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From routine to selective: how updated MRI guidelines reshape gadolinium use in Germany

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Abstract

Magnetic resonance imaging (MRI) is a critical diagnostic tool and monitoring modality for multiple sclerosis (MS), frequently employing gadolinium-based contrast agents (Gd). However, concerns regarding the accumulation of Gd have prompted international guidelines (MAGNIMS-CMSC-NAIMS, 2021) to advocate for the limitation of Gd utilization. Consequently, we assessed of the impact of the 2021 guidelines on the use of Gd in MRI in MS patients in Germany by conducting a retrospective analysis of MRI data from 12,833 MS patients in the German MS Register (2019–2024). Generalized additive models were employed to analyze Gd use trends over time by MRI type (cranial, spinal, combined). From 2020 to 2024, a significant decline in Gd use was observed, with percentages dropping from 74.2 to 41.2% in cranial MRI, from 78.2 to 39.2% in spinal MRI and from 81.8 to 59.0% in combined MRI ($p < 0.001$). The most substantial decline occurred within the initial five years of MS. Gd use in MS MRI scans has significantly decreased in line with the updated guidelines. Nevertheless, its persistent utilization in over one-third of cases necessitates further examination.

Keywords Relapsing multiple sclerosis, Magnetic resonance imaging, Gadolinium-based contrast

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Magnetic resonance imaging (MRI) remains central to diagnosing and monitoring multiple sclerosis (MS). Traditionally, gadolinium-based contrast agents (Gd) have been widely used to detect active inflammatory lesions, aiding in treatment decisions [1]. However, concerns about Gd accumulation and potential side effects [2] have prompted revisions to international guidelines [3].

In 2021, the MAGNIMS-CMSC-NAIMS consensus recommendations updated the guidelines on Gd use, advising it only in cases where clear additional benefit is expected, such as when confirming an MS diagnosis or if no suitable reference MRI is available [4]. This change reflects the need to balance diagnostic accuracy with patient safety, emphasizing a more cautious approach to Gd use in MS management. However, there is currently limited understanding of how effectively these updated guidelines have been implemented in clinical practice.

Our retrospective study utilized MRI data from 12,833 MS patients in the German MS Register (GMSR), encompassing 23,934 MRI scans. We employed generalized additive models to evaluate Gd use trends by MRI type (cranial, spinal, combined). The findings revealed a marked reduction in Gd administration: cranial MRI (74.2% in 2020 to 41.2% in 2024, $p < 0.001$), spinal MRI (78.2–39.2%, $p < 0.001$) and combined MRI (81.8–59.0%, $p < 0.001$). Notably, the most significant decline was observed within the first five years of disease onset, suggesting an increasing tendency to restrict Gd use to select clinical scenarios rather than routine follow-up scans (Fig. 1).

These results underscore the rapid implementation of guideline-driven changes in clinical practice. The observed decrease aligns with an emerging consensus to limit unnecessary Gd exposure while maintaining diagnostic accuracy [4]. However, despite this reduction, Gd was still used in over one-third of MRI scans in early 2024. This raises important questions regarding the ongoing necessity of contrast-enhanced imaging in certain cases. Possible explanations include the need to confirm active disease in complex cases, such as progressive MS or inconclusive imaging findings [5]. However, the assumption that the administration of Gd-based agents indicates an acute clinical event has recently been increasingly questioned, as many MS-specific disease progressions are not captured by conventional imaging methods [6].

Emerging evidence suggests that alternative MRI markers, such as the central vein sign and paramagnetic rim lesions, may provide comparable or superior insights into MS activity and progression [7]. Integrating these biomarkers into routine imaging protocols may further reduce reliance on Gd while preserving diagnostic accuracy [7]. However, prioritizing imaging sequences for these markers in daily routine seems to be a current challenge.

The variability in Gd-based contrast use among MS centers, influenced by institutional preferences or patient factors (e.g., high numbers of newly diagnosed cases), reflects inconsistencies with guidelines. A European survey supports this, showing routine Gd use during follow-ups in over 30% of institutions [8]. A more granular analysis of the clinical indications prompting contrast administration could help clarify whether deviations from guidelines are justified. It is crucial to determine whether continued Gd use primarily occurs in newly diagnosed patients requiring baseline scans, or in patients with ambiguous imaging findings like radiologically isolated syndrome findings requiring enhanced visualization [9]. Moreover, the discrepancy in Gd use may also reflect differing perceptions among clinicians regarding its necessity for evaluating disease progression or distinguishing pseudo-progression from true relapse. Understanding these patterns may inform future refinements to guideline recommendations and standardized imaging protocols across healthcare settings.

Additionally, patient perspectives on Gd administration warrant consideration. MS patients might express concerns about repeated contrast exposure, particularly in light of reports of Gd retention in brain tissue [3]. Enhanced patient education regarding the rationale behind reducing Gd use may facilitate shared decision-making and improve adherence to updated imaging protocols.

While our data do not fully capture the broader impact of this shift in clinical practice, future research should also clarify the specific consequences of decreasing Gd use in case of MS. Understanding whether reduced Gd administration compromises the diagnostic accuracy especially in terms of radiologically isolated syndrome [9], the detection of subclinical disease activity or influences therapeutic strategies is essential to maintaining disease monitoring and optimizing patient outcomes. Interestingly, emerging fluid biomarkers such as neurofilament light chain in sera, which serves as a marker of acute MS-related inflammation in the brain and spinal cord, could further refine the selective use of Gd by providing additional insights into disease activity and progression [10]. To further elucidate the clinical implications of the guideline adoption, future investigations should assess the following aspects: (1) the proportion of patients whose diagnoses are revised (e.g. tumour, neurosarcoidosis, vasculitis) following subsequent imaging with Gd administration; (2) the frequency of misdiagnoses or diagnostic delays attributable to the reduced use of Gd; and (3) the impact of the guidelines on therapeutic outcomes, including changes in disease activity, disability progression

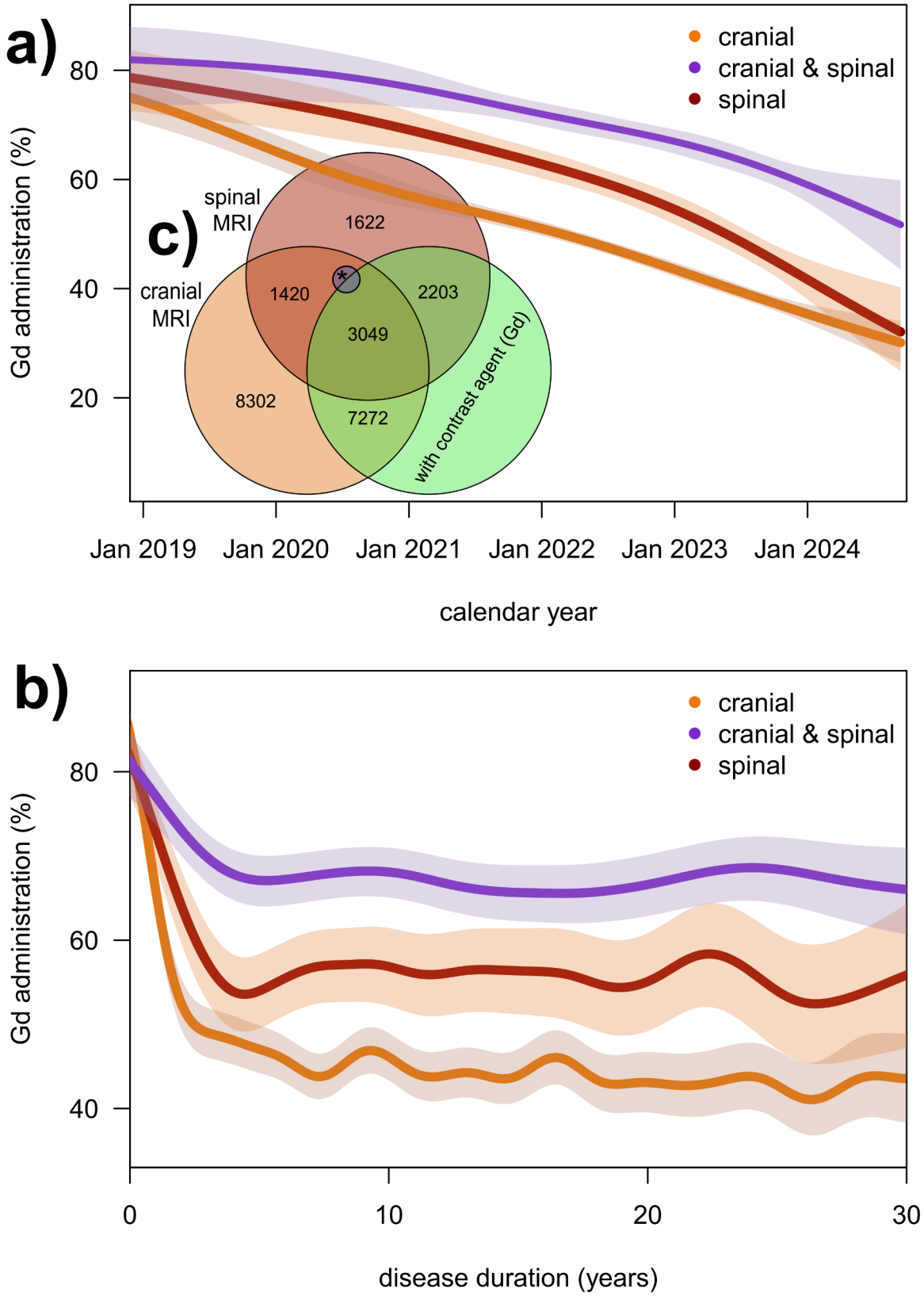

Fig. 1 (See legend on next page.)

(See figure on previous page.)

Fig. 1 Contrast agent use in MRI: Analysis by MRI type, location, year, and disease duration since 2019. **(a)** Frequency of Gd administration in MRI examinations by type/location of examination and calendar year. The shaded areas represent the associated 95% confidence intervals. **(b)** Frequency of contrast agent administration in MRI examinations broken down by type/location of examination and duration of disease. The shaded areas represent the corresponding 95% confidence intervals. **(c)** Venn diagram of MRI examinations since January 1, 2019 by type: cranial vs. spinal separated by with vs. without contrast agent administration. *There are 61 MRI examinations in which both a cranial and a spinal MRI were performed, but Gd was only used in one type of MRI (Gd may have been given between both MRI). These rare cases were excluded from further analyses. Gd– Gadolinium-based contrast agents; MRI– Magnetic Resonance Imaging

and relapse rates. Such analyses will yield critical insights into the potential consequences of the revised guidelines on patient outcomes and treatment strategies.

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Authors' contributions
Marc Pawlitzki: Conceptualization; Methodology; Writing– original draft. Alexander Stahmann: Conceptualization; Methodology; Writing– review & editing. Niklas Frahm: Writing– review & editing. Mathia Kirstein: Writing– review & editing. Melanie Peters: Writing– review & editing. Peter Flachenecker: Writing– review & editing. Tim Friede: Writing– review & editing. Kerstin Hellwig: Writing– review & editing. Dagmar Krefting: Writing– review & editing. Michaela Mai: Writing– review & editing. Clemens Warnke: Writing– review & editing. Uwe K. Zettl: Writing– review & editing. David Ellenberger: Conceptualization; Methodology; Analysis; Supervision; Writing– review & editing.

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Data availability
Anonymized data will be made available on request for any qualified investigator under the terms of the registry's usage and access guidelines and subject to the informed consent of the patients.

Declarations

Ethics approval and consent to participate
The registration of the GMSR took place at the German Register for Clinical Trials [Deutsches Register Klinischer Studien (DRKS); No. DRKS00011257]. The initial ethics vote was approved by University of Würzburg's institutional review board (Permit No. 142/12). All participants provided written consent for the utilization of their anonymized data for research purposes.

Consent for publication
Not applicable.

Competing interests
Marc Pawlitzki received honoraria for lecturing and travel expenses for attending meetings from Alexion, ArgenX, Bayer Health Care, Biogen, Hexal, Merck Serono, Novartis, Roche, Sanofi-Aventis, Takeda and Teva. His research is funded by ArgenX, Biogen, Demecan, Hexal, Horizon Merck Serono, Novartis, Roche, Viatris, Takeda and Teva. Niklas Frahm is an employee of the GMSR. Moreover, he is an employee of Rostock's University Medical Center and received travel funds for research meetings from Novartis. None resulted in a conflict of interest. Melanie Peters, David Ellenberger and Mathia Kirstein had no personal financial interests to disclose other than being employees of the GMSR. Alexander Stahmann has no personal financial interests to disclose, other than being the leader of the GMSR, which receives (project) funding from a range of public and corporate sponsors, recently including G-BA, The German Retirement Insurance, The German MS Trust, German MS Society, Bristol-Myers Squibb, Merck, Novartis, Roche and TG/Neuraxpharm, all outside this study. Peter Flachenecker has received speaker's fees and honoraria for advisory boards from Almirall, Bayer, Biogen Idec, BMS-Celgene, Coloplast, Genzyme, GW Pharma, Hexal, Janssen-Cilag, Novartis, Merck, Roche, Sanofi, Stadapharm and Teva. None resulted in a conflict of interest. Tim Friede has received personal fees for statistical consultancies (including data monitoring committees) from Actimed, Aslan, Bayer, BiosenseWebster, BMS, CSL Behring, Daiichi Sankyo, Enanta, Fresenius Kabi, Galapagos, IQVIA, Immunic, KyowaKirin, LivaNova, Minoryx, Novartis, PINK! gegen Brustkrebs, PPD, RECARDIO, Recordati, Relaxera, Roche, Servier, Viatris, Vifor and VICO Therapeutics. Kerstin Hellwig has received speaking fees and/or institutional grant support from Bayer, Biogen, BMS, Merck Serono, Novartis, Roche, Sanofi-Genzyme and Teva. None resulted in a conflict of interest. Dagmar Krefting has nothing to disclose. Michaela Mai is an employee of the German MS Society, federal association, which receives funding from a range of public and corporate sponsors, recently including BMG, G-BA, The German MS Trust, Biogen, BMS, Merck Serono, Novartis, Roche, Sanofi and Viatris. None resulted in a conflict of interest. Clemens Warnke has received institutional support from Novartis, Alexion, Sanofi Genzyme, Biogen, Merck and Roche. None resulted in a conflict of interest. Uwe K. Zettl has received speaking fees, travel support and /or financial support for research activities from Alexion, Almirall, Bayer, Biogen, Bristol Myers Squibb, Janssen, Merck Serono, Novartis, Octapharma, Roche, Sanofi Genzyme, Teva as well as EU, BMBF, BMWi and DFG. None resulted in a conflict of interest.

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