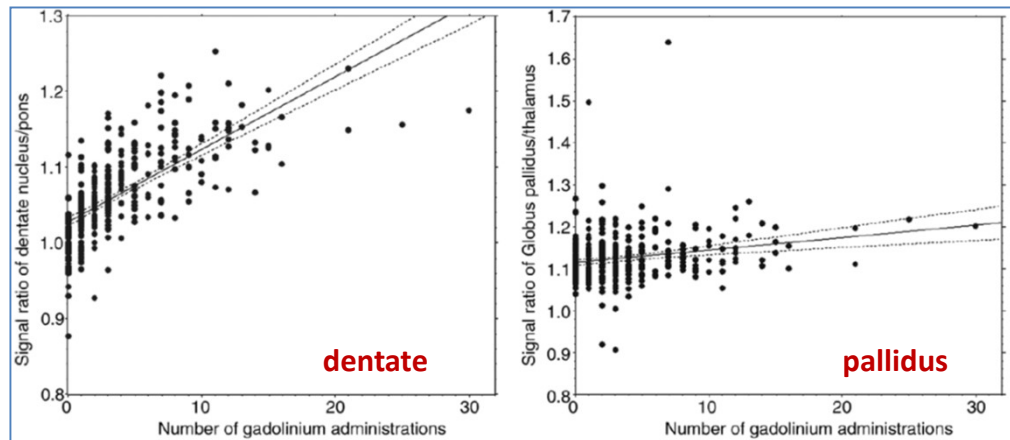
First study that correlated high SI in DN and GP with administration of GBCAs (linear). No clinical data



Kanda et al. Radiology 2014

## Design

- single center
- retrospective
- 19 patients
- normal liver and renal function
- no prior RT



# Gadolinium deposition (2014-2018)

Linear Macrocytic

Table 1. ECF MRI Contrast Agents That Have Been Used in the Clinic

ECF agent (trade name)	ECF agent (chemical code)	ECF agent (generic name)	approval date
Dotarem, Clariscan	Gd-DOTA	gadoterate meglumine	1989 (Europe) 2013 (United States)
ProHance	Gd-HPDO3A	gadoteridol	1992
Gadovist (Europe)	Gd-DO3A-butrol	gadobutrol	1998 (Europe)
Gadavist (United States)			2011 (United States)
Magnevist <sup>a</sup>	Gd-DTPA	gadopentetate dimeglumine	1988
Omniscan <sup>a</sup>	Gd-DTPA-BMA	gadodiamide	1993
Optimark <sup>a</sup>	Gd-DTPA-BMEA	gadoversetamide	1999
Multihance <sup>b,c</sup>	Gd-BOPTA	gadobenate dimeglumine	2004

<sup>a</sup>Agents suspended by the European Medicines Agency in 2017. <sup>b</sup>Agent available for limited, liver-specific indications in the EU. <sup>c</sup>Multipurpose agent that is also suitable for liver imaging.<sup>14</sup>

Wahsner et al. Chem Rev 2019

- Higher degree of gadolinium deposition with linear compounds versus macrocyclic
- Macrocyclic agents have higher thermodynamic, kinetic and conditional stability

Authors	Journal	Year	Chemical Structure	Linear Non-Ionic	Linear Ionic				Macrocytic Non-Ionic		Macrocytic Ionic	
					Molecule	gadodiamide	gadobenate dimeglumine	gadobenate dimeglumine	gadoxetate disodium	gadoteridol	gadobutrol	gadoterate meglumine
Kanda	Radiology	2014	#1									
Errante	Invest Radiol	2014	#2									
Kanda	Radiology	2015	#3									
Quattrocchi	Invest Radiol	2015	#4									
Radbruch	Radiology	2015	#5									
Miller	Pediatrics	2015	#6									
Ramalho	Radiology	2015	#7									
Stojanov	Eur Radiol	2015	#8									
Adin	AJNR	2015	#9									
McDonald	Radiology	2015	#10									
Weberling	Invest Radiol	2015	#11									
Radbruch	Invest Radiol	2015	#12									
Cao	AJR	2016	#13									
Ramalho	Eur Radiol	2016	#14									
Ramalho	AJNR	2016	#15									
Tedeschi	Eur Radiol	2016	#16									
Roberts	AJNR	2016	#17									
Tanaka	Eur Neurol	2016	#18									
Cao	Invest Radiol	2016	#19									
Hu	Pediatric Radiol	2016	#20									
Roberts	Brain Develop	2016	#21									
Khant	Magn Reson Med Sci	2016	#22									
Eisele	Medicine	2016	#23									
Radbruch	Invest Radiol	2016	#24									
Zhang	Radiology	2017	#25									
Eisele	JNFP	2017	#26									
Schlemm	Mult Scler	2017	#27									
Radbruch	Radiology	2017	#28									
Kuno	Radiology	2017	#29									
Bae	Eur Radiol	2017	#30									
Radbruch	Radiology	2017	#31									
Flood	Radiology	2017	#32									
Langner	Eur Radiol	2017	#33									
Kahn	Radiology	2017	#34									
Ichikawa	Invest Radiol	2017	#35									
Conte	Eur Radiol	2017	#36									
Tedeschi	Magn Reson Med Sci	2017	#37									
Espagnet	Ped Radiol	2017	#38									
Forslin	AJNR	2017	#39									
Roberts	Neurology	2017	#40									
Schneider	AJNR	2017	#41									
Eisele	J Neuroimaging	2017	#42									
Tibussek	Radiology	2017	#43									
Splendiani	Radiol med	2017	#44									
Lee	Plos One	2017	#45									
Björnerud	Radiology	2017	#46									
Yoo	Invest Radiol	2017	#47									
Muller	Clin Neuroradiol	2017	#48									
Kromrey	Eur Radiol	2017	#49									
Renz	Invest Radiol	2018	#50									
Lee	Plos One	2017	#51									

# Gad deposition in CNS

Neurologic and neuropsychologic consequences: **NONE**

Reference	Patients	Findings
Welk et al., 2016	99,739 patients with at least 1 dose of GBCAs	No significant increase hazard of <b>parkinsonism</b>
McDonald, 2017	1,092 patients with at least 1 dose of GBCAs	No prediction of <b>cognitive decline</b> , dementia and impairment of neuropsychological or motor performances
Perrotta et al., 2017	10 patients with $28.2 \pm 5.3$ doses of GBCAs	Neither <b>cerebellar syndrome</b> , nor symptoms or signs suggestive for cerebellar toxicity
Cocoza et al., 2019	74 <b>relapsing–remitting multiple sclerosis</b> with mean GBCAs injection at follow-up of $7.2 \pm 3.8$	DN T1 hyperintensity and DN R1 did not explained <b>EDSS changes</b> and significant clinical worsening
Mallio et al., 2019	15 Crohn’s disease patients with at least 4 GBCAs injections	Absence of <b>neurological and neurocognitive</b> psychological significant abnormalities
Zivadinov et al., 2019	203 patients with <b>multiple sclerosis</b> and mean GBCAs administrations of 9.2	No associations with clinical outcomes of <b>disease severity</b>
Vymazal et al., 2019	4 patients with glioblastoma multiforme and at least 50 GBCAs injections	No <b>neurological and neuropsychological</b> impairment related to gadolinium deposition in the DN and GP

# European Commission decision on use of Gd

- Use Gd only if essential; minimise repetitive Gd imaging when possible
- Use Gd at lowest dose needed
- Only **macrocyclic** agents for CNS studies

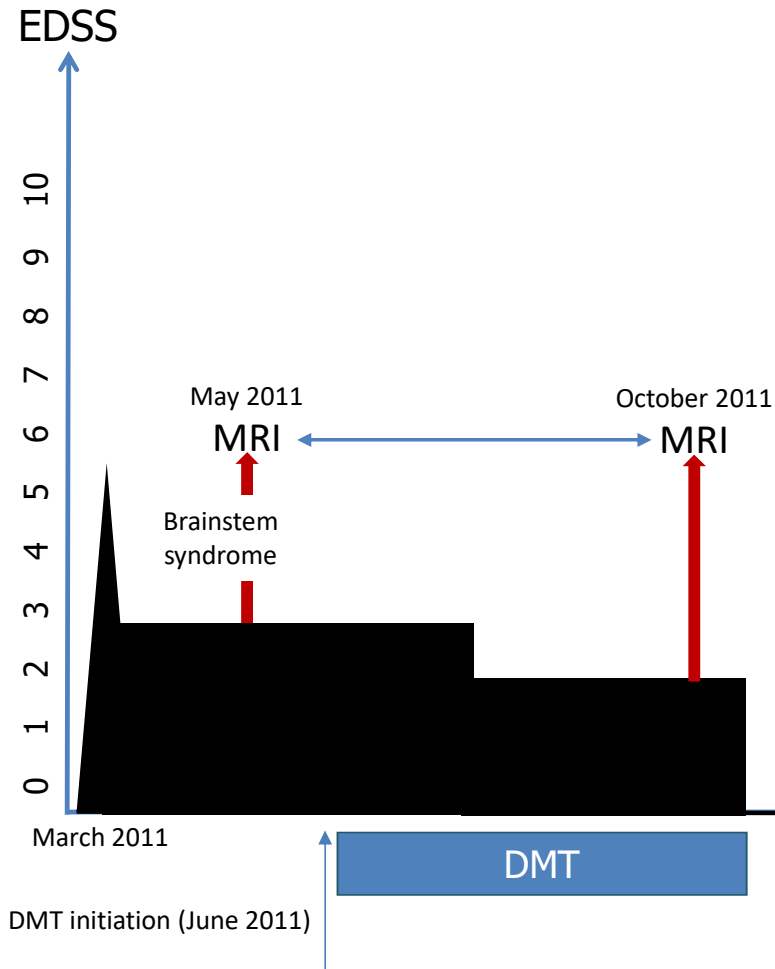
European Medicines Agency, <https://www.ema.europa.eu/en/medicines/human/referrals/gadolinium-containing-contrast-agents> (accessed 5 November 2019).



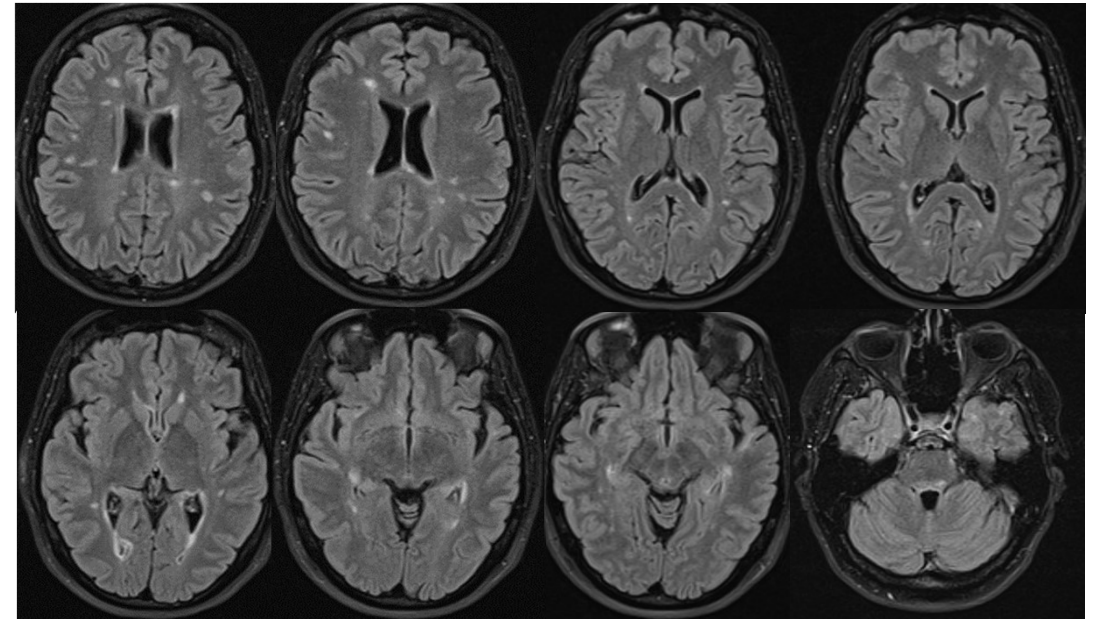
Despite lack of evidence of the clinical effects (in subjects with normal renal function) we must take special caution in patients at higher risk:

- Patients requiring multiple lifetime doses
- Patients with inflammatory conditions (likely increase Gad deposition)
  - Children, MS, inflammatory bowel disease

# 33 yo female. RRMS



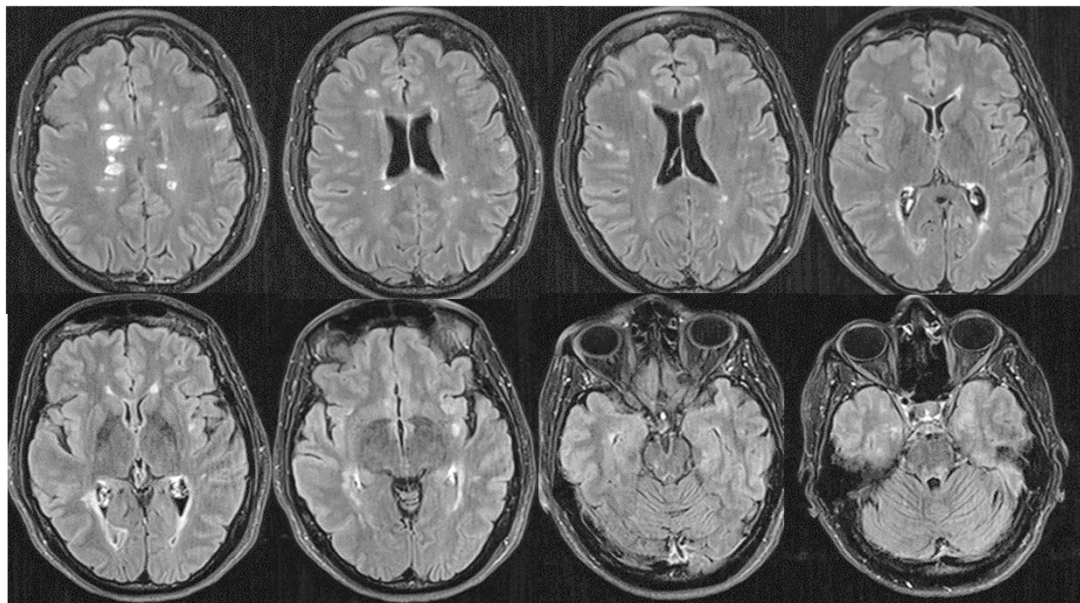
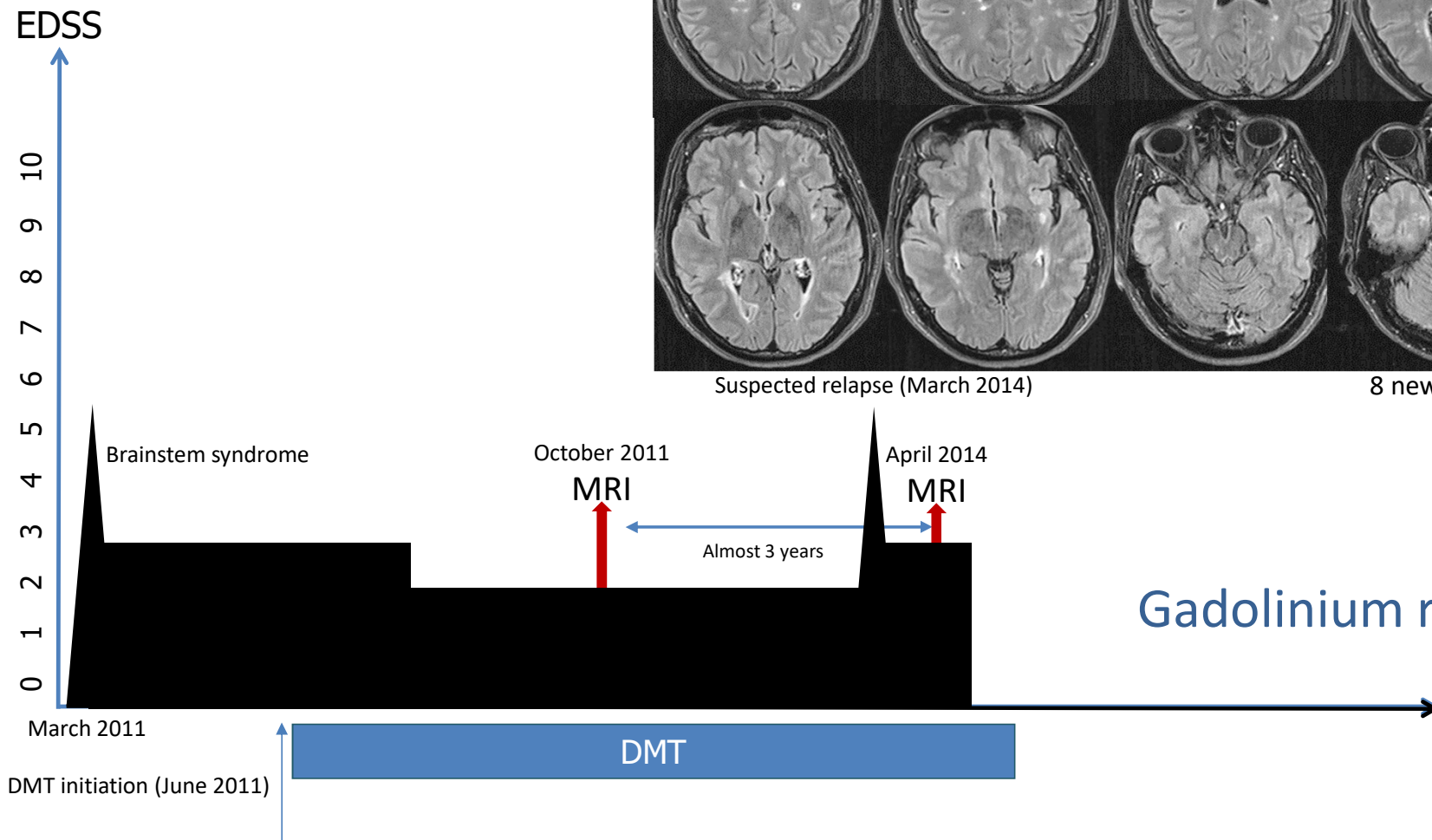
Rebaseline MRI: 4 months after treatment initiation



2 new T2 lesions

Gadolinium NOT required

# 33 yo female. RRMS



Suspected relapse (March 2014)

8 new T2 lesions

Brainstem syndrome

October 2011

April 2014

MRI

MRI

Almost 3 years

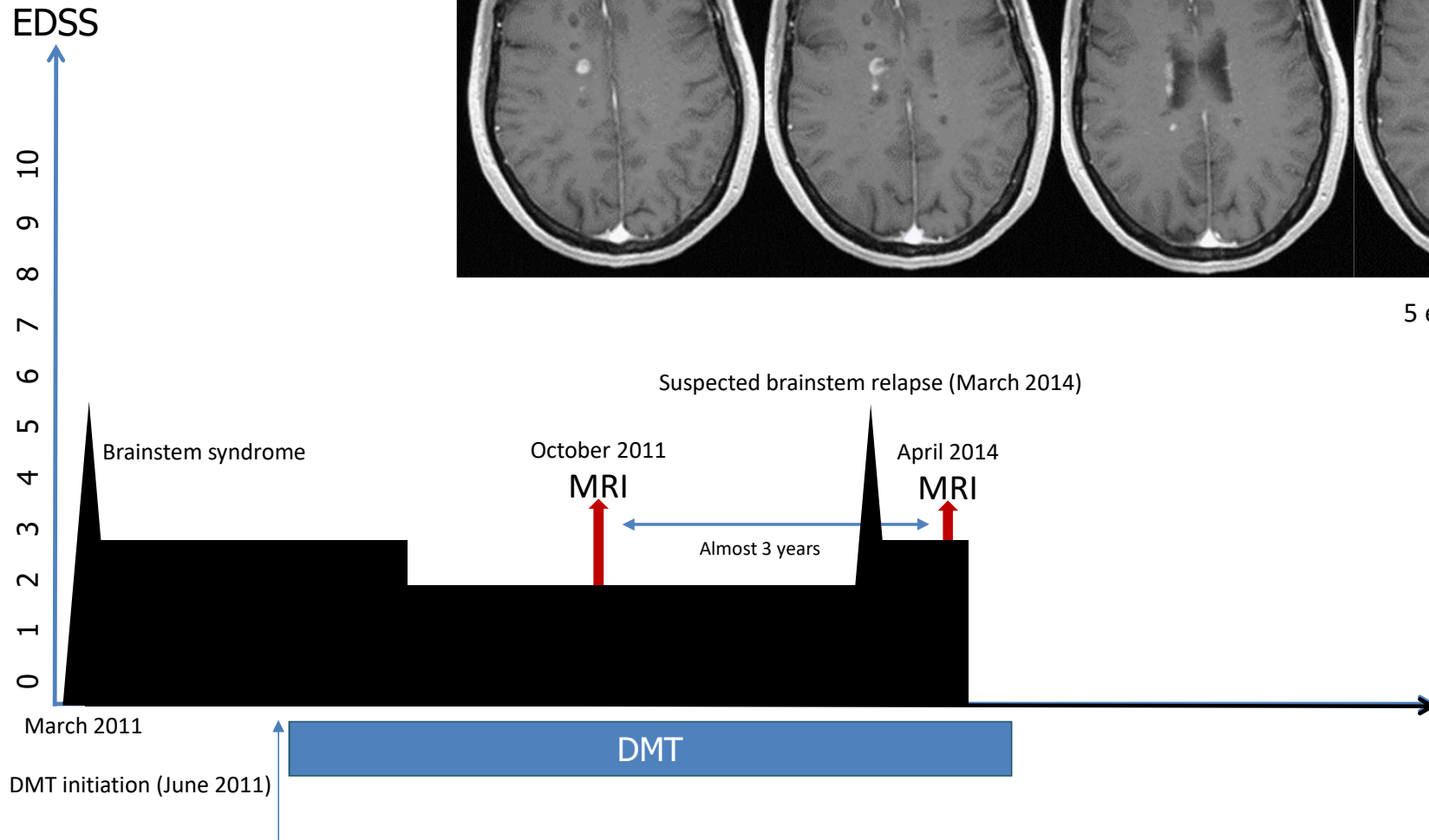
Gadolinium required

March 2011

DMT initiation (June 2011)

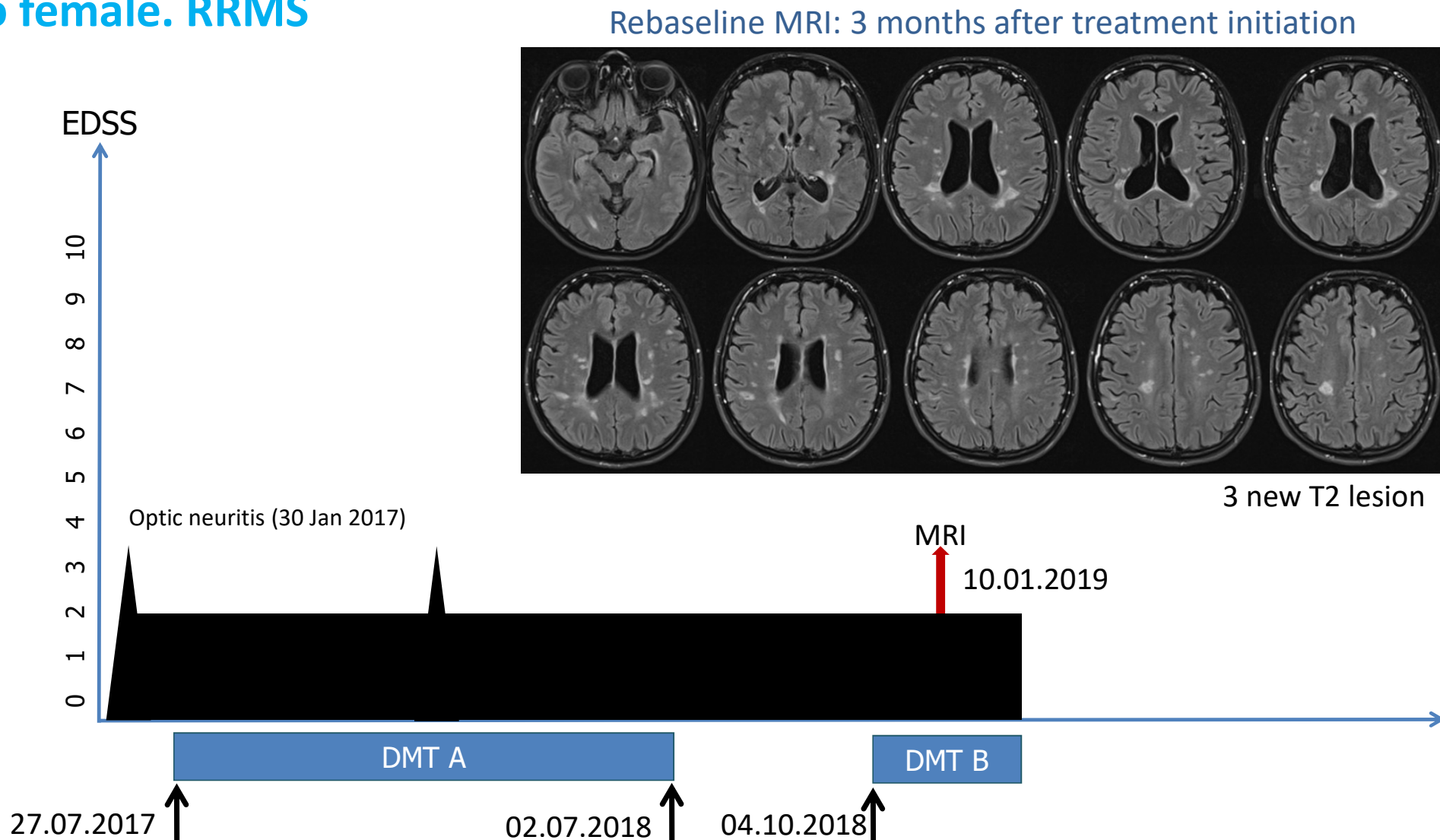
DMT

# 33 yo female. RRMS



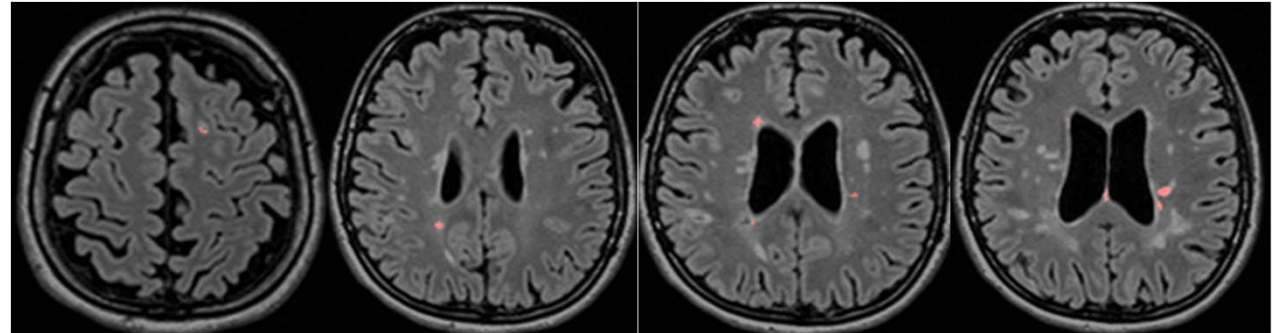


# 41 yo female. RRMS



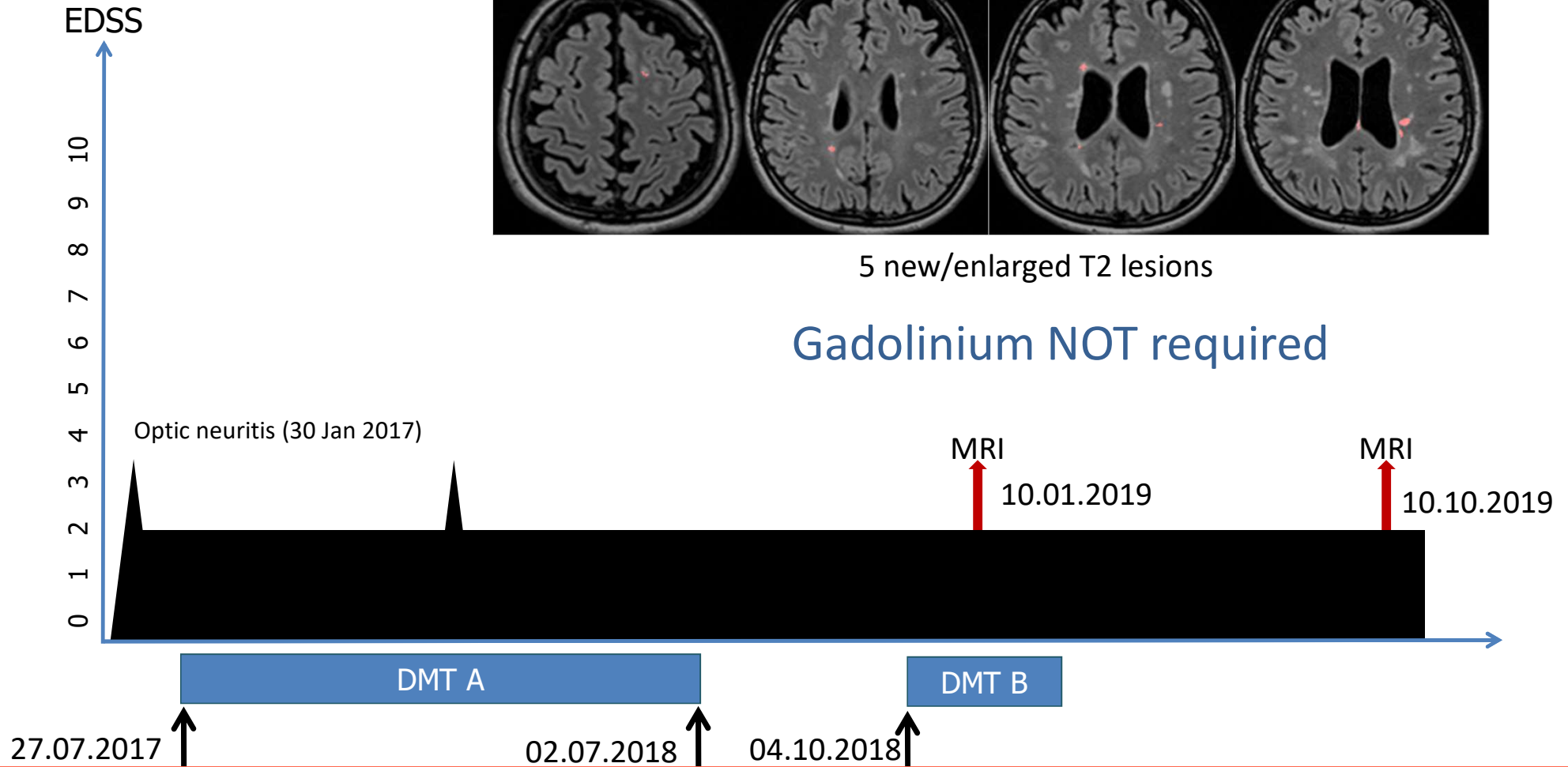
# 41 yo female. RRMS

Routine follow-up MRI: 12 months after treatment initiation



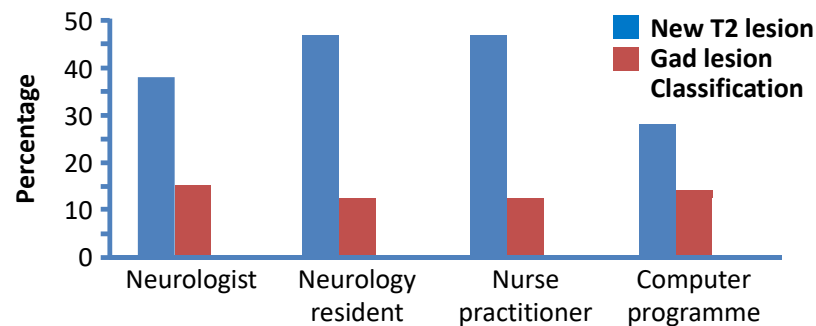
5 new/enlarged T2 lesions

Gadolinium NOT required



# MRI activity: challenges in visual assessment

- Poor quality scans
  - ✓ Thick slices (>3mm)
  - ✓ Repositioning
  - ✓ Non standardized protocol
  - ✓ Movement artifacts
- Small lesions
- Confluent non-active lesions



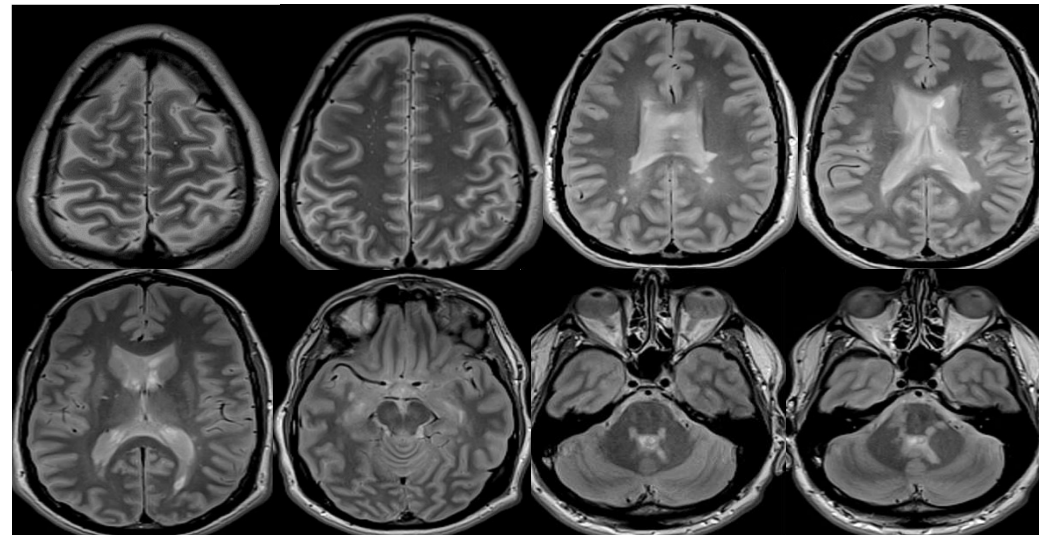
Erbayat Altay E et al. *JAMA Neurol* 2013;70:338–344.

## Concordance analysis compared with image analysis software:

- High (0.8-0.96) for Gd+ lesions
- Intermediate (0.6–0.8) for new T2 lesions
- Very poor (0.0–0.14) for enlarging T2 lesions

# MRI activity

Active lesions?

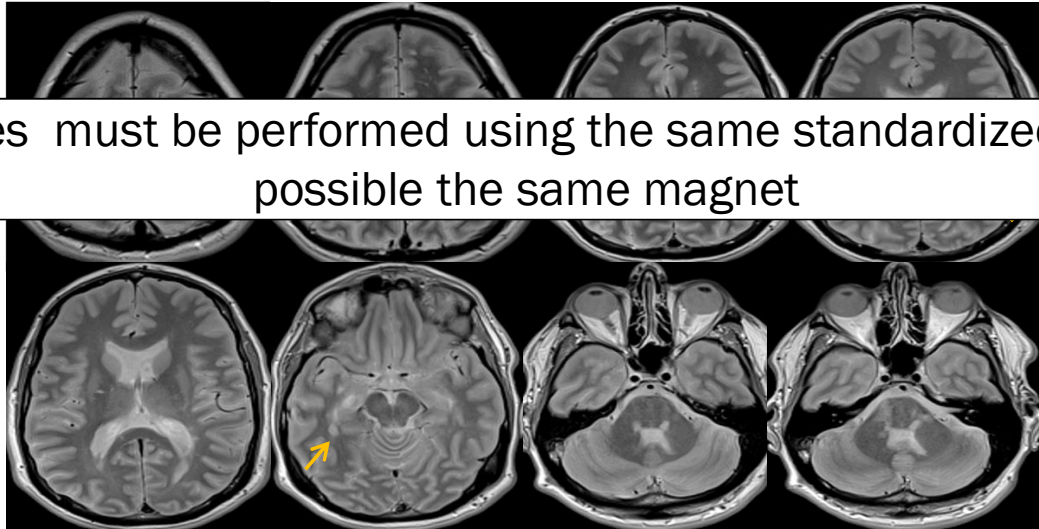


baseline

3 active lesions

- 2 new

1 enlarging



One year

Follow-up studies must be performed using the same standardized protocol, and if possible the same magnet

## MRI activity: Computer assisted detection of new/enlarged T2 lesions



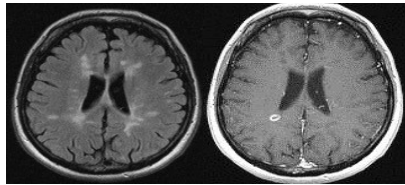
	Observer 1		Observer 2		CAD	
	Value	95% CI	Value	95% CI	Value	95% CI
<b>Sensitivity</b>	<b>76.32%</b>	59.76% to 88.56%	<b>89.47%</b>	75.20% to 97.06%	<b>97.37%</b>	86.19% to 99.93%
<b>Specificity</b>	<b>100.00%</b>	94.22% to 100.00%	<b>100.00%</b>	94.22% to 100.00%	<b>87.10%</b>	76.15% to 94.26%

## Recommendations for the use of GBCAs (monitoring)

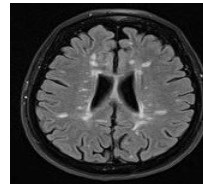
Clinical situation	Indication and objective
<b>Monitoring</b>	<p data-bbox="461 411 1146 451"><b>The use of gadolinium is recommended</b></p> <ul data-bbox="461 472 2168 738" style="list-style-type: none"><li data-bbox="461 472 2168 627">• In case of clinical suspicion of recent MS disease activity or if confirmation/demonstration of recent disease activity is required (MRI should be performed as soon as possible and before steroid treatment).</li><li data-bbox="461 639 2168 738">• In patients with diffuse and confluent chronic MS lesions, in which detection of disease activity based on new/enlarged T2 lesions would be extremely difficult</li></ul> <p data-bbox="461 855 1214 895"><b>The use of gadolinium is not recommended</b></p> <ul data-bbox="461 916 2168 1066" style="list-style-type: none"><li data-bbox="461 916 2168 959">• <b>In case of routine monitoring MRIs in patients without anticipated disease activity</b></li><li data-bbox="461 970 2168 1013">• In re-baseline MRI scans (after treatment initiation) unless unexpected clinical activity</li><li data-bbox="461 1024 875 1066">• For PML screening</li></ul>

# Brain MRI in monitoring MS

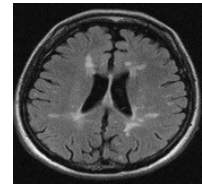
Initial	Re-Baseline	First follow-up <sup>a,b</sup>	Second follow-up <sup>a, b</sup>	Follow-ups <sup>a, b</sup>
Diagnostic <sup>c</sup> Pre-treatment	3–6 months after treatment onset	12 months after Re-Baseline	24 months after Re-Baseline	Every year <sup>d</sup>
Gd highly recommended	Gd optional <sup>e</sup>	Gd optional <sup>f</sup>	Gd optional	Gd optional <sup>e</sup>



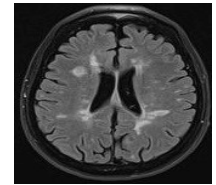
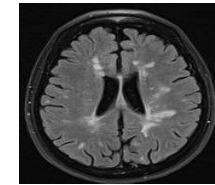
Assess markers of poor prognosis



Active lesions should be ignored (unless associated with clinical activity or unexpected high MRI activity)



Apply predictive response/prognostic scales/models



<sup>a</sup> Shorter follow-up MRI if isolated MRI activity or clinical activity; <sup>b</sup> Add spinal cord MRI if clinically indicated;

<sup>c</sup> Add spinal cord MRI for initial diagnosis or if never performed; <sup>d</sup> Less frequent MRIs in clinically stable patients treated with IFN or GA;

<sup>e</sup> Gd required if clinical activity/progression; <sup>f</sup> Particularly in patients receiving moderate efficacy DMTs.

Rovira A et al. Nat Rev Neurol. 2015; Wattjes M et al. Nat Rev Neurol. 2015; Traboulsee A et al. AJNR Am J Neuroradiol. 2016

# Conclusions

- GBCAs are extremely safe
- FDA/EMA measures have effectively cancelled the risk of NSF and reduced Gad deposition in the CNS
- The use of GBCAs continues to be invaluable during the diagnostic work-up of MS
- The policy of reducing GBCA use in monitoring MS is reasonable
  - Only use GBCAs when really needed!!!
  - Avoid routine GBCAs administration in monitoring MRIs obtained in clinically stable patients