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Tshea Dowers, Ali Helmi, Achire N. Mbanwi and Paula Alcaide-Leon

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ORIGINAL RESEARCH

Comparative Evaluation of Lower Gadolinium Doses for MR Imaging of Meningiomas: How Low Can We Go?

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ABSTRACT

BACKGROUND AND PURPOSE: Gadolinium-based contrast agents are widely used for meningioma imaging; however, concerns exist regarding their side effects, cost, and environmental impact. At the standard gadolinium dose, most meningiomas show avid contrast enhancement suggesting that administering a smaller dose may be feasible. The purpose of this study was to evaluate the impact of a lower gadolinium dose on the differentiation between meningiomas and adjacent intracranial tissues.

MATERIALS AND METHODS: 108 patients with presumed or confirmed meningiomas who underwent brain MRI at multiple doses of gadolinium were included in the study. The patients' MRIs were categorized into three groups based on the gadolinium dose administered: Micro (approximately 25% of the standard dose), Low (approximately 62% of the standard dose) and Standard dose. Multi-reader qualitative visual assessment and quantitative relative signal differences calculations were performed to evaluate tumor differentiation from the cortex and from the dural venous sinus. The relative signal differences for each dose were analyzed using ANOVA for quantitative assessment and NcNemar for qualitative assessment. Additionally, non-inferiority testing was used to compare the Low and Micro doses to the Standard dose.

RESULTS: Decreasing the gadolinium dose to a Low dose or a Micro dose resulted in a statistically significant decrease in signal difference between the tumor and the adjacent brain tissues ($p<0.02$). However, on visual assessment, the Low dose was non-inferior to the Standard dose. The proportion of cases with suboptimal differentiation was significantly higher for the Micro dose than for the Standard dose, both for the differentiation between the tumor and the cortex ($p=0.041$) and the differentiation between tumor and sinus ($p<0.001$).

CONCLUSIONS: Reducing the gadolinium dose to 62% of the standard level still allows for sufficient visual delineation of meningiomas from surrounding tissues. However, further reduction to 25% substantially compromises the ability to distinguish the tumor from adjacent structures and is, therefore, not advisable.

ABBREVIATIONS: GBCAs = Gadolinium-based contrast agents; SSS =Superior Sagittal Sinus.

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From the Department of Department of Medical Imaging, University of Toronto, Toronto, Ontario, Canada (T.D.; A.H.; A.N.M.; P.A-L.)

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Please address correspondence to Paula Alcaide-Leon Department of Medical Imaging, University of Toronto, Toronto, Ontario, Canada Paula.alcaideleon@uhn.ca.

SUMMARY SECTION

PREVIOUS LITERATURE: Several studies have looked at the effect of reducing the dose of gadolinium administered for brain tumor imaging. These studies found a directly proportional relationship between tumor enhancement and increasing doses of gadopenetate dimeglumine. Similarly, other studies have examined the effect of reducing the dose of a more highly concentrated gadolinium agent, gadobenate dimeglumine, when imaging various intracranial tumors and found that a reduced half dose of 0.05 mmol/kg is non-inferior to a full 0.1 mmol/kg, but at higher doses there was improved lesion-to-brain ratio and contrast-to-noise ratio.

KEY FINDINGS: Reducing gadolinium doses for meningioma follow-up MRIs to a Low dose (62% of standard) or Micro dose (25% of standard) resulted in statistically significant decreased signal difference between the tumor and adjacent brain, however, the Low dose still allowed for sufficient visual delineation of meningiomas from the surrounding brain.

KNOWLEDGE ADVANCEMENT: Meningiomas often require long-term imaging follow-up, leading to potential adverse effects from gadolinium-based contrast agents, increased costs, and environmental concerns. Our study findings can empower stakeholders to make informed decisions about reduced dose protocols, prioritizing patient well-being and optimizing healthcare resource allocation.

INTRODUCTION

Gadolinium-based contrast agents (GBCAs) are commonly used for MR imaging of meningiomas to detect and characterize these tumors, including small recurrent and residual tumors following surgical resection. A dose of 0.1 mg/kg is currently accepted for effective and safe imaging of meningiomas. However, at this dose, most meningiomas exhibit significant contrast enhancement, suggesting the feasibility of using a smaller dose of gadolinium to delineate the tumor. While some studies have explored the utility of using higher doses of gadolinium for imaging intracranial tumors [1,2], very few have investigated the use of doses lower than 0.1 mg/kg. Specifically, the use of lower gadolinium doses in tumors with avid contrast uptake, such as meningiomas, remains poorly established.

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Reducing the dose of gadolinium in meningioma imaging offers several advantages. Recent studies have highlighted the potential for gadolinium deposition in the globus pallidus and the dentate nuclei with repeated administration of Gadolinium-based contrast agents (GBCAs), raising safety concerns about their use [3]. Furthermore, although rare, cases of nephrogenic systemic fibrosis have been documented in patients with impaired kidney function receiving GBCAs [4] further emphasizing the importance of minimizing gadolinium dose. Thus, administering the lowest possible dose of gadolinium possible is crucial for minimizing the risk of these side effects particularly in this population who often undergo numerous follow-up MR examinations. Additionally, gadolinium contributes significantly to the cost of an MRI and reducing its dose would also result in substantial cost savings. Emerging evidence has shown that a significant amount of GBCAs are being released into the environment mainly via wastewater and because of their high stability, they are often not removed by wastewater treatment plants [5, 6]. The effects that this gadolinium waste poses to humans and the environment are relatively unknown but highlight the importance of reducing the amount of gadolinium used by hospital systems.

While many studies advocate for using non-contrast MRI for follow-up imaging of meningiomas, this approach is better suited for non-operated meningiomas particularly in certain locations, such as the convexity [7, 8]. In cases of small residual or recurrent meningiomas, contrast is usually needed for assessment. Additionally, information about prior surgery may not be readily available, necessitating a universal follow-up protocol that could also characterize small residual and recurrent tumors. Moreover, as meningiomas typically originate from the arachnoid cap cells along the intradural venous sinuses they frequently invade the walls of the sinuses, causing surgical and prognostic challenges [9]. Including gadolinium in the imaging protocol allows for assessment of adjacent dural venous sinus invasion, optimizing preoperative evaluation and surgical planning.

We aimed to explore the administration of a lower dose of gadolinium, rather than eliminating contrast altogether. This approach would help mitigate the side effects and costs associated with a full dose of gadolinium, while allowing assessment in challenging cases of small residual or recurrent tumors. The purpose of this study was to evaluate the impact of a lower gadolinium dose on the differentiation between meningiomas and adjacent intracranial tissues and assessment of tumor invasion into the adjacent dural venous sinus. We hypothesize that a lower gadolinium dose could yield comparable imaging outcomes to the standard dose. This article follows the STROBE reporting guidelines.

MATERIALS AND METHODS

Subjects

This single-institution retrospective cohort study was approved by our institutional Research Ethics Board and patient consent was waived.

As part of a quality improvement project to reduce gadolinium contrast expense, our institution initially observed that reducing the dose of gadovist administered in follow-up MRIs of meningiomas from the standard dose (0.1 mg/kg) to a fixed dose of 5 mg, regardless of weight, did not negatively impact our ability to characterize these tumors. Based on this experience, our institution further decreased the gadolinium dose used in these studies to 2 mg, irrespective of weight. As our institutional approach to image meningiomas has changed over the years, it resulted in a population of patients who have undergone brain MRI at multiple doses, allowing us to assess the efficacy of each dose. To identify the patients who had been imaged with multiple doses, we retrieved all brain MRIs with our institutional "Meningioma follow-up protocol" performed between January 2021 and May 2022 from our institution's PACS system, as this was the period where the lower doses were tested. Predefined inclusion criteria encompassed adults with presumed or confirmed intracranial meningiomas who had undergone a brain MRI at our institution with at least 2 different doses of gadolinium. Exclusion criteria consisted of uncertain diagnosis of meningioma or surgically resected meningiomas with no residual. For subjects who received the lower doses of 2 mg or 5 mg of gadolinium, the actual dose administered based on weight was calculated using biodata recorded in the radiology information system. The following dose level ranges were defined according to the distribution terciles: Micro (0.01 – 0.039 mg/kg), approximately 25% of the standard dose; Low (0.04 - 0.0849 mg/kg), approximately 62% of the standard dose and Standard (0.085 - 0.15 mg/kg). Each subject's MRIs were then categorized into the respective groups based on the administered dose.

MRI Protocol

Patients were scanned on 1.5T and 3T Siemens/GE scanners. Each MR study included an enhanced 3D-T1 MPRAGE or 3D-FSPGR sequence (1 mm slice thickness, no gap between slices).

Qualitative Assessment

One radiologist blinded to dosage with 3 years of experience reading brain MRIs rated the differentiation of the meningioma from the adjacent cortex and the dural venous sinuses for each of the doses on 3D post-contrast T1-weighted images. Although most meningiomas were not in contact with the venous sinuses, we compared the signal in the tumor with that in the superior sagittal sinus (SSS) to determine if it would be possible to detect venosus sinus invasion. The differentiation between the meningioma and the adjacent cortex and between the meningioma and the superior sagittal sinus was rated according to a 3-point scale: Optimal (adequate differentiation), acceptable (not optimal but it is still possible to differentiate between the tissues) and suboptimal (the tissues cannot be properly differentiated). When multiple meningiomas were present, one tumor was chosen at random for analysis and assessed consistently by all readers and for all doses. To estimate the interobserver agreement, a second reader with 3 years of experience rated a subset of 174 studies (70%). In cases

where there was a disagreement amongst readers, an arbitration read was performed by a more experienced radiologist (13 years of experience) and documented as final.

Quantitative Analysis

Quantitative analysis of signal intensity was performed on post-contrast T1-weighted images using an operator-defined ROI technique drawn over the tumor, adjacent brain cortex and SSS. The circular ROI tool was used, ensuring a minimum area of 0.02 cm^2 for cortex measurements and 0.01 cm^2 for the SSS. Signal intensity of the tumor was obtained over a large ROI encompassing most of the tumor and the obtained values were recorded. The relative signal difference between the tumor and the cortex was calculated using the following formula: $|S_{Tum}-S_{Cor}|/S_{Cor,}$ where S_{Tum} is the signal of the tumor; and S_{Cor} is the signal of the cortex. The relative Signal difference between the tumor and the superior sagittal sinus was calculated using the following formula: $|S_{Tum}-S_{SSS}|/S_{Cor,}$ where S_{SSS} is the signal of the superior sagittal sinus. To calculate the interobserver agreement, a second reader also extracted the ROI measurements in a subset of 174 of the studies. In the cases with double readings, the average of both values was used for analysis.

Statistical Analysis

Quantitative analysis: Not all patients underwent MRI scans with all three gadolinium doses, therefore mixed-effects analysis was selected for its ability to handle missing values, in contrast to repeated measures ANOVA. Post-hoc Tukey's method was used to create confidence intervals for all pairwise differences between those categories while controlling the family error rate. Inter-reader agreement was assessed using the interclass correlation coefficient.

Qualitative analysis: The proportion of suboptimal cases for each dose was compared for each pair of doses using the McNemar test. We compared only pairs of doses administered to the same patients (paired data). When differences in the outcomes were not significant, non-inferiority testing using a 0.1 non-inferiority margin with 90% power was performed. Inter-reader agreement was assessed using the kappa coefficient.

Statistical analysis was performed using GraphPad Prism version 9.2.0 for Windows, GraphPad Software, Boston, Massachusetts USA, www.graphpad.com, with a significance level of 0.05 for all statistical tests.

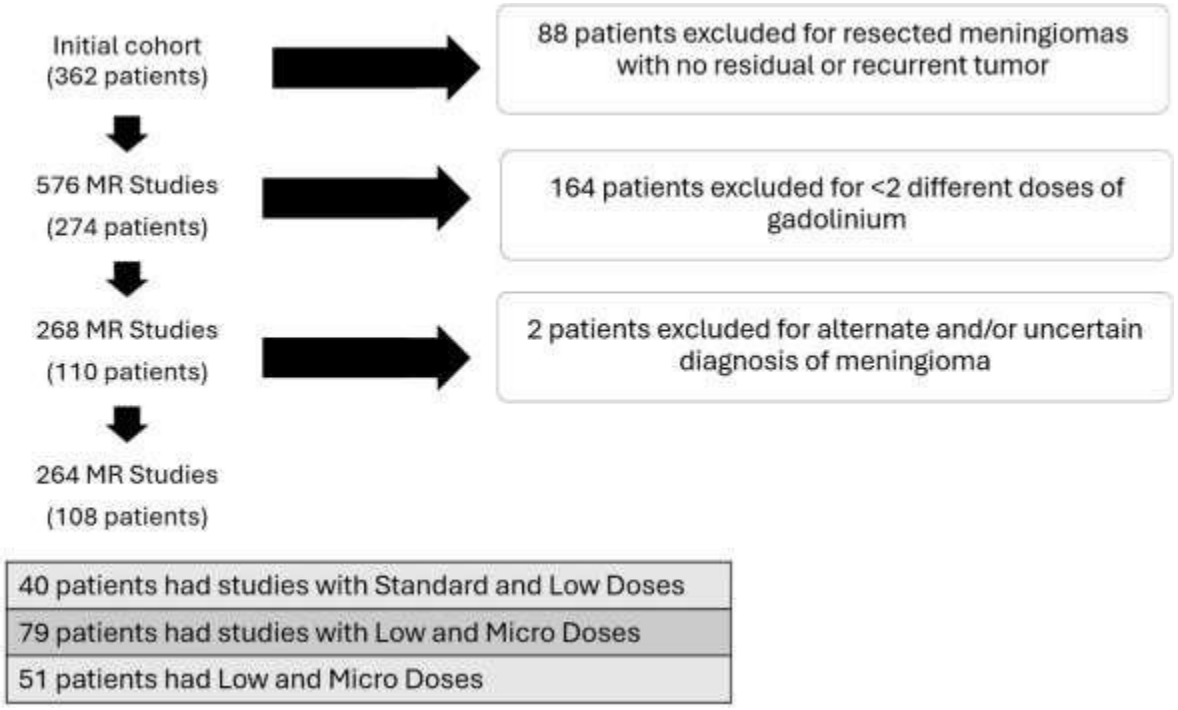

FIG 1. Flow diagram showing the steps in patient selection.

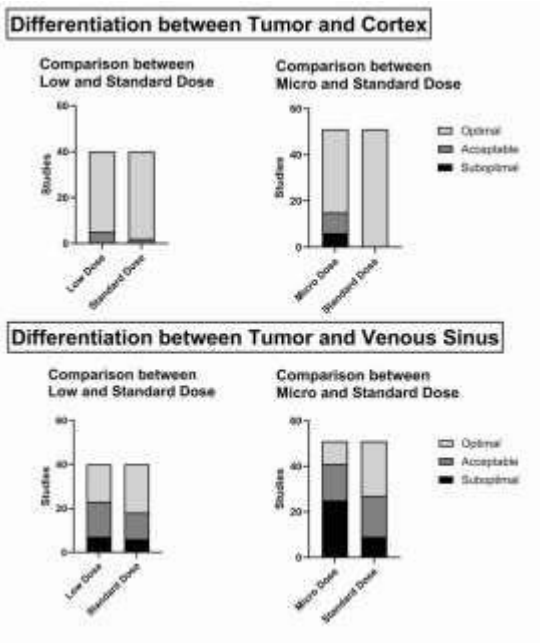

FIG 2. Ratings of different doses for the differentiation between tumor and cortex and tumor and venous sinus.

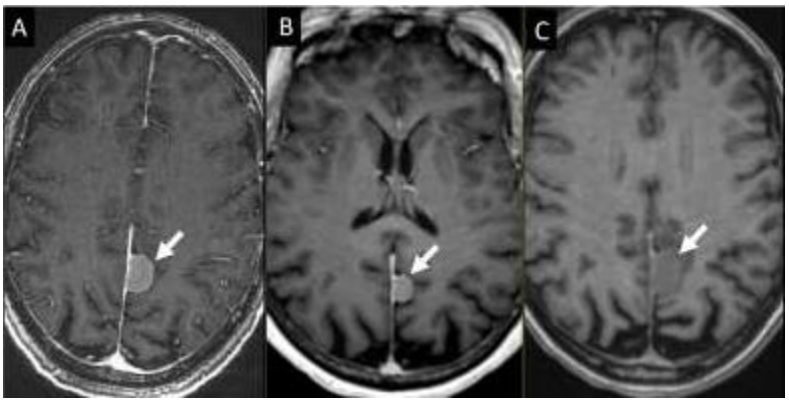

FIG 3. Axial T1-Weighted sequences from a patient with a left parafalcine meningioma (white arrow) at multiple time points using different contrast doses. The Standard (A) and Low (B) doses yield optimal contrast enhancement allowing for adequate delineation of the tumor. The Micro dose (C) results in insufficient contrast enhancement with poor delineation of the tumor from the adjacent brain.

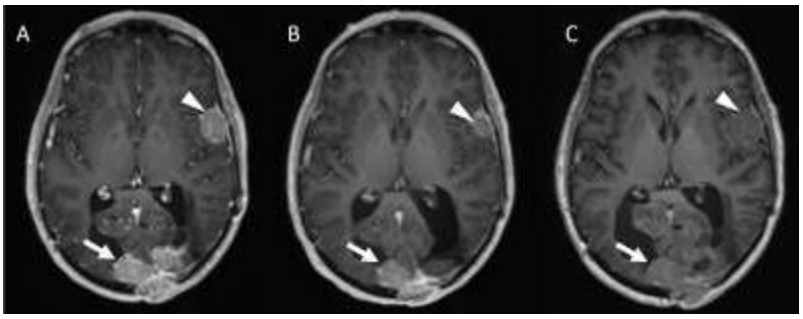

FIG 4. Axial T1-Weighted sequences from a patient with bilateral occipital (white arrow) and left pterional (white arrowhead) meningiomas at multiple time points using different contrast doses. The Standard (A) and Low (B) doses yield optimal contrast enhancement allowing for adequate delineation of the tumors. The Micro dose (C) results in insufficient contrast enhancement with poor delineation of the tumors from the adjacent brain.

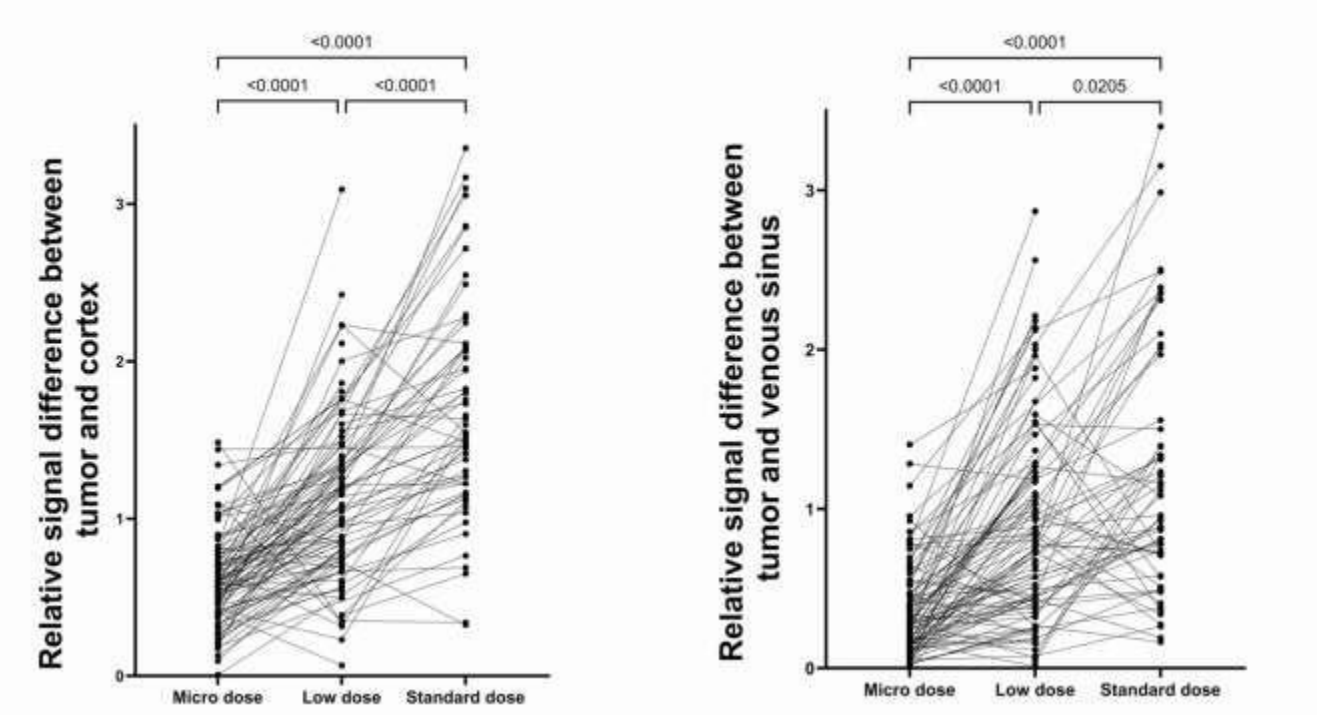

FIG 5. Values of relative signal intensity differences between the tumor and cortex and the tumor and sinus for each dose by patient. The values representing the same patients are connected by lines.

RESULTS

The initial search identified 576 MR studies from 274 subjects. Figure 1 shows a flowchart detailing patient selection. A total of 108 subjects were enrolled in the study (85 females and 23 males). The mean patient age at date of the first available MRI scan was 63.1 years (range 34-86 years). A total of 247 MRI studies were analyzed. Of the 108 patients, 31 patients had studies at all 3 doses (standard, low and micro); 40 patients had studies at the standard and low doses; 51 patients had studies at the standard and micro doses and 79 patients had studies at the low and micro doses. Most studies had a single intracranial meningioma (200 out of 247, 81%), 26 studies had 2 meningiomas (10.5%), and 21 studies had 3 or more meningiomas (8.5%). Twenty-five patients had histologically confirmed meningiomas and 83 patients had non-confirmed, presumed, meningiomas.

The ratings from the qualitative assessment of the tumors are summarized in Table 1-4 and Figure 2. When comparing the Standard and Low dose, there were no significant differences in the proportion of cases with suboptimal differentiation between the tumor and cortex and between the tumor and venous sinus ($p=1.0$). The low dose was non-inferior to the standard dose in the proportion of cases with suboptimal differentiation between the tumor and cortex with 90% power, but calculation of confidence intervals was not possible given the lack of an observed difference. The low dose was non-inferior to the standard dose in the proportion of cases with suboptimal differentiation between the tumor and venous sinus because the left confidence limit (-0.094) of the difference in proportions was contained within the non-inferiority margin (-0.1). The proportion of cases with suboptimal differentiation was significantly different between the Standard and Micro dose, both for the differentiation between the tumor and the cortex ($p=0.041$) and the differentiation between tumor and sinus ($p<0.001$). Comparing the Low and Micro dose, the proportion of cases with suboptimal differentiation was also significantly different between these dose groups for both the differentiation between the tumor and cortex ($p<0.001$) and the differentiation between the tumor and sinus ($p<0.0001$). Figures 3 and 4 show the impact of lowering the GBCA dose in the contrast enhancement of meningiomas. There was excellent inter-reader agreement for the qualitative grading of tumor differentiation from the sinus (kappa = 0.74, 95% CI 0.66-0.82) and moderate agreement for differentiation of the tumor from the cortex (kappa = 0.51, 95% CI 0.35-0.66).

The mixed effect analysis of the relative signal difference between the tumor and the cortex and the relative signal difference between the tumor and sinus showed that there was a statistical difference between the 3 different doses ($p<0.0001$). The Tukey's multiple comparisons test showed that all the comparisons (micro vs low, micro vs standard and low vs standard) showed a significant difference ($p<0.02$). The mean (± SD) values for relative signal differences between the tumor and cortex and tumor and sinus at the Standard, Low and Micro doses are summarized in Table 9. Figure 5 shows the relative signal difference between the tumor and the cortex and between the tumor and the venous sinus for the different dose categories. Although, overall, we observed improved differentiation with higher doses, a few cases showed the opposite. We believe this is most likely related to partial contrast extravasation or other injection issues. Intraclass correlation coefficient analysis showed excellent correlation between the ROI measurements of both readers (intraclass correlation coefficient = 0.908 - 0.931, $P<0.001$).

DISCUSSION

Decreasing the gadolinium dose in the follow-up MRIs of meningiomas to a Low dose (62% of standard) or a Micro dose (25% of the standard) resulted in a statistically significant decrease in signal difference between the tumor and the adjacent brain as well as between the tumor and the venous sinuses on quantitative analysis. However, these quantitative differences were only clinically relevant for the Micro dose, as the Low dose was non-inferior to the Standard dose in terms of proportion of cases with suboptimal differentiation. A further reduction in contrast dose to a Micro dose (25% of Standard) significantly increased the proportion of suboptimal cases.

Our results agree with previous studies which found a directly proportional relationship between lesion enhancement and increasing dose of contrast agent [10]; for example, Haustein et al, who assessed the efficacy of gadopentetate dimeglumine, at concentrations of 0.025 mmol/kg, 0.05 mmol/kg and 0.1 mmol/kg for imaging varying intracranial tumors [11]. Our study differs from this one, however, in several points, namely that we examined a different contrast agent, gadobutrol, and focused solely on assessment of meningiomas rather than multiple various intracranial tumors.

There have been prior studies, like ours, which have looked at the effect of reducing the dose of gadolinium administered. However, these studies specifically studied whether more highly concentrated gadolinium agents, namely gadobenate dimeglumine could be suited for reduced dose protocols [12]. In their study, Delano et al compared 0.05 mmol/kg and 0.1 mmol/kg gadobenate in patients undergoing MRI of various intracranial tumors and found that while a dose of 0.05 mmol/kg was found noninferior to a full 0.1 mmol/kg dose, significantly higher lesion to brain ratio and CNR was observed with higher doses.

Previous studies have suggested that non-contrast sequences alone are sufficient for follow up imaging of intracranial meningiomas [7-8, 13]. A recent study by Boto et al. [14] demonstrated robust agreement between T1 3D-Gd and T2WI sequences of meningioma diameter and volume suggesting that noncontrast T2W1 sequences are sufficient for follow up of untreated meningiomas. However, they did not include small volume and residual operated tumors. Similarly, a recent study by Raban et al. [15] demonstrated that volumetric T2WI detects changes in meningioma volume with comparable accuracy to gold standard T1 3D-Gd imaging, however, their results were only reliable for tumors with higher tumor volumes and posterior fossa locations. The key distinction between our study and prior investigations is that we also included patients with small residual and recurrent meningiomas, which constitute a substantial proportion of those undergoing repeat brain MRIs.

Previous studies advocating for the use of non-contrast imaging have found that visualization of venous sinus invasion by meningiomas is often hindered on T1 Gd-weighted sequences without black blood technique [14], as enhancement of the meningioma is sometimes difficult to distinguish from opacification of the venous sinus itself, and that vascular invasion is often better depicted on T2WI sequences as an absence of flow void and by direct visualization of the edges of the meningioma itself. Similarly, our study also revealed that the differentiation of meningiomas from the adjacent dural venous sinuses is challenging. At the standard dose, 12% of studies showed suboptimal differentiation between the tumor and sinus, and this percentage increased to 18% and 46% at the low and micro doses, respectively, hindering accurate assessment of tumor sinus invasion. Although T1-W 3D GE sequences are commonly used for meningioma follow up, the assessment of venous sinus invasion is limited with this technique and a black blood sequence would be preferred.

Meningiomas, although typically slow-growing tumors, can show significant growth in a considerable proportion of patients [16]. Consequently, long-term imaging follow-up with repeat exposure to GBCAs is often required, which may lead to potential adverse health effects such as gadolinium deposition in tissues and nephrogenic systemic fibrosis in those with kidney issues [4, 17-18]. Contrast administration also increases imaging costs and is becoming an environmental concern as gadolinium is increasingly detected in waste waters, becoming a new water microcontaminant [5, 6]. Future research in this area could focus on cost-effectiveness analyses that will provide valuable information for informed decision-making. This approach empowers stakeholders to make more informed choices that prioritize patient well-being but also optimize resource allocation, ensuring that healthcare resources are utilized judiciously.

We believe that one of the strengths of our study is that we did not exclude skull base, small or operated meningiomas, making our results more generalizable and allowing greater external validity than if we had only focused on convexity meningiomas as in other studies [7]. There are a few limitations: First, in part of our cohort the meningioma diagnosis had been confirmed with histopathology, but not in all cases. Therefore, we cannot exclude the possibility that other dural based lesions such as solitary fibrous tumors were also included. Second, our analysis included a “range of doses” when defining standard, low and micro doses, instead of specific dosage which increases the complexity of application of results in clinical practice. Additionally, the dose of contrast that patients within the same group received was variable. For example, some subjects in the Micro group may have received only 10% of a standard dose while others may have received up to 40%. Grouping the patients into such broad dose ranges does not allow for concrete recommendations on the optimal dose, but smaller dose ranges would have prevented meaningful comparisons due to small sample size. Third, the time between contrast administration and imaging is known to impact contrast enhancement. Given the retrospective nature of the study, time from contrast administration to imaging was not under our control and may have varied between studies. Fourth, different doses were given at different timepoints, and although we expect enhancing characteristics of these tumors to be largely stable over time, we cannot confirm this type

of stability. Overall, the goal of imaging follow-up of meningiomas is to determine whether interval growth or, more rarely, tumor regression has occurred. This was not the primary outcome of our study because the different doses were scanned at different timepoints and therefore we would not have been able to truly compare the different doses to the outcome of progression.

Table 1: Comparison between Standard and Low dose in the differentiation between tumor and cortex.

Dose	Suboptimal	Acceptable	Optimal	Total
Standard	0 (0%)	2 (5%)	38 (95%)	40 (100%)
Low	0 (0%)	5 (12.5%)	35 (87.5%)	40 (100%)

Table 2: Comparison between Standard and Micro dose in the differentiation between tumor and cortex.

Dose	Suboptimal	Acceptable	Optimal	Total
Standard	0 (0%)	0 (0%)	51 (100%)	51 (100%)
Micro	6 (11.8%)	9 (17.6%)	36 (70.6%)	51 (100%)

Table 3: Comparison between Low and Micro dose in the differentiation between tumor and cortex.

Dose	Suboptimal	Acceptable	Optimal	Total
Low	2 (2.5%)	7 (8.9%)	70 (88.6%)	79 (100%)
Micro	16 (20.2%)	15 (19%)	48 (60.8%)	79 (100%)

Table 4: Comparison between Standard and Low dose in the differentiation between tumor and venous sinus.

	Suboptimal	Acceptable	Optimal	Total
Standard	6 (15%)	12 (30%)	22 (55%)	40 (100%)
Low	7 (17.5%)	16 (40%)	17 (42.5%)	40 (100%)

Table 5: Comparison between Standard and Micro dose in the differentiation between tumor and venous sinus.

	Suboptimal	Acceptable	Optimal	Total
Standard	9 (17.6%)	18 (35.3%)	24 (47.1%)	51 (100%)
Micro	25 (49%)	16 (31.4%)	10 (19.6%)	51 (100%)

Table 6: Comparison between Low and Micro dose in the differentiation between tumor and venous sinus.

Dose	Suboptimal	Acceptable	Optimal	Total
Low	15 (19%)	27 (34.2%)	37 (46.8%)	79 (100%)
Micro	39 (49.4%)	23 (29.1%)	17 (21.5%)	79 (100%)

Table 7: Comparison between Standard, Low and Micro dose in the differentiation between tumor and cortex.

Dose	Suboptimal	Acceptable	Optimal	Total
Standard	0 (0%)	0 (0%)	31 (100%)	31 (100%)
Low	0 (0%)	3 (9.7%)	28 (90.3%)	31 (100%)
Micro	4 (12.9%)	4 (12.9%)	23 (74.2%)	31 (100%)

Table 8: Comparison between Standard, Low and Micro dose in the differentiation between tumor and venous sinus.

Dose	Suboptimal	Acceptable	Optimal	Total
Standard	4 (12.9%)	12 (38.7%)	15 (48.4%)	31 (100%)
Low	6 (19.4%)	14 (45.2%)	11 (35.4%)	31 (100%)
Micro	19 (61.3%)	7 (22.6%)	5 (16.1%)	31 (100%)

Table 9: Mean (± SD) values for relative signal differences between the tumor and cortex and tumor and sinus at the Standard, Low and Micro doses.

Tumor vs SSS/Cortex			
	Micro dose	Low dose	Standard dose
Number of studies	99	88	60
Mean (± SD)	0.36 (± 0.29)	0.94 (± 0.66)	1.22 (± 0.79)
Tumor vs Cortex/Cortex			
Number of values	99	88	60
Mean (± SD)	0.61 (± 0.29)	1.09 (± 0.54)	1.76 (± 0.79)

CONCLUSIONS

We examined the implications of reducing the gadolinium dose in follow-up MRI scans for patients with meningiomas. Our data indicates that decreasing the gadolinium dose to 62% of the standard dose significantly decreases the relative signal difference between the tumor and the brain but this reduction has little diagnostic impact. A further decrease in dose to 25% of the standard dose is not recommended as it significantly raises the proportion of suboptimal studies.

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