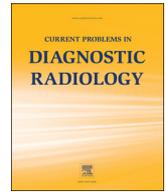




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The Impact of Gadolinium Deposition on Radiology Practice: An International Survey of Radiologists



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Rationale and Objectives: Brain deposition of gadolinium following the administration of gadolinium-based contrast agents (GBCAs) was initially reported in 2014. Gadolinium deposition is now recognized as a dose-dependent consequence of exposure. The potential clinical implications are not yet understood. The purpose of this study was to determine radiologists' reporting practices in response to gadolinium deposition.

Materials and Methods: An electronic survey querying radiologists' practices regarding gadolinium deposition was distributed by Radiopaedia.org from November–December 2015.

Results: Our study sample included 94 total respondents (50% academic; 27% private practice; 23% hybrid) from 30 different countries (USA 18%). Fifty-seven (62%) radiologists had observed brain gadolinium deposition on MRI brain studies however more than half of these (30 of 57) reported detecting dentate T1 shortening only rarely (< 1/month). Among respondents, 58% (52 of 89) do not or would not include the finding in the radiology report; only 12 (13%) report the finding in the impression of their reports. The most common reason for not reporting gadolinium deposition was the risk of provoking unnecessary patient anxiety (29%, 20 of 70). Recent data on gadolinium deposition has led to a reported practice change in 24 of 87 (28%) of respondents.

Conclusion: Recognition of, and attitudes toward, brain gadolinium deposition were inconsistent in this worldwide sample. Most surveyed radiologists do not routinely report dentate T1 shortening as a marker of gadolinium deposition. Fear of provoking patient/clinician anxiety and an incomplete understanding of the implications of gadolinium deposition contribute to inconsistencies in reporting.

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Purpose

Gadolinium-based contrast agents (GBCAs) are retained in the human brain as a dose-dependent consequence of exposure manifested by T1 shortening within several distinct brain regions including the cerebellar dentate nuclei.^{1–3} Less than a decade previously, the finding of hyperintense T1 signal within the dentate nuclei had been attributed to a variable etiologies including prior therapeutic brain irradiation⁴ and also as a marker of the secondary progressive subtype of multiple sclerosis.⁵ In 2014 Kanda et al⁶ and Errante et al³ first attributed dentate T1 shortening to GBCA exposure. Subsequent work including autopsy

studies has confirmed brain deposition of gadolinium (GD) even in patients with normal renal function.¹ Although the link between GBCA deposition and dentate T1 shortening is now well established, the clinical significance of intracranial GD accumulation, if any, remains unknown. Nonetheless, some radiologists and their practices are not waiting for that evidence and instead are proactively making changes in the way they utilize GBCAs. To our knowledge, radiologists' recognition of GD deposition and attitudes toward it have not been examined. The purpose of our study was to describe radiologists' reporting styles and practice patterns relevant to GBCA deposition.

Materials and Methods

Study Population and Survey

We conducted an online survey of radiologists using SurveyMonkey.com over 17 days spanning November–December 2015. A 10-question survey was distributed by study authors through Radiopaedia.org using social media including Facebook.com and Twitter.com. Queries included basic respondent characteristics

Components of the work were presented at the Annual Meeting of the American Society of Neuroradiology held in May 2016.

Potential Conflicts of Interest: E.K.: paid consultant for Bracco Diagnostics and Guerbet, F.G.: CEO and editor of Radiopaedia.org

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Table

Survey questions
(1) How often do you notice T1 shortening in the dentate nucleus in patients with prior exposure to gadolinium-based contrast agents (GBCA)?
(2) When encountered, do you report dentate T1 shortening and attribute it to prior exposure to gadolinium-based contrast agents?
(3) If no to question 2, why have you chosen not to report MR findings of gadolinium deposition in the brain?
(4) Has your practice changed which patients receive GBCAs or dosing in response to recent data on gadolinium deposition?
(5) Does your practice add up or report a patient's total lifetime administered gadolinium dosage or number of contrast-enhanced MR examinations?
(6) Does your practice obtain consent for patients before GBCA administration?
(7) Does your local Institutional Review Board/Ethics Board require a statement regarding gadolinium deposition in the consent for MRI research study participants?
(8) What is your radiology practice type?
(9) How would you describe your primary area of practice?
(10) Where is your practice located?

such as practice type and location, frequency of detection of GD deposition, and reporting habits (Table). Poll results were conveyed using descriptive statistics.

Results

Study Group

Our study included survey data from 94 respondent radiologists from 30 different countries (USA 18%) on 6 continents. Not all respondents answered every question resulting in a variable denominator. Close to half (47 of 93) of the survey respondents described their practice as academic, 27% (25 of 93) private practice, and 23% (21 of 93) reported a hybrid practice. Fourteen of the respondents were radiology residents or fellows. The majority of respondents reported their primary area of practice as neuroradiology (52) followed by general radiology (28), musculoskeletal and body radiology (19 each), and pediatric radiology, women's imaging, thoracic and/or cardiac imaging, nuclear medicine, interventional radiology, and ultrasound each of which constituted 8% or less of the sample.

Detection and Reporting of GD Deposition

Detection of brain GD deposition as manifested by dentate T1 shortening was reported by 57 of 92 (62%) of survey respondents. Among all surveyed, only a minority (8 of 92, 9%) encountered GD deposition on a very frequent basis (2 or more per week) and 19 (21%) encountered the finding "often" (estimated 2 or more per month). A larger proportion of respondents (33%, 30 of 92) have encountered imaging evidence of GD deposition rarely (< 1 case per month). Thirty-five of the question respondents (38%) reported to have never encountered dentate T1 shortening.

Among all surveyed, 58% (52 of 89 question respondents) do not or would not include the finding in the radiology report. Whereas 28% of those surveyed (25 of 89) report or would report deposition in the body of the radiology report, only 13% (12 of 89) responded that this information merits inclusion in the impression section of the radiology report. Considering only those respondents who have personally encountered dentate T1 shortening ($n = 57$), 27 of 57 (47%) have chosen to not report the finding, 19 of 57 (33%) report the finding only in the "findings" section, and

11 of 57 (19%) include this information in the "impression" section of the radiology report.

The most common reason for not reporting GD deposition was the perceived risk of provoking unnecessary patient anxiety, cited by 29% (20 of 70) of respondents. Other cited reasons included the notion that GD deposition is not an actionable finding based on our current understanding (14 respondents), questions regarding the causal link between exposure to GBCAs and dentate T1 shortening,¹⁰ the risk of drawing attention for potential litigation,⁷ and the risk of negative impact on referring clinicians.⁶

Impact on Practice

Our survey also explored the impact of the discovery of GD deposition on radiology practice. Among survey respondents, 28% (24 of 87) reported that recent data on GD deposition has led to a reported change in their practice. Most commonly, this entailed increased use of, or a complete switch to, macrocyclic agents. Others reported elevation of their threshold for administering GBCA and a greater reliance on nonenhanced MR imaging for cases in which contrast was deemed to be of limited benefit. Less than 20% (15 of 87 question respondents) of practices record patients total lifetime administered dose of GBCAs.

Regarding consent for the clinical administration of GBCAs, 52% of surveyed radiologists (47 of 91) reported obtaining written informed consent before all contrast-enhanced examinations. A small percentage of practices (10%, 9 of 91) obtain written consent only for selected patients such as those with a documented history of renal impairment and just under 32% (29 of 91) of respondents reported that in their practices no consent is obtained before the administration of GBCAs. Practice location was specified for 28 of the 29 practices who do not obtain consent before GBCA administration. Of these, 20 of 28 were located outside of the United States. Our survey also queried whether respondents' local institutional review board or ethics board required a statement regarding GD deposition in the consent for MRI research study participants. Just under half of those surveyed answered "no" (42 of 91), 11 answered "yes," and the remainder were "unsure."

Discussion

Recent evidence has established a causal link between T1 shortening in specific brain regions and cumulative exposure to

certain GBCAs.^{1,2,7,8} The response of the radiology community to this data in terms of reporting and effects on practice patterns has, to our knowledge, not yet been examined. The aim of our study was to describe the impact of data regarding GD deposition on radiologists from among a worldwide sample. We found high variability regarding radiologists' recognition and reporting of dentate T1 shortening as a marker of brain GD deposition. In regard to varying recognition, several factors are at play. Although evidence now clearly attributes dentate T1 shortening to cumulative exposure to GBCAs^{1,2} this is a relatively recent discovery that may not be widely disseminated throughout the medical and radiologic communities. In addition, referral patterns and patient populations of individual practices vary and such differences will impact the incidence of GD deposition. For instance, radiologists practicing at a tertiary care center with a large population of patients undergoing annual surveillance for multiple sclerosis are much more likely to encounter patients with high cumulative dose exposure than radiologists in a rural community setting. Nevertheless, the ubiquity of MR imaging in the developed world and the frequency with which GBCAs are prescribed (estimates of total dosages of GBCA exceed 200 million as of 2012)⁹ suggest that many radiologists even outside of high volume referral centers and academic institutions will commonly encounter patients with a history of high cumulative exposure to GBCAs.

Whether or not GD deposition in the brain of patients receiving GBCAs will negatively impact the health and well-being of those patients is as yet unknown. It is now known that deposition occurs even in the setting of normal renal function¹ and therefore, in contrast to nephrogenic systemic fibrosis, any potential detriments may not be limited to a small subset of patients with severely impaired renal dysfunction. As such, cautious approach seems prudent at this juncture. Based on the current evidence, regulatory agencies including the United States Food and Drug Administration¹⁰ and the European Medicines Agency¹¹ are conducting ongoing investigations into the potential risks of GD deposition in brain tissue following the use of GBCAs. Large, long term studies may be required in order to determine whether clinical detriments occur as the result of GD deposition. Based on this current knowledge gap, some have voiced the opinion that any alteration of current practice secondary to GD deposition is premature.¹² In contrast, our survey found that as of December 2015 more than 1/4 of surveyed radiologists have already changed their practice with regard to GBCAs on the basis of the currently existing data.

Although our study did not address attitudes toward specific GBCAs, other studies have shed light on the relative contribution of various GBCAs to GD deposition and have shown variability in the propensity of agents from different classes to accumulate within neural tissue. For instance, in their 2015 rat study Robert et al¹³ showed that total GD concentration in the cerebellum was 4–14 times higher after linear GBCAs as compared to the macrocyclic agent gadoterate meglumine (Dotarem; Guerbet, Aulnay-sous-Bois, France). In human subjects, Cao et al¹⁴ found no statistically significant increased in dentate T1 signal intensity in patients exposed to multiple doses of gadobutrol (Gadavist; Bayer HealthCare), another macrocyclic GBCA. Some groups have voiced the opinion that macrocyclics as a class do not cause observable T1 shortening on brain MRI.¹⁵ In contrast, the Stojanov¹⁶ group's report of dentate T1 shortening in patients with relapsing, remitting multiple sclerosis exposed to gadobutrol suggests that radiologic apparent effects may not be entirely absent from the macrocyclic class. In another human study, Murata et al¹⁷ determined agent-specific average GD deposition ratios by examining autopsy specimens of subjects exposed to a single GBCA and found that dentate deposition varied among same-class agents as gadobutrol, a cyclic agent, exhibited the highest ratio at 0.11 µg/g/mmol, followed by gadodiamide (linear) (Omniscan; GE Healthcare,

Waukesha, Wis) 0.098 µg/g/mmol, gadobenate (linear) ([MultiHance, Bracco Imaging, Milan, Italy) 0.008 µg/g/mmol, and gadoteridol [cyclic] (ProHance, Gd-HP-DO3A; Bracco Diagnostics, Monroe, NJ) at 0.003 µg/g/mmol.¹⁷ Larger multicenter studies will be important to clarify the relative impact of class vs agent-specific factors in the propensity to deposit within neural tissue.

Science, and therefore medicine, is an ever-changing endeavor that evolves in response to advances in knowledge. A portion of what we hold to be true today may be considered short-sighted or proven wrong in subsequent years. We now know that dentate T1 shortening can be attributed to GD but as yet the scientific community has not rigorously examined whether or not such GD deposition is harmful. It is well known that the absence of evidence is not evidence of absence and therefore prudence in the way in which the radiology community responds to GD deposition seems warranted. The current knowledge gap leaves some radiologists wondering how best to serve our patients and referring physicians, as evidenced by the variability with which respondents in our study report dentate T1 shortening.

Our study has several limitations. We did not query respondents as to the specific GBCA used in their practices. Given the informal survey format, we anticipated that the use of multiple GBCAs within some practices and uncertainty regarding specific GBCAs used in prior examinations could lead to inaccurate specific agent data. Assessment of the role of certain GBCAs in GD deposition would instead be best addressed by a prospective trial or well documented retrospective study design and is beyond the scope of our current project. Our study design using social media for survey distribution raises the possibility of a skew toward responses from younger radiologists and potential nonresponse bias. Some individuals may have chosen not to respond in part because they were not previously aware of GD deposition. The inclusion of radiology fellows and residents in our survey (15% of survey respondents) could have impacted data on practice patterns given that these individuals may have limited knowledge of departmental policies. Despite these potential limitations, we believe our data highlight the current heterogeneity of response to the issue of GD deposition, and suggest that our profession may benefit from the development of guidelines by representative bodies.

In summary, we found a wide disparity in the rate at which radiologists recognize GD deposition and a variety of opinions as to how, or even if, such findings should be reported. That the most commonly cited reason for not reporting GD deposition in our study was the unnecessary provocation of patient anxiety indicates that further study of the potential negative consequences of GD deposition is needed. Time will tell whether or not GD deposition represents a real risk to our patients. Until we know whether intracranial GD deposition has negative health consequences, radiologists must be cognizant of the way in which we report the imaging manifestations of GD deposition in the brain and consider the potential impact of what we report on our patients, referring physicians, and ourselves.

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