Bibliographic Cite	Literature Type	Level of Evidence	Purpose	Population	Intervention and Outcome Measures	Results/ Recommendations	Study Limitations
Barisano G, Bigjahan B, Metting S, et al. Signal hyperintensity on unenhanced T1-weighted brain and cervical cord MR images after multiple doses of linear gadolinium-based contrast agent.	single center retrospective	low level of evidence	To assess the effects of linear gadolinium-based contrast agents on the T1 signal intensity of 3 cerebral areas (dentate nucleus, globus pallidus, and the less studied substantia nigra) and the cervical spinal cord in a population of patients with MS.	A single-center population of 100 (67 women and 33 men; mean age, 41.6 +/- 11.8 years) patients with MS. Inclusion criteria were: 1) a relapsing-remitting MS diagnosis according to the McDonald criteria; 2) first and last contrast-enhancedMR imaging scans of the brain and the cervical spine performed at our institution; and 3) injections of exclusively L-GBCA.	Patients underwent 2–16 contrast-enhanced MRIs. Fifty patients received 5 linear gadolinium injections, and 50 patients had 6 injections: fifty-two patients had both Gd-DTPA and gadobenate dimeglumine injections, and 48 patients received only gadobenate dimeglumine. A quantitative analysis of signal intensity changes was independently performed by 2 readers on the first and last MR imaging scan. The globus pallidus-to-thalamus, substantia nigra-to-midbrain, dentate nucleus-to-middle cerebellar peduncle, and the cervical spinal cord-to-pons signal intensity ratios were calculated.	An increase of globus pallidus-to-thalamus (mean, 0.0251 +/-0.0432; P < .001), dentate nucleus-to-middle cerebellar peduncle (mean, 0.0266 +/- 0.0841; P < .002), and substantia nigra-to-midbrain (mean, 0.0262 +/- 0.0673; P < .001) signal intensity ratios after multiple administrations of linear gadolinium-based contrast agents was observed. These changes were significantly higher in patients who received 6 injections (P < .001) and positively correlated with the number of injections and the accumulated dose of contrast. No significant changes were detected in the spinal cord (mean, 0.0008 +/- 0.0089; P = .400). The authors conclude that patients with MS receiving 6 linear gadolinium-based contrast agent injections showed a significant increase in the signal intensity of the globus pallidus, dentate nucleus, and substantia nigra; no detectable changes were observed in the cervical spinal cord.	Limitations of the study include its retrospective nature and the absence of pathologic correlation with neuroimaging findings. Moreover, as with most published articles investigating gadolinium deposition, any GBCA injections in addition to the ones reported in clinical records could not be excluded in the study population. The authors note that the lack of a control group does not exclude the possibility of SI changes due to MS.
Brownlee WJ, Altmann DR, Alves Da Mota P, et al. Association of asymptomatic spinal cord lesions and atrophy with disability 5 years after a clinically isolated syndrome. Multiple Sclerosis. 2017;23(5):665-74.	single center prospective	high level of evidence	To investigate longitudinal changes in spinal cord lesions and atrophy in patients with a non-spinal clinically isolated syndrome (CIS), and how they relate to the development of a disability.	131 patients (mean age: 32.6 years, 83 (63%) females) with a non-spinal CIS who had brain and spinal cord imaging at the time of CIS and approximately 5 years later (median: 5.2 years, range: 3.0-7.9 years).	Brain magnetic resonance imaging (MRI) measures consisted of T2-hyperintense and T1-hypointense lesion loads plus brain atrophy. Spinal cord MRI measures consisted of lesion number and the upper cervical cord cross-sectional area (UCCA). Disability was measured using the Expanded Disability Status Scale (EDSS). Multiple linear regression was used to identify independent predictors of disability after 5 years.	During follow-up, 93 (71%) patients were diagnosed with MS. Baseline spinal cord lesion number, change in cord lesion number and change in UCCA were independently associated with EDSS (R2=0.53) at follow-up. Including brain T2 lesion load and brain atrophy only modestly increased the predictive power of the model (R2=0.64). Asymptomatic spinal cord lesions and spinal cord atrophy contribute to the development of MS-related disability over the first 5 years after a non-spinal CIS.	Only a minority of patients developed significant disability over the 5-year follow-up period. Whether early spinal cord MRI abnormalities retain their prognostic significance in the longer term is uncertain. Second, the study did not include a matched healthy control group for comparison. Third, patients with optic neuritis are over-represented in this cohort with only a relatively small number of patients with other nonspinal CIS types. Fourth, authors did not consider the location of brain and spinal cord lesions.
Brownlee WJ, Altmann DR, Prados F, et al. Early imaging predictors of long-term outcomes in relapse-onset multiple sclerosis. Brain. 2019; 142(8):2276-2287.	multicenter prospective study	low level of evidence	To investigate early MRI predictors of key long-term outcomes including secondary progressive multiple sclerosis, physical disability and cognitive performance, 15 years after a clinically isolated syndrome.	A cohort of patients with clinically isolated syndrome (n = 178) were included. Inclusions criteria was: (i) age 16–50 years; (ii) a 'typical' syndrome suggestive of multiple sclerosis e.g. unilateral optic neuritis, partial myelitis, brainstem / cerebellar syndrome; and (iii) no previous history of neurological symptoms.	Patients were prospectively recruited within 3 months of clinical disease onset and studied with MRI scans of the brain and spinal cord at study entry (baseline) and after 1 and 3 years. MRI measures at each time point included: supratentorial, infratentorial, spinal cord and gadolinium-enhancing lesion number, brain and spinal cord volumetric measures. The patients were followed-up clinically after 15 years to determine disease course, and disability was assessed using the Expanded Disability Status Scale, Paced Auditory Serial Addition Test and Symbol Digit Modalities Test. Multivariable logistic regression and multivariable linear regression models identified independent MRI predictors of secondary progressive multiple sclerosis and Expanded Disability Status Scale, Paced Auditory Serial Addition Test and Symbol Digit Modalities Test, respectively.	After 15 years, 166 (93%) patients were assessed clinically: 119 (72%) had multiple sclerosis [94 (57%) relapsing-remitting, 25 (15%) secondary progressive], 45 (27%) remained clinically isolated syndrome and two (1%) developed other disorders. Physical disability was overall low in the multiple sclerosis patients (median Expanded Disability Status Scale 2, range 0–10); 71% were untreated. Baseline gadolinium-enhancing (odds ratio 3.16, P50.01) and spinal cord lesions (odds ratio 4.71, P50.01) were independently associated with secondary progressive multiple sclerosis at 15 years. Baseline gadolinium-enhancing (b = 1.32, P50.01) and spinal cord lesions (b = 1.53, P50.01) showed a consistent association with Expanded Disability Status Scale at 15 years. The authors conclude that early focal inflammatory disease activity and spinal cord lesions are predictors of very long-term disease outcomes in relapse-onset multiple sclerosis.	First, an inherent limitation to all longitudinal observational studies is dropout of subjects over time. Not all patients initially recruited into the study had follow-up MRI scans at 1 year and 3 years (90% had at least one follow-up MRI). Second, clinical status after 15 years was assessed in a significant number of patients by telephone interview because not all patients were able to return for a follow-up visit to be examined in person. Finally, although the mean duration of follow-up was over 15 years, the course of MS often unfolds over much longer and the number of people developing secondary progression and worsening disability in this cohort is likely to increase with time.
Chung KK, Altmann D, Barkhof F, et al. A 30-year clinical and magnetic resonance imaging observational study of multiple sclerosis and clinically isolated syndromes. Ann Neurol. 2020; 87(1):63-74.	multicenter prospective study	low level of evidence	To determine the long-term clinical outcomes in MS, and to identify early prognostic features of these outcomes.	One hundred thirty-two people presenting with a clinically isolated syndrome.	Patients were prospectively recruited between 1984 and 1987, and followed up clinically and radiologically 1, 5, 10, 14, 20, and now 30 years later. All available notes and magnetic resonance imaging scans were reviewed, and MS was defined according to the 2010 McDonald criteria.	Clinical outcome data were obtained in 120 participants at 30 years. Eighty were known to have developed MS by 30 years. Expanded Disability Status Scale (EDSS) scores were available in 107 participants, of whom 77 had MS; 32 (42%) remained fully ambulatory (EDSS scores ≤3.5), all of whom had relapsing–remitting MS (RRMS), 3 (4%) had RRMS and EDSS scores >3.5, 26 (34%) had secondary progressive MS (all had EDSS scores >3.5), and MS contributed to death in 16 (20%). Of those with MS, 11 received disease-modifying therapy. The strongest early predictors (within 5 years of presentation) of secondary progressive MS at 30 years were presence of baseline infratentorial lesions and deep white matter lesions at 1 year. The authors conclude that, thirty years after onset, in a largely untreated cohort, there was a divergence of MS outcomes; some people accrued substantial disability early on, whereas others ran a more favorable long-term course. These outcomes could, in part, be predicted by radiological findings from within 1 year of first presentation.	What is considered a nondisabling outcome may differ substantially depending on whose perspective it is from, and patient-reported outcomes have not been assessed. Second, at the inception of this cohort, MRI was a new technique, and image quality was not as good as is achievable now; given this, analyses of the earlier images will be less reliable than later ones. Third, symptoms attributable to spinal cord involvement were not systematically assessed early on in this cohort, and spinal cord imaging was not routinely obtained. Finally, cohort originated from one neurosciences center, and therefore there may be limitations in generalizability.

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Eden D, Gros C, Badji A, et al. Spatial distribution of multiple sclerosis lesions in the cervical spinal cord. Brain. 2019; 142(3):633-646.	multicenter prospective study	moderate level of evidence	To explore the spatial distribution of multiple sclerosis lesions in the cervical spinal cord, with respect to clinical status.	642 suspected or confirmed multiple sclerosis patients (31 clinically isolated syndrome, and 416 relapsing-remitting, 84 secondary progressive, and 73 primary progressive multiple sclerosis) from 13 clinical sites.	Cervical spine lesions were manually delineated on T2- and T2*-weighted axial and sagittal MRI scans acquired at 3 or 7 T. With an automatic publicly-available analysis pipeline we produced voxelwise lesion frequency maps to identify predilection sites in various patient groups characterized by clinical subtype, Expanded Disability Status Scale score and disease duration. We also measured absolute and normalized lesion volumes in several regions of interest using an atlas-based approach, and evaluated differences within and between groups.	The central cord area was more often affected by lesions in primary progressive than relapse-remitting patients ($P < 0.001$). Between white and grey matter, the absolute lesion volume in the white matter was greater than in the grey matter in all phenotypes ($P < 0.001$); however when normalizing by each region, normalized lesion volumes were comparable between white and grey matter in primary progressive patients. Lesions appearing in the lateral funiculi and central cord area were significantly correlated with Expanded Disability Status Scale score ($P < 0.001$). High lesion frequencies were observed in patients with a more aggressive disease course, rather than long disease duration. Lesions located in the lateral funiculi and central cord area of the cervical spine may influence clinical status in multiple sclerosis. This work shows the added value of cervical spine lesions, and provides an avenue for evaluating the distribution of spinal cord lesions in various patient groups.	Limitations in this study include variation in MRI data and image quality arising from non-uniform protocol across multiple acquisition sites, which may have led to differences in lesions identification across sites. Other issues include the occurrence of partial cervical spine coverage in some axial scans leading to reliance on sagittal scans, which were shown to be less superior for lesion detectability and is greater impacted by partial volume effect.
Eichinger P, Schon S, Pongratz V, et al. Accuracy of unenhanced MRI in the detection of new brain lesions in multiple sclerosis. Radiology. 2019; 291(2):429-435.	single center retrospective study	low level of evidence	To investigate whether the use of contrast material has an effect on the detection of new or enlarged MS lesions and, consequently, the assessment of interval progression.	507 follow-up MR images obtained in 359 patients with MS (mean age, 38.2 years +/- 6 10.3; 246 women, 113 men).	In this retrospective study based on a local prospective observational cohort, MR images were evaluated. With use of subtraction maps, nonenhanced images (double inversion recovery [DIR], fluid-attenuated inversion recovery [FLAIR]) and contrast material– enhanced (gadoterate meglumine, 0.1 mmol/kg) T1-weighted images were separately assessed for new or enlarged lesions in independent readings by two readers blinded to each other's findings and to clinical information. Primary outcome was the percentage of new or enlarged lesions detected only on contrast-enhanced T1-weighted images and the assessment of interval progression. Interval progression was defined as at least one new or unequivocally enlarged lesion on follow-up MR images.	Of 507 follow-up images, 264 showed interval progression, with a total of 1992 new or enlarged and 207 contrastenhancing lesions. Four of these lesions (on three MR images) were retrospectively detected on only the nonenhanced images, corresponding to 1.9% (four of 207) of the enhancing and 0.2% (four of 1992) of all new or enlarged lesions. Nine enhancing lesions were not detected on FLAIR-based subtraction maps (nine of 1442, 0.6%). In none of the 507 images did the contrast-enhanced sequences reveal interval progression that was missed in the readouts of the nonenhanced sequences, with use of either DIR- or FLAIR-based subtraction maps. Interrater agreement was high for all three measures, with intraclass correlation coefficients of 0.91 with FLAIR, 0.94 with DIR, and 0.99 with contrast-enhanced T1-weighted imaging.	Results were achieved with 3.0-T MRI with use of three-dimensional sequences and a single contrast agent (gadoterate dimeglumine). It is unclear whether they can be translated to 1.5-T MRI and/or two-dimensional sequences. Also, the DIR sequence used in the study is not commonly included in MS protocols. Finally, although nonenhanced sequences are sufficient for the reliable assessment of interval progression, gadolinium enhancement reveals additional temporal information regarding lesion age.
Granella F, Tsantes E, Graziuso S, et al. Spinal cord lesions are frequently asymtomatic in relapsing-remitting multiple sclerosis: A retrospective MRI survey. J Neurol. 2019; 266(12):3031-3037.	single center retrospective	low level of evidence	To investigate the frequency of asymptomatic SC combined unique activity (CUA, new/enlarging T2 or gadolinium-positive [Gd+] lesions) on MRI in a cohort of patients diagnosed with clinically isolated syndrome (CIS) or relapsing–remitting MS (RRMS).	340 scans with SC-CUA (as defined) in 230 predominantly female patients with mean ± SD age at MRI of 37.7 ± 10.61 years, 93.8% of scans were from patients who had a RR course and 60.6% were receiving DMT.	Retrospectively investigated all scans showing SC-CUA in patients with CIS or RRMS referred to a single Italian MS centre. Authors determined whether they were symptomatic and whether they had associated brain radiological activity.	In 340 SC-MRI scans with SC-CUA (230 patients), SC-CUA was asymptomatic in 31.2%; 12.1% of SC-CUA had neither clinical activity nor brain radiological activity (44.5% and 25.4%, respectively, considering only follow-up SC-CUA). At multivariate analysis asymptomatic SC-CUAs were associated with older age at onset (34.0 ± 10.37 vs 31.0 ± 9.99 years, p = 0.006), non-spinal onset (76.4 vs 47.4%, p < 0.001), lower EDSS score at MRI (1.8 ± 0.93 vs 2.4 ± 1.28, p = 0.001) and lower number of Gd+ SC lesions (0.1 ± 0.33 vs 0.3 ± 0.54, p = 0.04), compared to symptomatic SC CUAs. The authors conclude that a substantial proportion of our patients had SC-CUA without clinical symptoms and/or without concomitant brain MRI activity. In these patients, SC-CUA was the only sign of disease activity, suggesting that regular SC-MRI follow-up is required for reliable assessment of radiological activity and may improve the management of patients with MS.	The study has some limitations, such as its observational retrospective design, small sample size and the clinical practice setting. In addition, although all scans were performed on the same 3 T MR scanner, following a protocol in accordance with Italian Guidelines, technical limitations (e.g., partial volume effects, breathing and swallowing artefacts, cerebrospinal fluid and blood flow) make SC-MRI studies more challenging than brain MRI studies.
Hua LH, Donlon SL, Sobhanian MJ, et al. Thoracic spinal cord lesions are influenced by the degree of cervical spine involvement in multiple sclerosis. Spinal Cord. 2015;53(7):520-5.	single center cross sectional	moderate level of evidence	To determine whether cervical spinal cord lesions predict the presence of thoracic cord lesions in multiple sclerosis (MS) patients.	All MS patients at a single MS clinic with MRI studies of the brain, cervical and thoracic spine obtained during a single scanning session, were acquired during a 1-year period. A total of 687 patients were evaluated, and patients were excluded because of a diagnosis of other neurological disorders, not meeting the 2010 McDonald criteria for MS (n=222) or incomplete neuraxis imaging (n=339). The study cohort comprised 126 patients and primarily comprised women (74.6%), ages 14–71 years (median 39 years, IQR 32–49 years), who were white (61.9%) and with a relapsing remitting disease course (90.5%).	All patients who were seen in a single MS clinic during the calendar year with MRI studies of the brain, cervical and thoracic spine performed were consecutively included in the study. Scans were acquired at varying MRI facilities; however, the acquisition of the brain, cervical and thoracic spinal cord during the same scanning session was required. Clinical and radiological data were comprehensively reviewed to ensure that patients fulfilled the 2010 McDonald criteria for MS. Clinical, demographic and imaging covariates were used in a multivariate regression model to refine predictors of thoracic cord involvement.	There was an increase in the odds ratio (OR) of thoracic spine involvement when any cervical spine lesion was present (OR=6.08, 95% confidence interval (2.21-16.68), P<0.001). The multivariate logistic regression model demonstrated a substantial and significant increase in the odds of thoracic spine involvement when more than two cervical spine lesions were present, two lesions (OR 4.44, (0.91-21.60), P=0.06), three lesions (OR 19.76, (3.51-111.17), P=0.001), four or more lesions (OR 20.49, (1.97-213.23), P=0.012) and diffuse lesions (OR 71.94, (5.28-979.88), P=0.001), when adjusting for significant covariates including clinical symptoms, brain lesions, disease duration and treatment exposure. Thoracic spinal cord lesions appear to be predicated on the degree of cervical spine involvement in patients with MS, a risk that appears to be independent of brain findings or clinical features.	Limitations include the lack of systematically acquired data with uniform MRI protocols, the cross-sectional nature of the study design, the modest number of patients studied and susceptibility of the study cohort to ascertainment bias, as only patients with imaging studies of the brain, cervical and thoracic spinal cord obtained during a single imaging session were included.

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Kim SH, Hyun JW, Joung A, et al. Occurrence of Asymptomatic Acute Neuromyelitis Optica Spectrum Disorder-Typical Brain Lesions during an Attack of Optic Neuritis or Myelitis. PLoS ONE [Electronic Resource]. 2016;11(12):e0167783.	single center retrospective	low level of evidence	To investigate the frequency of asymptomatic acute brain MRI abnormalities accompanying optic neuritis (ON) or myelitis in neuromyelitis optica spectrum disorder (NMOSD) patients with aquaporin-4 antibodies (AQP4-Ab).	Of the 233 patients in the cohort, 11 patients were excluded due to the lack of brain MRI data. A total of 784 brain MRI scans were performed in 222 patients, of which 324 scans in 165 patients were performed during attacks of ON or myelitis	All MRI scans were performed using a 1.5-T or a 3.0-T machine. Brain scans included T2-weighted imaging, fluid-attenuated inversion recovery (FLAIR), gadolinium-enhanced T1-weighted imaging, and/or diffusion-weighted imaging. Brain MRI was performed within 2 weeks after an acute attack and prior to administration of steroids. Asymptomatic brain lesions were defined as the absence of clinically overt acute brain lesion-related symptoms. All evaluations were performed by two neurologists and one neuroradiologist, and consensus in the results was achieved.	The most common asymptomatic brain abnormalities included edematous corpus callosum lesions (n=17), followed by lesions on the internal capsule and/or cerebral peduncle lesions (n=9), periependymal cerebral lesions surrounding the lateral ventricles (n=3), and hypothalamic lesions (n=1). If asymptomatic NMOSD-typical brain abnormalities were considered as evidence for DIS, while also assuming that the AGP4-IgG status was unknown, the median time to diagnosis using the 2015 diagnosis criteria for NMOSD was shortened from 28 months to 6 months (p = 0.008). Asymptomatic acute NMOSD-typical brain lesions can be accompanied by an acute attack of ON or myelitis. Identifying these asymptomatic brain lesions may help facilitate earlier diagnosis of NMOSD.	Readers were not blinded or no comment was made about the blinding of the readers. Single reader or no inter-reader reliability was calculated.
Kuhle J, Disanto G, Dobson R, et al. Conversion from clinically isolated syndrome to multiple sclerosis: A large multicentre study. Multiple Sclerosis. 2015;21(8):1013-24.	multi-center retrospective	high level of evidence	To explore which clinical and biochemical variables predict conversion from clinically isolated syndrome (CIS) to clinically definite multiple sclerosis (CDMS) in a large international cohort.	33 centers provided serum samples from 1047 CIS cases (mean age 32; 68% female) with at least 2 years' follow-up.	Age, sex, clinical presentation, T2-hyperintense lesions, cerebrospinal fluid (CSF) oligoclonal bands (OCBs), CSF IgG index, CSF cell count, serum 25-hydroxyvitamin D3 (25-OH-D), cotinine and IgG titres against Epstein-Barr nuclear antigen 1 (EBNA-s) and cytomegalovirus were tested for association with risk of CDMS.	At median follow-up of 4.31 years, 623 CIS cases converted to CDMS. Predictors of conversion in multivariable analyses were OCB (HR = 2.18, 95% CI = 1.71-2.77, p < 0.001), number of T2 lesions (two to nine lesions vs 0/1 lesions: HR = 1.97, 95% CI = 1.52-2.55, p < 0.001; >9 lesions vs 0/1 lesions: HR = 2.74, 95% CI = 2.04-3.68, p < 0.001) and age at CIS (HR per year inversely increase = 0.98, 95% CI = 0.98-0.99, p < 0.001). Lower 25-OH-D levels were associated with CDMS in univariable analysis, but this was attenuated in the multivariable model. OCB positivity was associated with higher EBNA-1 IgG titres.The authors validated MRI lesion load, OCB and age at CIS as the strongest independent predictors of conversion to CDMS in this multicentre setting.	Patients with indeterminate results from the diagnostic test were excluded or no comment was made about how indeterminate results were handled. Readers were not blinded or no comment was made about the blinding of the readers. Single reader or no inter-reader reliability was calculated.
Narayana PA, Coronado I, Sujit S, et al. Deep learning for predicting enhancing lesions in multiple sclerosis from noncontrast MRI. Radiology. 2020; 294(2):398-404.	multicenter prospective study	moderate level of evidence	To evaluate whether deep learning can predict enhancing lesions on MRI scans obtained without the use of contrast material.	1008 participants (mean age, 37.7 years +/- 9.7; 730 women) with relapsing-remitting MS. Patients aged 18–60 years with an Expanded Disability Status Scale score of 0–5.5 were included. Sixty-eight centers participated in this study.	This study involved prospective analysis of existing MRI data. A convolutional neural network was used for classification of enhancing lesions on unenhanced MRI scans. This classification was performed for each slice, and the slice scores were combined by using a fully connected network to produce participant-wise predictions. The network input consisted of 1970 multiparametric MRI scans from 1008 patients recruited from 2005 to 2009. Enhanced lesions on postcontrast T1-weighted images served as the ground truth. The network performance was assessed by using fivefold cross-validation. Statistical analysis of the network performance included calculation of lesion detection rates and areas under the receiver operating characteristic curve (AUCs).	MRI scans were analyzed. At least one enhancing lesion was observed in 519 participants. The sensitivity and specificity averaged across the five test sets were 78% +/- 4.3 and 73% +/- 2.7, respectively, for slice-wise prediction. The corresponding participant-wise values were 72% +/- 9.0 and 70% +/- 6.3. The diagnostic performances (AUCs) were 0.82 +/- 0.02 and 0.75 +/- 0.03 for slice-wise and participant-wise enhancement prediction, respectively. The authors conclude that deep learning used with conventional MRI identified enhanced lesions in multiple sclerosis from images from unenhanced multiparametric MRI with moderate to high accuracy.	Although the study was based on a relatively large cohort, the number of patients with enhancing lesions is much smaller than the total number of patients with T2-hyperintense lesions. For generalizability of the model, it is essential that further testing be conducted on a heterogeneous data set. Another limitation of this study was that it was based on conventional MRI sequences.
Nazerian P, Vanni S, Tarocchi C, et al. Causes of diplopia in the emergency department: diagnostic accuracy of clinical assessment and of head computed tomography. Eur J Emerg Med. 2014;21(2):118-24.	single center prospective	moderate level of evidence	To evaluate the prevaluence of different diseases causing diplopia and the role of medical history, clinical examination, and unenhanced head computed tomography (UHCT) in the identification of secondary diplopia.	260 diplopic patients presenting to the ED were enrolled prospectively.	Cardiovascular risk factors and associated neurological signs and symptoms were reported. UHCT was performed in the ED.	Secondary diplopia was diagnosed in 93 of 260 (35.8%) diplopic patients. Among patients with secondary diplopia, the most frequent diagnoses were stroke (45.2%), multiple sclerosis (18.3%), brain tumors (11.8%), and cerebral aneurysms (7.5%). The prevalence of cardiovascular risk factors was similar in primary and secondary diplopia. Among the 118 (45.4%) patients without associated neurological signs or symptoms (isolated diplopia), secondary diplopia was diagnosed in 13 (11%); UHCT was negative in all 13 cases, with a derived null sensitivity. Eighty of 142 (56.3%) patients with associated signs or symptoms had secondary diplopia. The presence of signs or symptoms associated with diplopia showed a sensitivity of 87% [95% confidence interval (CI): 80-92%] and a specificity of 63% (95% CI: 59-66%) for the diagnosis of secondary diplopia. In this group, UHCT identified 30 of 80 (37.5%) cases, increasing the specificity to 98% (95% CI: 96-99%).	Readers were not blinded or no comment was made about the blinding of the readers. Single reader or no inter-reader reliability was calculated.

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Rudie JD, Mattay RR, Schindler M, et al. An initiative to reduce unnecessary gadolinium-based contrast in multiple sclerosis patients. J Am Coll Radiol. 2019; 16(9 Pt A):1158-1164.	single center prospective	low level of evidence	To implement a prospective quality improvement project whereby IV contrast would be reserved only for patients with evidence of new disease activity on noncontrast images.	Total number of subjects included in the study were 153. This was out of a possible 424 patients that received the MS protocol during that same time period, but did not participate in the study due to one of the exclusion criteria.	Authors leveraged an in-house computer-assisted-detection (CAD) software and 3-D laboratory radiology technologists to perform real-time preliminary assessments of the CAD-processed T2/FLAIR noncontrast images as a basis for deciding whether to inject contrast. Prior to implementation, authors held multidisciplinary meetings with neurology, neuroradiology and MR technologists, and distributed surveys to objectively assess opinions and obstacles to clinical implementation. They evaluated reduction in GBCA utilization and technologist performance relative to final neuroradiologist interpretations.	During a 2-month trial period, 153 patients were imaged under the new protocol. Technologists using the CAD software were able to identify patients with new or enlarging lesions on FLAIR images with 95% accuracy and 97% negative predictive value relative to final neuroradiologist interpretations, which allowed authors to avoid the use of contrast and additional imaging sequences in 87% of patients. The authors conclude that a multidisciplinary effort to implement a quality improvement project to limit contrast in MS patients receiving follow up MRIs allowed for improved safety and cost by targeting patients that would benefit from the use of intravenous contrast in real-time.	These results are still considered preliminary given the relatively small time period, thus continued careful evaluation of the advantages and disadvantages of this protocol on patient outcomes is warranted. A limitation of more widespread clinical implementation of the selective protocol is that the vast majority of radiology departments do not use CAD or AI systems for assistance in interpretation, which makes the task of comparing two 3D MRI timepoints much slower and challenging.
Sadigh G, Saindane AM, Waldman AD, et al. Comparison of unenhanced and gadolinium-enhanced imaging in multiple sclerosis: Is contrast needed for routine follow-up MRI? AJNR Am J Neuroradiol. 2019; 40(9):1476-1480.	single center retrospective	low level of evidence	To evaluate whether enhancing multiple sclerosis lesions on follow-up MR imaging can be detected by visual assessment of unenhanced double inversion recovery and FLAIR sequences.	172 adult patients (131 women and 41 men, with a median age of 42 years) with a known diagnosis of multiple sclerosis. These were consecutive patients older than 18 years of age with a clinical diagnosis of MS who underwent brain MR imaging using the MS protocol at the outpatient radiology clinic of the authors' institution between September 2016 and April 2018. Only patients with an established diagnosis of MS as determined by the medical record and documented by a neurologist were included.	A total of 252 consecutive MRIs were reviewed. The co-presence or absence of associated double inversion recovery and FLAIR signal abnormality within contrastenhancing lesions was recorded by 3 neuroradiologists. In a subset of patients with prior comparisons, the number of progressive lesions on each of the 3 sequences was assessed.	A total of 34 of 252 MRIs (13%) demonstrated 55 enhancing lesions, of which 52 (95%) had corresponding hyperintensity on double inversion recovery and FLAIR. All lesions were concordant between double inversion recovery and FLAIR, and the 3 enhancing lesions not visible on either sequence were small (<2 mm) and cortical/subcortical (n = 2) or periventricular (n = 1). A total of 17 (22%) of the 76 MRIs with a prior comparison had imaging evidence of disease progression: Ten (59%) of these showed new lesions on double inversion recovery or FLAIR only, 6 (35%) showed progression on all sequences, and 1 (6%) was detectable only on postcontrast T1, being located in a region of confluent double inversion recovery and FLAIR abnormality. The authors conclude that there was a high concordance between enhancing lesions and hyperintensity on either double inversion recovery or FLAIR. Serial follow-up using double inversion recovery or FLAIR alone may capture most imaging progression, but isolated enhancing lesions in confluent areas of white matter abnormality could present a pitfall for this approach.	Study is limited by retrospective methodology, small sample size, a short follow-up period, and a lower number of patients with available serial imaging. Authors included only patients followed on a single 3T scanner at their outpatient clinic, where most of the patients with MS are being scanned. This approach limited the number of prior comparisons they could include and also limits the generalizability of our results to other magnet strengths.
Solomon AJ, Bourdette DN, Cross AH, et al. The contemporary spectrum of multiple sclerosis misdiagnosis: A multicenter study. Neurology. 2016;87(13):1393-9.	multi-center cross sectional	moderate level of evidence	To characterize patients misdiagnosed with multiple sclerosis (MS).	Neurologists at 4 academic MS centers submitted data on 110 patients determined to have been misdiagnosed with MS. Ninety-three (85%) were women and 17 (15%) were men. Mean age was 49 +/- 11 years with a range from 21 to 77 years. Fifty-one patients (46%) were classified as “definite” and 59 (54%) as “probable” misdiagnoses.	Patients were identified by participating neurologists during clinical evaluations either prospectively during the 13 months of the study or shortly before study initiation. Patients were classified as having “definite misdiagnosis” when an alternative diagnosis was definitively made based on clinical, laboratory, and neuroimaging evaluation and “probable misdiagnosis” when an alternative diagnosis was suspected and diagnostic criteria for MS were not met.	Of 110 misdiagnosed patients, 51 (46%) were classified as "definite" and 59 (54%) "probable" misdiagnoses according to study definitions. Alternate diagnoses included migraine alone or in combination with other diagnoses 24 (22%), fibromyalgia 16 (15%), nonspecific or nonlocalizing neurologic symptoms with abnormal MRI 13 (12%), conversion or psychogenic disorders 12 (11%), and neuromyelitis optica spectrum disorder 7 (6%). Duration of misdiagnosis was 10 years or longer in 36 (33%) and an earlier opportunity to make a correct diagnosis was identified for 79 patients (72%). Seventy-seven (70%) received disease-modifying therapy and 34 (31%) experienced unnecessary morbidity because of misdiagnosis. Four (4%) participated in a research study of an MS therapy. Leading factors contributing to misdiagnosis were consideration of symptoms atypical for demyelinating disease, lack of corroborative objective evidence of a CNS lesion as satisfying criteria for MS attacks, and overreliance on MRI abnormalities in patients with nonspecific neurologic symptoms. Misdiagnosis of MS leads to unnecessary and potentially harmful risks to patients. Misinterpretation and misapplication of MS clinical and radiographic diagnostic criteria are important contemporary contributors to misdiagnosis.	Neurologists participating in the study may have been incorrect in their assessment of misdiagnosis in some cases. Given the lack of specific biomarkers for the disorders mistaken for MS identified in this study, it is possible that neurologists might disagree on their assessment of the correct clinical diagnosis in some cases. Selection and referral bias likely influenced patient characteristics.
Tintore M, Otero-Romero S, Rio J, et al. Contribution of the symptomatic lesion in establishing MS diagnosis and prognosis. Neurology. 2016;87(13):1368-74.	single center prospective	high level of evidence	To study the contribution of the symptomatic lesion in establishing multiple sclerosis (MS) diagnosis and prognosis.	The authors performed an observational study based on a prospective clinically isolated syndrome (CIS) cohort of 1,107 patients recruited for clinical and brain MRI follow-up from 1995 to 2014. Eligible patients (n = 954) were divided into 4 groups according to baseline MRI: patients with a normal MRI (n = 290); patients with a single asymptomatic lesion (n = 18); patients with a single cord/brainstem symptomatic lesion (n = 35); and patients with more than 1 lesion (n = 611).	For each group, the authors studied the risk of second attack, with 2005 McDonald MS and Expanded Disability Status Scale 3.0, using univariable and multivariable regression models adjusted by age, sex, oligoclonal bands, and disease-modifying treatments. The authors tested the diagnostic performance of a modified dissemination in space (DIS) criterion that includes symptomatic lesions in the total count and compared it to the DIS criteria (at least 1 asymptomatic lesion in at least 2 of the 4 MS characteristic MS locations) for all patients and for the subgroup of patients with brainstem or spinal cord topography.	Patients with a cord/brainstem single symptomatic lesion have a higher risk of second attack and disability accumulation than patients with 0 lesions but have a similar risk compared to patients with 1 asymptomatic lesion. Diagnostic properties are reasonably maintained when the symptomatic lesion qualifies for DIS. Despite the recommendations of the 2010 McDonald criteria, symptomatic lesions should be taken into account when considering the diagnosis and prognosis of patients with CIS.	Readers were not blinded or no comment was made about the blinding of the readers. Single reader or no inter-reader reliability was calculated.

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Treaba CA, Balasa R, Podeanu DM, et al. Cerebral lesions of multiple sclerosis: is gadolinium always irreplaceable in assessing lesion activity? Diagn Interv Radiol. 2014;20(2):178-84.	single center retrospective	low level of evidence	To identify imaging characteristics on conventional magnetic resonance imaging that could predict multiple sclerosis (MS) brain lesion activity without contrast media administration.	Magnetic resonance data sets of forty-two patients (10 males and 32 females; aged 19 to 54 years, mean age, 33 years; mean disease duration of 3.4 years, range, 1–8 years) with relapsing-remitting MS who presented symptoms or signs suggestive of new disease activity were retrospectively reviewed.	The authors classified the MS lesions into three types according to different patterns present on T2-weighted images and evaluated their relationship with the contrast uptake. Evolving aspects of each type of lesion were observed in 18 patients during a follow-up period ranging from nine to 36 months.	On T2-weighted images, only the pattern consisting of a thin border of decreased intensity compared with the lesion's center and perifocal edema (Type II) reached diagnostic accuracy in terms of its relationship with gadolinium enhancement (P = 0.006). The sensitivity was 0.461, and the specificity was 0.698. In contrast, enhancement was not significantly related to the pattern consisting of a lesion center that was homogeneously brighter than its periphery (Type I) or less-hyperintense T2 focal lesions with either homogeneous or inhomogeneous center (Type III) (P > 0.05 for both). The assessment of MS lesion activity should include a careful evaluation of T2-weighted images in addition to contrast enhancement assessment. The presence of an accompanying peripheral thin rim of hypointensity on T2-weighted images related best with contrast enhancement and subsequent lesion activity and may represent an additional pattern for disease activity assessment when gadolinium examination is contraindicated or influenced by prior therapy.	The retrospective design of this study precluded the standardization of techniques and the similarity of the follow-up intervals. In addition, the fact that the examinations were performed on different units (1 and 1.5 T) with different parameters of pulse sequences decreased the uniformity of the study. Second, infratentorial lesions were neither counted nor appreciated in this study. Third, contrast enhancement was used as the standard for determining the active lesions even if the use of this single criterion might have been insufficient for lesion activity detection.
Uher T, Vaneckova M, Sobisek L, et al. Combining clinical and magnetic resonance imaging markers enhances prediction of 12-year disability in multiple sclerosis. Multiple Sclerosis. 2017;23(1):51-61.	multi-center Observational cohort within a previously-published double-blind RCT.	high level of evidence	To examine the accuracy of the early prediction of 12-year disability outcomes using clinical and magnetic resonance imaging (MRI) parameters.	A total of 177 patients (mean age of 30.6 years; 78% female) from the original Avonex-Steroids-Azathioprine study were included.	Participants underwent 3-month clinical follow-ups. Cox models were used to model the associations between clinical and MRI markers at baseline or after 12months with sustained disability progression (SDP) over the 12-year observation period.	At baseline, T2 lesion number, T1 and T2 lesion volumes, corpus callosum (CC), and thalamic fraction were the best predictors of SDP (hazard ratio (HR)=1.7-4.6; p0.001-0.012). At 12months, Expanded Disability Status Scale (EDSS) and its change, number of new or enlarging T2 lesions, and CC volume % change were the best predictors of SDP over the follow-up (HR=1.7-3.5; p 0.001-0.017). A composite score was generated from a subset of the best predictors of SDP. Scores of 4 had greater specificity (90%-100%) and were associated with greater cumulative risk of SDP (HR=3.2-21.6; p<0.001) compared to the individual predictors. The combination of established MRI and clinical indices with MRI volumetric predictors improves the prediction of SDP over long-term follow-up and may provide valuable information for therapeutic decisions.	All patients enrolled in the ASA study were treated with IFNβ-1a during the first 12 months, had $\geq$ 2 T2 lesions, $\geq$ 2 oligoclonal bands in the cerebrospinal fluid, and high relapse activity preceding study baseline. Hence, the anti-inflammatory effect of DMTs and inclusion criteria limits the generalizability of our findings to the whole population of RRMS patients.
Zecca C, Disanto G, Sormani MP, et al. Relevance of asymptomatic spinal MRI lesions in patients with multiple sclerosis. Multiple Sclerosis. 2016;22(6):782-91.	single center retrospective cohort	low level of evidence	To assess the prognostic value of asymptomatic spinal cord lesions (a-SL) in predicting MS course.	Relapsing-remitting MS patients who received serial MRI (brain and spinal) at baseline (t1) and within 12 to 36 months (t2) during clinical stability, and had a follow-up (t2-t3) $\geq$ 24 months were included. 103 total patients (65 females, median age 43 years) were included. All patients meeting the following criteria were excluded: being affected with neurological diseases other than MS; having changed immune-modulating therapy between t1 and t2; incomplete or missing MRI scans according to the inclusion criteria.	All patients included in the study received a standardized protocol of clinical follow-up that includes a complete neurological examination with EDSS assessment every six months, and a neurological visit including an EDSS assessment within two weeks in case of any neurological worsening. All S- and B-MRI included in the analysis were performed with a standardized protocol and using a 1.5T scanner. Relapses and disability progression were evaluated between t2 and t3. An interclass correlation was calculated as measure of agreement (reliability) between the two readers both for spinal cord and brain lesions.	After a median t1-t2 interval of 17 (IQR 13-26) months, 25.2% and 43.7% patients had 1 new a-SL (a-SL+) and asymptomatic brain lesions (a-BL+), respectively. Relapse risk between t2 and t3 (median interval: 42 (IQR 32-57.5) months) was significantly increased in a-SL+ and/or a-BL+ vs a-BL- and a-SL- (HR = 2.31, 95% CI = 1.13-4.72, p = 0.02). No differences in the risk of disability progression were found in a-SL+ and/or a-BL+ vs a-SL- and a-BL-. a-SL occur in one-quarter of clinically stable RRMS, and combined with a-BL contribute significantly in predicting future disease course.	Retrospective design is flawed by potential selection bias. In particular, as compared to those patients who were excluded from the study, the included ones had higher lesion loads, in particular within the spinal cord.

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