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GADOLINIUM RETENTION IN HUMANS: SURVEY OF RADIOLOGISTS AND IMPACT ON DAILY PRACTICE*

İNSANDA GADOLİNYUM BİRİKİMİ: RADYOLOJİ UZMANLARI VE KLİNİK UYGULAMALAR ÜZERİNDEKİ ETKİSİ

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ABSTRACT

Objective: We sought to assess the 1) awareness and impact of emerging gadolinium retention data on preferences of radiologists in their practice, and 2) factors that influence the attitudes about gadolinium use and risk. This study also documents various specifics of radiology practice in Turkey.

Methods: A twenty-one question survey was directed to radiologists who were at least one year from completion of residency and/or fellowship training. A survey link was emailed to the members of the Turkish Society of Radiology and was active for four weeks. The results were statistically analyzed.

Results: Three hundred and thirty-five radiologists completed the survey. At the time of this survey, 89% of respondents were aware of gadolinium retention in the brain. Forty-five percent of respondents said they decreased the amount of gadolinium administered and/or frequency of gadolinium-enhanced scans since the emergence of the gadolinium retention data. Eighty-eight percent of radiologists, who were aware of the molecular classification of different gadolinium agents, used a macrocyclic agent. Thirty-nine percent (n=130) had switched to a macrocyclic agent from a linear agent within the previous three years. Radiologists' attitudes toward gadolinium retention were significantly associated with their background factors such as experience in radiology, subspecialty training, and daily work definition, amongst others. Observence of hyperintense dentate nuclei due to gadolinium retention was uncommon in daily practice.

Conclusions: Gadolinium retention publications have affected the practice of contrast enhanced Magnetic resonance imaging (MRI) scans, mostly in the form of switching to a macrocyclic gadolinium agent and decreasing utilization of gadolinium in general for some indications. These changes varied among radiologists by background factors.

Keywords: Gadolinium, magnetic resonance imaging, surveys and questionnaires, radiologists, cerebellar nuclei

ÖZET

Amaç: Bu çalışmada, 1) Son yıllarda ortaya konulan, insan beyninde gadolinyum birikimi verileri hakkında radyologların farkındalığı, klinik uygulamaları ve tercihleri üzerindeki etkisi ve 2) Gadolinyum kullanımı ve riski hakkındaki yaklaşımları etkileyen faktörlerin değerlendirilmesi amaçlandı. Ayrıca bu çalışmada, Türkiye'deki radyoloji pratiği hakkında önemli bilgiler sunuldu.

Yöntem: İhtisas veya yan dal eğitiminin tamamlanmasından en az bir yıl geçmiş olan radyologlara yönelik 21 soruluk anket hazırlandı. Türk Radyoloji Derneği üyelerine e-posta ile gönderilen anket linki dört hafta boyunca aktifti.

Bulgular: Üç yüz otuz beş kişi anketi tamamladı. Katılımcıların %89'u beyinde gadolinyum birikimi hakkındaki gelişmelerden haberdardı. Katılımcıların %45'i gadolinyum birikimi verilerinin ortaya çıkmasından bu yana uyguladıkları gadolinyum miktarını ve/veya gadolinyum gerektiren görüntülemelerin sıklığını azalttığını söyledi. Gadolinyum ajanlarının moleküler sınıflandırmasının farkında olan radyologların %88'i makrosiklik bir ajan kullandığını belirtti. Yüzde 39'u (n=130) önceki üç yıl içinde (2015-2018) lineer bir ajandan makrosiklik bir ajana geçtigini bildirdi. Radyologların gadolinyum birikimine yönelik yaklaşımı, radyoloji deneyimi, üst ihtisas eğitimi, kurumu ve bir radyoloji konferansına katılım sıklığı gibi kişiye özel faktörlerle önemli ölçüde ilişkiliydi. Katılımcıların günlük klinik pratikte gadolinyum birikimine bağlı gelişen hiperintens dentat nukleus gözlemleme sıklığı düşüktü.

Sonuç: Gadolinyum birikimi çalışmaları, radyologların MR görüntüleme pratiğini ve yaklaşımını, çoğunlukla makrosiklik gadolinyum ajanlarına geçiş ve gadolinyum kullanımını azaltmak suretiyle etkilemiştir. Bu değişiklikler, radyologların bireysel koşullarına göre değişiklik göstermektedir.

Anahtar Kelimeler: Gadolinyum, manyetik rezonans görüntüleme, anketler, radyoloji uzmanları, serebellar çekirdekler

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INTRODUCTION

Since the original reports of intracranial gadolinium retention/deposition in 2014, a number of studies have been published that attribute Hyperintense Dentate Nuclei (HDN) on T1-weighted MR images to repeated administrations of intravenous gadolinium (1-8). The clinical ramifications of gadolinium deposition have been debated and not yet substantiated, but the possible unwanted outcomes have worried practitioners, patients, drug companies and government organizations (9-11). On the other hand, while alternative contrast agents are being investigated, gadolinium is still integral to many Magnetic resonance imaging (MRI) protocols (12, 13). Involvement of radiologists in study ordering, appropriateness of scan indication, optimum protocoling and patient engagement are among the new areas of emphasis on utilization (14-16). Despite the numerous publications and significant research activity around the potential impact of gadolinium retention in the human body, little is known about the impact of these initiatives on daily radiology practice. Practice diversity exists across the globe. This study was based in Turkey, a country where the majority of radiologists individually prescribe gadolinium for their patients prior to MRI scans. Thus, their personal preferences may have a direct impact on the landscape of gadolinium utilization. This is important, as the study was conducted in a period when there was no limitation on the utilization of linear gadolinium molecules in the market yet. In this regard, the aim of this study was two fold: 1) to assess the awareness and impact of emerging gadolinium retention data on the preferences of radiologists in their practice, and 2) analyze the factors that influence the attitudes about gadolinium use and risk.

METHODS

A survey was created using www.surveymonkey.com (San Mateo, CA) (see Appendix 1). The survey was anonymous with no personal information like name, sex, race, age or the name of the institution being asked, thus, as per ethical committee regulations, the study did not require IRB processing. All respondents read a written informed consent and agreed to participate prior to proceeding with the survey questions. Each question included a 'no response' choice to allow participants not to share their opinions. The survey was addressed to radiologists who were at least one year from completion of residency and/or fellowship training. A closed survey link was emailed to the members of the Turkish Society of Radiology and a reminder email was sent two weeks later. The survey was active during four weeks (October-November 2018). The survey was set to allow only one individual response per device, to prevent repetitive responses. A total of 21 multiple-choice questions were asked. Participants were able to skip any question.

Statistical analyses were performed using SPSS version 21.0 for Windows (SPSS, Chicago, Ill). Descriptive statistics are presented. Decimals of percentages were rounded, as the actual numbers of samples (n) were provided. Respondents were grouped according to types of institution, scope of daily radiology practice, experience in radiology, and frequency of their attendance at radiology conferences/meetings. Normality of the variables' dispersion was tested with the Kolmogorov-Smirnov test. Nonparametric Kruskal-Wallis H Test was used to test the difference between the groups, because all tested variables showed a non-Gaussian dispersion ($p<0.0001$ on Kolmogorov-Smirnov test for all variables). Groups were statistically analyzed and significant data for each subgroup are presented in a table (Table 1).

RESULTS

Three hundred and thirty-five members of Turkish Society of Radiology with at least one year of experience after radiology training completed the survey.

Background of respondents

Thirty-one percent (n=103/335) of respondents were affiliated with government-run community hospitals, 48% (n=160) with academic institutions, and 21% were affiliated with a private practice (n=64 private hospital; n=7 imaging centers). Seventy-two percent (n=242/335) of respondents defined their daily radiology practice as a general diagnostic radiology, 22% (n=72) as a diagnostic subspecialty, and 6% (n=21) as an interventional subspecialty. There was significant difference between participants' daily work definition based on their institution. Most of the community hospitals and private practice radiologists (94% and 83%, respectively) were performing general radiology as opposed to academic center radiologists (53%, ($p<0.0001$)). 50% (n=167) of respondents were 1 to 5 years from their previous training period (either fellowship or residency), 19% (n=63) were 5 to 10 years, 10% (n=33) were 10 to 15 years, and 20% (n=67) were more than 15 years after their training period. Thirty-six percent (n=122) of respondents attended a radiology conference less frequently than once a year, 30% (n=101) attended once a year, and 30% (n=100) attended more frequently than once a year with 2% (n=5) attending conferences at least once a month. Forty-two percent of general radiology practitioners were attending a scientific conference less frequently than a year, as opposed to subspecialists and interventional radiologists (25% and 10%, respectively ($p=0.02$)).

Awareness of radiologists and adoption in clinical practice

Twenty-two percent (n=84) did not know the class (macrocyclic or linear) of gadolinium agent they used. Twenty-six percent (n=86) were using a macrocyclic gadolinium

Table 1. Grouped survey results with respect to background factors of respondents

	Daily work definiton				Decision of gadolinium administration					Who prescribe gadolinium		
	General diagnostic radiology	Interventional radiology	Subspeciality	p value	Radiologist prior to scan	Radiologist during the scan	Clinician	Radiologist and clinician's collaboration	p value	Radiologist	Clinician	p value
Community hospital	94% (n=97)	2% (n=2)	4% (n=4)	<.0001	11% (n=11)	3% (n=3)	74% (n=72)	14% (n=14)	.021	83% (n=84)	17% (n=17)	<.0001
Academic centers	53% (n=85)	11% (n=17)	37% (n=58)		26% (n=41)	7% (n=11)	55% (n=88)	12% (n=20)		92% (n=147)	7% (n=11)	
Private practice	83% (n=59)	3% (n=2)	14% (n=10)		9% (n=6)	35% (n=25)	21% (n=15)	35% (n=25)		62% (n=44)	35% (n=25)	

	Renal function tests prior to a gadolinium enhanced scan						Recording prior Gadolinium administrations			Agent specific consent form prior to scan		
	Not testing	eGFR	Serum creatinine level	Both creatinine and eGFR	Don't know	p	Yes	No	p value	Yes	No	
Community hospital	38% (n=39)	6% (n=6)	32% (n=33)	12% (n=12)	13% (n=13)	.003	31% (n=32)	69% (n=71)	<.0001	59% (61)	41% (n=42)	P<0.01
Academic centers	29% (n=47)	6% (n=10)	24% (n=39)	29% (n=46)	11% (n=18)		38% (n=61)	62% (n=99)		55% (88)	45% (n=72)	
Private practice	42% (n=30)	10% (n=7)	32% (n=23)	14% (n=10)	1% (n=1)		61% (n=43)	39% (n=28)		75% (53)	23% (n=16)	

	Frequency of HDN observation					Time passed since the previous residency or fellowship					Radiologists involved in bulk purchase			
	Never	Weekly	Monthly	Yearly	p value	1-5 years	5-10 years	10-15 years	>15 years	p value	No	Yes	Don't know	p value
Community hospital	72% (n=74)	2% (n=2)	12% (n=12)	11% (n=11)	.001	63% (n=65)	21% (n=22)	7% (n=7)	8% (n=8)	<.0001	54% (n=56)	25% (n=26)	20% (n=21)	<.0001
Academic centers	65% (n=104)	4% (n=7)	13% (n=21)	16% (n=26)		51% (n=81)	16% (n=26)	11% (n=18)	19% (n=31)		22% (n=36)	44% (n=70)	34% (n=54)	
Private practice	47% (n=33)	3% (n=2)	21% (n=15)	28% (n=20)		28% (n=20)	21% (n=15)	11% (n=8)	39% (n=28)		41% (n=29)	45% (n=32)	14% (n=10)	

	Awareness of Gadolinium retention in human body						Recently switching to a different class of gadolinium agent					
	Unaware	since 2015	since 2016	since 2017	since 2018	p value	Don't know the class	Continues linear	Continues macrocyclic	To macrocyclic	To linear	p value
Community hospital	14% (n=14)	29% (n=30)	28% (n=29)	27% (n=28)	2% (n=2)	.007	24% (n=25)	7% (n=7)	24% (n=25)	39% (n=40)	4% (n=4)	.001
Academic centers	4% (n=6)	34% (n=55)	36% (n=58)	18% (n=28)	8% (n=13)		19% (n=31)	6% (n=9)	25% (n=40)	45% (n=72)	4% (n=6)	
Private practice	25% (n=18)	30% (n=21)	24% (n=17)	18% (n=13)	1% (n=1)		39% (n=28)	4% (n=3)	30% (n=21)	24% (n=17)	N/A	

Table 1. Grouped survey results with respect to background factors of respondents (Continued)

	Decision of gadolinium administration					Radiologists involved in bulk purchase				Time passed since the previous residency or fellowship				
	Radiologist prior to scan	Radiologist during the scan	Clinician	Radiologist and clinician's collaboration	p value	Yes	No	Don't know	p value	1-5 years	5-10 Years	10-15 Years	>15 years	p value
General diagnostic radiology	12% (n=28)	10% (n=24)	61% (n=147)	17% (n=42)	.001	43% (n=104)	31% (n=76)	26% (n=62)	.014	55% (n=132)	19% (n=47)	8% (n=19)	16% (n=39)	.001
Interventional radiology	29% (n=6)	10% (n=2)	43% (n=9)	19% (n=4)		33% (n=7)	48% (n=10)	19% (n=4)		52% (n=11)	19% (n=4)	5% (n=1)	24% (n=5)	
Subspeciality	33% (n=24)	18% (n=13)	31% (n=22)	18% (n=13)		15% (n=11)	58% (n=42)	26% (n=19)		33% (n=24)	17% (n=12)	18% (n=13)	32% (n=23)	

	Awareness of gadolinium retention in human body						Frequency of attendance to radiology meeting/conferences				
	Unaware	Since 2015	since 2016	Since 2017	Since 2018	p value	more than once a month	once a year	more than once a year	less than once a year	p value
General diagnostic radiology	12% (n=30)	29% (n=70)	30% (n=73)	22% (n=54)	6% (n=14)	.035	1% (n=3)	29% (n=71)	24% (n=59)	42% (n=102)	.02
Interventional radiology	N/A	24% (n=5)	48% (n=10)	29% (n=6)	N/A		N/A	43% (n=9)	48% (n=10)	10% (n=2)	
Subspeciality	11% (n=8)	44% (n=32)	29% (n=21)	13% (n=9)	3% (n=2)		3% (n=2)	29% (n=21)	43% (n=31)	25% (n=18)	

	Timing of Gad agent switch				Type of institution			
	Within previous three months	A year ago	1-3 years ago	p value	Community hospital	Academic center	Private practice	p value
General diagnostic radiology	12% (n=29)	33% (n=79)	12% (n=28)	.003	40% (n=97)	35% (n=85)	24% (n=59)	.015
Interventional radiology	5% (n=1)	38% (n=8)	24% (n=5)		10% (n=2)	81% (n=17)	10% (n=2)	
Subspeciality	8% (n=6)	28% (n=20)	32% (n=23)					

Table 1. Grouped survey results with respect to background factors of respondents (Continued)

	Type of institution				Daily work definiton				Decision of gadolinium administration				
	Community hospital	Academic center	Private practice	p value	General diagnostic radiology	Interventional radiology	Subspeciality	p value	Radiologist prior to scan	Radiologist during the scan	Clinician	Radiologist and clinician's collaboration	p value
1-5 years from residency	39% (n=65)	49% (n=81)	12% (n=20)	<.0001	79% (n=132)	7% (n=11)	14% (n=24)	.001	15% (n=25)	7% (n=11)	63% (n=105)	15% (n=25)	.033
5-10 years from residency	35% (n=22)	41% (n=26)	24% (n=15)		75% (n=47)	6% (n=4)	19% (n=12)		13% (n=8)	13% (n=8)	57% (n=36)	17% (n=11)	
10- 15 years from residency	21% (n=7)	56% (n=18)	24% (n=8)		58% (n=19)	3% (n=1)	39% (n=13)		18% (n=6)	9% (n=3)	42% (n=14)	30% (n=10)	
>15 years from residency	12% (n=8)	46% (n=31)	42% (n=28)		58% (n=39)	8% (n=5)	34% (n=23)		27% (n=18)	25% (n=17)	28% (n=19)	19% (n=13)	

	Recording prior gadolinium administrations			Details of gadolinium agent on MRI report			Frequency of HDN observation				
	Yes	No	p value	Yes	No	p value	Never	Weekly	Monthly	Yearly	p value
1-5 years from residency	34% (n=56)	67% (n=111)	.006	25% (n=41)	75% (n=126)	.001	68% (n=114)	2% (n=3)	13% (n=21)	16% (n=27)	.022
5-10 years from residency	37% (n=23)	64% (n=40)		29% (n=18)	71% (n=45)		70% (n=44)	3% (n=2)	11% (n=7)	13% (n=8)	
10- 15 years from residency	58% (n=19)	42% (n=14)		30% (n=10)	64% (n=21)		46% (n=15)	N/A	24% (n=8)	27% (n=9)	
>15 years from residency	54% (n=36)	46% (n=31)		51% (n=34)	48% (n=32)		52% (n=35)	9% (n=6)	16% (n=11)	19% (n=13)	

	Daily work definiton				Who prescribe gadolinium			Recently switching to a different class of gadolinium agent					
	General diagnostic radiology	Subspeciality	Interventional radiology	p value	Radiologist	Clinician	p value	Don't know the class	Continues linear	Continues macrocyclic	To macrocyclic	To linear	p value
more than once a month	60% (n=3)	N/A	40% (n=2)	.001	80% (n=4)	20% (n=1)	<.0001	N/A	N/A	N/A	40% (n=2)	60% (n=3)	<.0001
one conference a year	70% (n=71)	9% (n=9)	21% (n=21)		88% (n=89)	9% (n=9)		17% (n=17)	7% (n=7)	30% (n=30)	42% (n=42)	4% (n=4)	
more than once a year	59% (n=59)	10% (n=10)	31% (n=31)		92% (n=92)	7% (n=7)		14% (n=14)	6% (n=6)	24% (n=24)	53% (n=53)	3% (n=3)	
less than once a year	84% (n=102)	2% (n=2)	18% (n=15)		71% (n=87)	27% (n=33)		41% (n=50)	5% (n=6)	22% (n=27)	26% (n=32)	3% (n=3)	

Table 1. Grouped survey results with respect to background factors of respondents (Continued)

	Awareness of gadolinium retention in human body					
	Unaware	**since 2015**	**since 2016**	**since 2017**	**since 2018**	**p value**
At least once a month	N/A	80% (n=4)	20% (n=1)	N/A	N/A	<0.01
More than one conference per year	2% (n=2)	34% (n=34)	42% (n=42)	21% (n=21)	1% (n=1)	
One conference per year	7% (n=7)	44% (n=44)	27% (n=27)	17% (n=17)	6% (n=6)	
less than one conference per year	22% (n=27)	19% (n=23)	28% (n=34)	24% (n=29)	7% (n=9)	

agent and had not change it in the previous three years, 39% (n=130) were using a linear gadolinium agent and switched it to a macrocyclic agent in the previous three years, 6% (n=19) were still using linear gadolinium agents, 3% (n=10) were using a macrocyclic gadolinium agent and switched to a linear agent in the previous three years. In terms of the timing of change within the previous three-year period; 11% (n=36) switched to a gadolinium agent within the previous three months, 32% (n=107) in the previous year, 17% (n=56) within the previous three years. Thirty-six percent (n=107) switched because of gadolinium retention, 26% (n=77) because of NSF risk, and 11% (n=33) switched because of the agent's cost. In terms of gadolinium deposition, 11% (n=38) were unaware of emerging gadolinium retention data. This ratio was highest among those who attended a radiology conference less frequently than once a year (see Table 1 for details). Thirty-two percent (n=107) came to know of gadolinium deposition risk in 2015, 31% (n=104) in 2016, 21% (n=69) in 2017, and 5% (n=16) in 2018. Thirty-six percent (n=121) had not read the statements of the following organizations about gadolinium retention. Thirty-nine percent (n=132) read the American College of Radiology (ACR) and American Society of Neuroradiology (ASNR) statements, 7% (n=24) read the US Food and Drug Administration (FDA) statement, 15% (n=50) read the European Medicines Agency's (EMA) pharmaceutical risk assessment committee statement on the matter. In terms of the impact of knowledge of gadolinium retention on practitioners' clinical practice, 45% (n=152) said they decreased the amount and/or frequency of gadolinium-enhanced scans since the time that they found out about gadolinium deposition risk, while 46% (n=156) did not. Respondents were asked to rate the frequency of cases in which they faced diagnostic difficulty because of a reluctance to administer gadolinium. Twenty-two percent (n=73) answered 'never', 59% (n=195) answered 'seldom' and 19% (n=63) answered 'frequently'. On the frequency of encountering HDN on pre-contrast MRI studies, 64% of radiologists (n=211) said 'never', 18% (n=58) said 'once a year', 15% (n=48) said 'once a month', 3% (n=11) said 'once a week'. While 58% (n=54) respondents did report the existence of an HDN on their final MRI reports, 42% (n=39) did not. The highest HDN observation rates were seen in academic centers (Table 1). Forty-four percent (n=105) of respondents would include the generic name and amount of gadolinium agent used for a scan in their final MRI report, 56% (n=131) would not. One percent (n=3) of respondents faced a medico-legal problem or a complaint by patients and/or their relatives because of gadolinium administration, 99% (n=330) did not. All three of those who had a medico-legal problem were between 1-5 years from residency.

The rate at which radiologists detected HDN was highest among academic centers, followed by private practices and community hospitals, respectively (p:0.001), see

Table 1 for details). Awareness of gadolinium retention was highest among academic centers and was followed by community hospitals and private practice (94%, 86% and 75% respectively (p=0.07) see Table 1 for details). Thirty-nine percent of private practice members were unaware of the class of gadolinium agent they were using as opposed to 24% in community hospitals and 19% in academic centers (p=0.001). Forty-five percent of academic centers switched from linear to macrocyclic agents and this was followed by community hospitals (39%) and private practices (24%, p=0.01). Unawareness rates of gadolinium deposition was inversely correlated with how frequently the physicians attended a radiology conference (22%, 7%, 2% and 0% in groups with; less frequent than once a year, once a year, more frequent than once a year and once a month, respectively (p<0.01)).

Routine MRI workflow and protocoling

According to 53% (n=173) of respondents, the referring physician would decide whether to include post-gadolinium sequences for a given MRI scan. This practice was significantly common in community hospitals (Table 1). The remaining respondents said a radiologist would be involved in the decision-making process in the following roles: Prior to a particular scan, radiologist would decide whether gadolinium administration is needed (17%, n=58); at the time of a scan, after evaluating initial sequences (12%, n=29); and prior to a scan after a discussion with referring physician based on clinical indication (18%, n=59). The rate of a radiologist's role in the decision-making process of gadolinium injection was the highest among subspecialty-focused radiology practitioners and experienced radiologists (Table 1). Interestingly, private practice radiologists had higher rates of involvement in gadolinium protocoling compared to academic centers and community hospitals (74% versus 55% and 21%, respectively (p=0.021)). For outpatient MRI scans, a radiologist would prescribe gadolinium in 84% (n=280), while the rest were prescribed by a referring physician (16%, n=55). Thirty-eight percent (n=128) of respondents were consulted in the hospital's gadolinium purchase process for inpatient services, while 36% (n=122) were not. Twenty-five percent (n=85) said they were unaware of the hospital's purchase process. Twenty-eight percent (n=95) of respondents were routinely testing serum creatinine levels before an MRI scan, 7% (n=23) tested eGFR levels and 20% (n=68) tested both creatinine and eGFR levels on a routine basis. Thirty-five percent (n=117) tested neither parameter and 10% (n=32) were unaware of renal function testing status prior to an MRI scan in their institution. Kidney function testing was highest in academic centers, followed by community hospitals and private practices (p=0.03, see Table 1 for details). Sixty percent (n=202) of participants offered agent specific (e.g. linear vs macrocyclic gadolinium) consent forms to patients prior to MRI scans, while 39% (n=131) did not. Forty-one percent (n=136) of participants recorded a cumulative dose of gadolinium administration from prior studies before undergoing an MRI scan, while 59% (n=199) did not. The rate of recording cumulative gadolinium administration from prior studies, including outside studies, was highest by radiologists in private practice (61% compared to 38% and 31% in academic centers and community hospitals, respectively (p<0.0001)). Agent specific consent acquisition was most common among private practice practitioners followed by community hospitals and academic centers (75%, 59% and 55%, respectively (p<0.001)).

DISCUSSION

Awareness of gadolinium retention has had a significant impact on practitioners' approaches to contrast enhanced MRI scans, as nearly a half of our study participants decreased the amount of gadolinium administration per scan, and/or decreased the frequency of gadolinium-enhanced scans since they became aware of the gadolinium retention risk. This stance did not show any significant association with respondents' background factors like institution, experience and practice type. Currently, the vast majority of participants in our present study use a macrocyclic agent, with more than half of them having switched to it within the previous three years (2015-2018), mostly during 2018. The rate of switching to a macrocyclic agent was highest among academic centers. This may be because they were the most concerned about gadolinium deposition, they were the heaviest users of linear agents prior to recognizing the gadolinium deposition controversy, or because of economic factors not explored by this study. Certainly the manufacturers of gadolinium agents have been marketing on the basis of reduced gadolinium deposition since the reports of HDN have arisen. In terms of reasoning, among those who switched to a different class of gadolinium, most stated they had done so because of recent gadolinium retention data, and this was followed by NSF risk and the agent's cost. Moreover, despite several published studies in high impact journals (1-30), a tenth of radiologists are still unaware of gadolinium retention issues. This ratio was highest among those who attended a radiology conference less frequently than once a year. Frequency of attendance at a scientific conference was most common amongst interventional radiology practitioners. The awareness rate of gadolinium deposition was correlated with how frequently the radiologist attended a radiology conference. This signifies that despite the ubiquity of online and offline learning tools, conventional conferences are still an important source of practitioners' update on HDN. On the other hand, observance of retained intracranial gadolinium is uncommon, as more than a half of our respondents had never noticed HDN in their daily practice, which maybe resultant of the scarcity of MRI utilization in their practice. The highest HDN observa-

tion rates were seen in academic centers. In terms of MRI protocoling, in practice of more than a half of our survey respondents, ordering physicians make the decision whether to administer gadolinium at the time of the study request. This practice was very common in community hospitals. The rate of a radiologist's role in the decision-making process of gadolinium injection was the highest in private practices and among subspecialty-focused radiology practitioners and experienced radiologists. Despite the professional responsibility of radiologists in study protocoling, the present study shows that in the majority of cases, particularly in government-run and community hospitals, referring physicians are the primary decision-makers of the gadolinium necessity for a given scan (53%). However, radiologists still determine the particular gadolinium agent to be used in the vast majority of practices (84%), regardless of the type of institution.

Gadolinium, a rare earth metal, has been documented to remain in the human brain for as long as eleven years and possibly longer (4). It is also retained in the skin, bones and liver, along with other organs and has different chemical forms and uncertain in vivo behavior (17-22). After such gadolinium retention reports emerged, safety concerns were raised and linear agents, which deposit more frequently in tissue, were eventually suspended from the contrast agent market in many countries (9). Public attention to gadolinium retention reports increased the number of people with symptoms attributed to their gadolinium injection history, which also sparked medico-legal issues (10, 11). In the present study, a medicolegal case associated with a patient's gadolinium administration history was an extremely rare occasion. Although practitioners remain wary, adverse clinical outcomes of intracranial gadolinium retention have not been proved to date. In their survey study of gadolinium related symptoms, Semelka et al. reported a variety of symptoms including, but not limited to, headache and bone pain (10). However, their study suffered from selection bias, as symptoms were self-reported by patients who underwent repeated doses of gadolinium administration and attributed their symptoms to this history. Along with new clinical regulations in gadolinium applications, possible ways to decrease cumulative gadolinium exposure in chronic patients like multiple sclerosis are being investigated (23, 24). Gong et al. succeeded in decreasing the amount of gadolinium needed for a brain MRI by up to 10% of the regular dose by using a series of image enhancing al algorithms (25).

The present study also has critical findings in terms of radiology practice in Turkey. Participants in our study were affiliated with academic facilities, community hospitals and private practices, in decreasing order. Young radiologists were more commonly affiliated with community hospitals, possibly resulting from an ongoing Turkish government policy of obligatory duty in underserved areas after completion of a residency program. The majority of survey respondents defined their daily basis practice as general diagnostic radiology (low percentages of subspecialty focused practice). This is in line with the radiology training landscape reported by the European Society of Radiology (ESR), which showed fellowship training was not well established in European countries when compared with North America (26). Gadolinium retention data affected the majority of radiologists in this survey. Nonetheless, in the English literature, very few studies are available on impact of emerging gadolinium retention data on daily radiology practice and gadolinium enhanced MRI exercises (27-29). Despite diversity in adopted methods and their small sample sizes, available studies' overall results are in line with our present study. In their online open survey study conducted on Radiopedia.com, Fitzgerald et al. reported that 24 of 87 (28%) respondents made a change in their practice by either switching to a macrocyclic agent or decreasing the number of contrast enhanced MRI scans (29). This percentage is lower than our findings; however, their study was conducted at an earlier stage of gadolinium retention awareness. In an international survey study conducted on 58 neurosurgeons and neuroendocrinologists by Nachtigal et al., 28% of respondents were unaware of gadolinium retention risk (28). In their study 11% of respondents were unaware of the class of gadolinium agent they prescribed, a mildly lower rate than our findings (28). There is also a scarcity of studies focusing on contrast enhanced MRI exercises like gadolinium protocoling, consent forms, and renal function testing. In a study conducted on 162 pediatric radiologists (mostly academic centers from the USA), 25% of respondents would not contact the clinician and thus, the ordering physician would decide the MRI protocol as far as gadolinium administration (27). In our study this rate was significantly higher (53%). Together, our studies show that referring clinicians are deciding whether to administer contrast on MRI studies to a large extent. This may have caused unwarranted gadolinium injections (28).

More than a half of respondents in our study performed routine renal function testing prior to an enhanced MRI scan, mostly by testing serum creatinine levels. There was significant association between renal function testing and the type of institution. Academic centers had the highest renal function testing rates. In their aforementioned study, Blumfield et al. reported that 59% of their respondents required renal function testing only in selected cases (27). Two thirds of our respondents had distinct consent forms for each gadolinium class; same as the frequency of recording prior individual gadolinium administrations before undergoing an MRI scan. Prior exposure data recording was significantly higher among private practices and experienced radiologists. Recording prior administrations of gadolinium is important, as

gadolinium retention has been shown to be dose-dependent (30).

In terms of reporting practices, more than a half of our respondents did not include the generic name and amount of gadolinium agent used for the scan in their final MRI report. Experienced radiologists had significantly higher reporting rates. More than half of those who encounter HDN would report this finding in their MRI report. Fitzgerald et al. reported that 38% of participants in their study had never seen HDN and 58% of their respondents would report HDN in the final MRI report, in line with our present findings.

The present study was conducted on a large cohort of radiologists from Turkey, thus the findings may not necessarily reflect the worldwide situation. However, findings of the current study were comparable to that of globally conducted studies (26, 28, 29). Because the name of institutions was not queried, the specific number of institutions participating in this study could not be quantified. Heterogeneity within the practice of a certain institution was not queried, as the study aimed to investigate the radiologists' personal stance rather than institutional practices.

CONCLUSION

Gadolinium retention publications have affected radiologists' preferences in the practice of contrast enhanced MRI scans, mostly in the form of switching to a macrocyclic gadolinium agent and decreasing utilization of gadolinium. These changes varied among radiologists by background factors such as experience in radiology, practice setting, and subspecialty training. Some of our findings about the practice of radiology in Turkey are potentially actionable. There may be a need for greater involvement of radiologists in study protocoling and gadolinium decision-making.

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Appendix 1: Survey questions.

This survey is designed solely for scientific research purposes and there is no financial relation with any company, institution or organization. The survey does not require any personal information. Please do not participate in the survey if one full year has not passed since your residency and/or fellowship training. To be part of this study, your current radiology practice should include MRI studies, please do not participate otherwise.

1-What kind of institution do you work for?

2-Which of the following best describes your daily radiology practice?

3-Who decides whether an MRI examination in your institution will be performed with or without IV contrast agent application?

4-If gadolinium is prescribed to patients before scan as part of your practice, who prescribes MR contrast agent in your hospital?

5- If contrast agents are provided by hospital itself, does hospital management consult radiologists before making bulk purchases of MRI contrast agent?

6-Do you routinely check kidney function before your patients are given gadolinium?

7-Do you question your patients' exposure and amount of gadolinium before the contrast-enhanced MRI is performed?

8- Are you aware of molecular classes (linear or macrocyclic) of gadolinium agents? If so, have you changed the contrast agent you have prescribed in the previous three years?

9-If yes, why?

10- If yes, when did you change it?

11-How often do you attend to scientific conferences/meetings?

12- How many years ago did you complete your residency/fellowship training?

13-Have you heard that gadolinium accumulates in the brain after a certain amount of exposure in some individuals with a history of contrast-enhanced MRI scans? If so, when did you first get to know it? (Please jump to the 15th question if your answer to the first part of this question is No).

14-Did you change the amount or frequency of contrast agent application after being aware of gadolinium accumulation in the human brain?

15-Do you include in your MRI report the name and amount of contrast material given to the patient during scan?

16-Do you have a drug-specific consent form for the patients and/or relatives before administration of a contrast agent?

17- Have you ever observed a hyperintense dentate nucleus at your routine clinical MRI readings? If so how often do you observe?

18-Do you report hyperintense dentate nucleus in your MRI report?

19-Are you aware of the following medical institutions' announces about gadolinium accumulation in the brain? (click all that apply).

20-Did you experience any diagnostic difficulties because you hesitated to use contrast media in your clinical practice?

21-Have you received any feedback from your patients about the accumulation of gadolinium in the brain or have you had any medical-legal problems?