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CONTRAST MEDIA

Gadolinium deposition in the brain: association with various GBCAs using a generalized additive model

Sohi Bae[1] · Ho-Joon Lee[1] · Kyunghwa Han[1] · Yae-Won Park[1] · Yoon Seong Choi[1] · Sung Soo Ahn[1] · Jinna Kim[1] · Seung-Koo Lee[1]

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Abstract

Objectives To determine the relationship between the number of administrations of various gadolinium-based contrast agents (GBCAs) and increased T1 signal intensity in the globus pallidus (GP) and dentate nucleus (DN).

Methods This retrospective study included 122 patients who underwent double-dose GBCA-enhanced magnetic resonance imaging. Two radiologists calculated GP-to-thalamus (TH) signal intensity ratio, DN-to-pons signal intensity ratio and relative change (R_{change}) between the baseline and final examinations. Interobserver agreement was evaluated. The relationships between R_{change} and several factors, including number of each GBCA administrations, were analysed using a generalized additive model.

Results Six patients (4.9%) received linear GBCAs (mean 20.8 number of administration; range 15–30), 44 patients (36.1%) received macrocyclic GBCAs (mean 26.1; range 14–51) and 72 patients (59.0%) received both types of GBCAs (mean 31.5; range 12–65). Interobserver agreement was almost perfect (0.99; 95% CI: 0.99–0.99). R_{change} (DN:pons) was associated with gadodiamide ($p = 0.006$) and gadopentetate dimeglumine ($p < 0.001$), but not with other GBCAs. R_{change} (GP:TH) was not associated with GBCA administration.

Conclusions Previous administration of linear agents gadoiamide and gadopentetate dimeglumine is associated with increased T1 signal intensity in the DN, whereas macrocyclic GBCAs do not show an association.

✉ Seung-Koo Lee
SLEE@yuhs.ac

[1] Department of Radiology, Severance Hospital, Research Institute of Radiological Science, Yonsei University College of Medicine, 50-1 Yonsei-ro, Seodaemun-gu, Seoul 03722, Korea

Key points

- *Certain linear GBCAs are associated with T1 signal change in the dentate nucleus.*
- *The signal change is related to the administration number of certain linear GBCAs.*
- *Difference in signal change may reflect differences in stability of agents.*

Keywords Gadolinium · Magnetic resonance imaging · Dentate nucleus · Globus pallidus · Contrast media

Abbreviations

BBB	Blood-brain barrier
CSF	Cerebrospinal fluid
DN	Dentate nucleus
eGFR	Estimated glomerular infiltration rate
GAM	Generalized additive model
GBCA	Gadolinium-based contrast agent
GP	Globus pallidus
MRI	Magnetic resonance imaging
NSF	Nephrogenic systemic fibrosis
R_{change}	Relative change
ROI	Region of interest
TH	Thalamus

Introduction

Gadolinium-based contrast agents (GBCAs) have been widely used, with more than 200 million doses administered worldwide for more than a quarter of a century [1]. Because free Gd^{3+} ion is toxic, it is chelated with a suitable ligand molecule. The biochemical properties of various GBCAs are determined by the chemical structure of the chelator, which can be linear

or macrocyclic and ionic or nonionic [2]. Chelated GBCAs show fast clearance *in vivo*, with 98% clearance within 24 h via renal excretion [3], and were regarded as safe and stable until 2006.

In 2006, it was first suggested that GBCAs might be the cause of nephrogenic systemic fibrosis (NSF) [4], a devastating systemic disease in patients with renal insufficiency. The widely accepted mechanism of NSF is 'transmetallation theory'. Endogeneous cations (e.g. Zn^{2+}, Cu^{2+}, Ca^{2+} ions) can compete with Gd^{3+} ions for the ligand. The released free Gd^{3+} ions can deposit in the tissues when retained *in vivo* by decreased renal function. This theory explained why NSF developed only in patients with significant renal disease and most commonly when patients were administered nonionic linear GBCAs, which are theoretically the most vulnerable chemical structure to dechelation [5].

The possibility of gadolinium deposition in the brain of patients with normal renal function was first proposed in 2014 [6]. Increased signal intensity in the globus pallidus (GP) and dentate nucleus (DN) on T1-weighted magnetic resonance imaging (MRI) was observed in patients with multiple previous GBCA exposures. Subsequent postmortem studies [7, 8] confirmed gadolinium deposition in these areas of T1 shortening using inductively coupled plasma mass spectrometry. To date, multiple studies regarding increased T1 hyperintensity in the GP and/or DN associated with linear agents have been published [6–17]. For macrocyclic agents, the controversy still remains. Most studies have shown no significant correlation between the T1 signal intensity change and exposure to macrocyclic agents [10, 12–14]. However, a previous study reported increased T1 signal intensity after multiple administrations of gadobutrol, a macrocyclic agent [18]. In addition, a recent study using inductively coupled plasma mass spectrometry detected gadolinium deposition in the brain with macrocyclic agents [19], which supports deposition of macrocyclic agents.

There have been several reports comparing the effect of two agents [6, 10, 12, 20]. However, as far we know, there have been no reports comparing the effect of more than two types of GBCA in one institute, although there have been studies in autopsy [8, 19] and an animal model [21].

In our institution we have administered double-dose GBCAs in patients with cancer to increase the detection sensitivity of brain metastasis since 2005 [22], and have reported the diagnostic yield of the double-dose enhanced examinations in relation to the size of brain lesions, or type of administered contrast agents [23, 24]. The purpose of our study is to determine the relationship between the number of administrations of various GBCAs and increased T1 signal intensity in the GP and DN in patients exposed to high doses of gadolinium to possibly reveal differences in gadolinium deposition between different agents based on the 10 years' experience with double-dose enhanced MRI.

Materials and methods

This single-centre retrospective study was approved by our institutional review board. The requirement for informed consent was waived.

Patients

We extracted data for 179 consecutive patients who underwent double-dose MRI at least ten times. For imaging analysis, we included unenhanced T1-weighted imaging only performed with fast spin echo with inversion recovery examined in 3 T MRI and excluded examinations performed with different sequences or in 1.5 T MRI. We excluded examinations without documented information about the type and volume of administered GBCAs in the electronic medical record. The baseline MRI examination for evaluation was the first contrast-enhanced brain MRI study satisfying these conditions, whereas the final MRI examination represented the last one. We excluded patients who underwent contrast-enhanced MRI prior to the baseline examination (n = 36) and who were administered gadoxetate disodium at least once (n = 14). We also excluded patients with fewer than six administrations of GBCAs between baseline and final examinations (n = 3) based on a previous study reporting an increase in T1 signal intensity of DN in patients with six or more enhanced MRI scans [9]. Images of unsatisfactory quality due to MRI artifacts or brain lesions involving both sides of the GP, DN, thalamus (TH) or pons were excluded (n = 4). Finally, 122 patients were included in this study (Fig. 1).

Data analysis

From patient medical records, we extracted sex, age, interval between baseline and final MRI examinations, history of brain surgery, chemotherapy and radiation therapy, diagnosis of present illness, renal function, liver function, and number and type of all GBCAs administered. Radiation was defined as whole-brain radiation or tumour-selective radiation therapy.

Renal function was assessed by calculating estimated glomerular infiltration rate (eGFR) from blood samples taken at the time of the final MRI exam. Abnormal renal function was defined as eGFR less than 60 ml/min per 1.73 m^2. Abnormal liver function was defined as abnormal serum concentrations of aspartate aminotransferase or alanine aminotransferase. The number and type of GBCAs administered were obtained for all types of enhanced MRI performed between baseline and final MRI examinations, including spine MRI, abdomen MRI or bone MRI. The GBCAs used at our institution during this time period included gadodiamide (Omniscan; GE Healthcare, Princeton, NJ, USA), gadopentetate dimeglumine (Magnevist; Bayer Healthcare Pharmaceuticals, Whippany, NJ, USA), gadobutrol (Gadovist; Bayer Healthcare

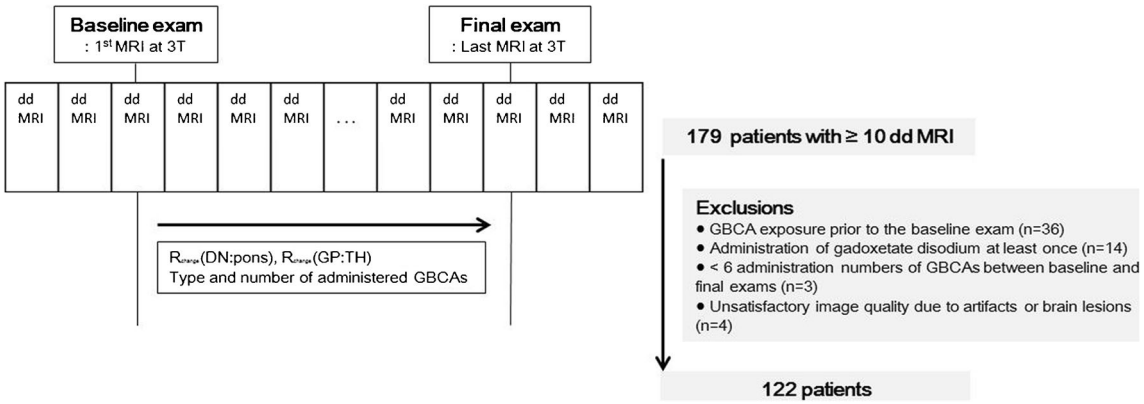


Fig. 1 Study population. *MRI* magnetic resonance imaging, *dd* double-dose enhanced, *GBCA* gadolinium-based contrast agent, R_{change} relative change, *DN:pons* dentate nucleus-to-pons ratio, *GP:TH* globus pallidus-to-thalamus ratio

Pharmaceuticals), and gadoterate meglumine (Dotarem; Guerbet, Bloomington, IN, USA).

Imaging protocols

MRI was performed with eight different 3 T MRI units (Achieva, Philips Medical System, The Netherlands; Ingenia, Philips Medical System; Discovery MR750, GE Medical Systems, Milwaukee, WI, USA,; and Triotim, Siemens, Erlangen, Germany). Axial unenhanced T1-weighted MRI was obtained with fast spin-echo with inversion recovery with the following parameters: repetition time ms/echo time ms, 2,000/10; inversion time, 1,000 ms; section thickness, 5 mm; spacing, 2 mm; matrix size, 256 x 256; echo train length, eight. Double-dose (0.2 mmol/kg) GBCA-enhanced brain MRI was performed, corresponding to 0.2 ml/kg of gadobutrol and 0.4 ml/kg of gadodiamide, gadopentate dimeglumine and gadoterate meglumine.

Imaging analysis

Quantitative analysis was conducted independently by two radiologists (S.K. and S.B., with 30 and 5 years of experience, respectively), who were blinded to patient information. A region of interest (ROI) was drawn in the bilateral GP, TH, DN and pons of both baseline and final unenhanced T1-weighted MRI. If the anatomical boundary was unclear on the T1-weighted images, T2-weighted images were additionally used for guidance. The measured values of right and left sides were averaged for all possible structures. The GP:TH signal intensity ratio was defined as the mean signal intensity of the GP divided by that of the TH, and DN:pons was defined as the mean signal intensity of the DN divided by that of the TH. GP:TH and DN:pons were calculated for the baseline and final MRI of all patients. The relative change (R_{change}) of GP:TH and DN:pons was determined by the following formulas: R_{change} (GP:TH) = (GP:TH_x-GP:TH_0)/GP:TH_0 and R_{change} (DN:pons) = (DN:$pons_x$-DN:$pons_0$)/DN:$pons_0$, where x refers to the final MRI and 0 refers to the baseline MRI in the same patient.

Statistical analysis

Interobserver agreement between the ROI measurements for each structure for two readers was evaluated with Lin concordance correlation [25]. Lin concordance correlation coefficients less than 0.9 indicate poor agreement; 0.90–0.95, moderate agreement; >0.95–0.99, substantial agreement; and >0.99, almost perfect agreement.

R_{change} (GP:TH) and R_{change} (DN:pons) were evaluated with a generalized additive model (GAM) [26], a method of non-parametric regression analysis. A generalized cross-validation criterion was used as a smoothing parameter estimation method. The model was defined as follows: R_{change} = sex + s(age) + s(interval) + neurosurgery + chemotherapy + radiation therapy + renal function + s(administered number of gadodiamide) + s(administered number of gadopentate dimeglumine) + s(administered number gadobutrol) + s(administered number of gadoterate meglumine). The function 's' was defined as the smoothing function with penalized regression splines.

Statistical analyses were conducted using statistical software (R, Statistical Package version 3.3.0; R Foundation for Statistical Computing, Vienna, Austria; www.R-project.org). The mgcv package was used to apply the GAM function. Statistical significance was defined as a P value less than 0.05.

Results

Of the 244 evaluated MRI examinations from 122 patients, left GP was excluded in one patient (in final), left TH was excluded in one patient (in final), right DN was excluded in two patients (two in baseline and final), and left DN was excluded in three patients (one in final, two in baseline and final) due to the presence of metastatic lesions involving these

structures. Right DN was excluded in one patient (in baseline) and left DN was excluded in one patient (in baseline and final) due to the presence of an artifact. In these patients, the ratios were calculated based on the values of the contralateral side alone. GPs and DNs of 41 patients who underwent whole brain radiation therapy were included for image analysis, whereas GPs and DNs with metastatic lesions with/without tumour selective radiotherapy were excluded from the image analysis.

A summary of patient data is shown in Table 1. No patients were diagnosed with NSF. Twenty-three patients (18.9%) underwent brain surgery and 121 (99.2%) underwent chemotherapy. 111 patients (91.0%) had a history of targeted or whole-brain radiation therapy. 120 patients (98.4%) developed brain metastasis finally. 117 patients (96.0%) had normal renal function and all patients had normal liver function.

Between baseline and final MRI examinations, six patients (4.9%) received only linear GBCAs (mean, 20.8 number of administration; range, 15–30), 44 patients (36.1%) received only macrocyclic GBCAs (mean, 26.1; range, 14–51), and 72 patients (59.0%) received both types of GBCAs (mean 31.5; range, 12–65) (Fig. 2).

Interobserver agreement was almost perfect for ROI measurement of all eight evaluated structures (0.99; 95% confidence interval: 0.99–0.99). R_{change} (DN:pons) was significantly associated with number of administrations of gadodiamide ($p = 0.006$) and gadopentetate dimeglumine ($p < 0.001$). Sex, age, interval, neurosurgery, chemotherapy, radiation therapy, renal function and number of administrations of gadobutrol and gadoteratate meglumine were not related to R_{change} (DN:pons) (Table 2). Figure 3 shows the relationship between R_{change} (DN:pons) and the number of administrations of various GBCAs, using the GAM function to smooth the curve. R_{change} (GP:TH) was not significantly associated with the number of exposures to all types of GBCAs and other variables (Table 3). Figure 4 shows the relationship between R_{change} (GP:TH) and the number of administrations of various GBCAs.

Discussion

In this study, we showed the different effects of various GBCAs on T1 signal intensity in the DN and GP. Macrocyclic agents were not associated with signal change in the DN or GP even at high-dose accumulation conditions. In contrast, two linear agents – gadodiamide and gadopentetate dimeglumine – were associated with an increased signal in the DN.

The different effects of linear and macrocyclic GBCAs can be attributed to differences in complex stabilities. Macrocyclic GBCAs are more stable than linear agents because Gd^{3+} is caged in the rigid macrocyclic ring system and more energy is needed to dissociate gadolinium from the macrocycle leading to a lower tendency for gadolinium dissociation or transmetallation, as has been proved in previous studies [27, 28]. This favours the hypothesis that dissociation of Gd^{3+} from its chelating ligand molecule is part of the mechanism of gadolinium deposition in the brain. However, the chemical form of gadolinium deposited in the neuronal tissues has not been fully investigated and it remains unclear whether it is intact GBCA, free Gd^{3+} ion or other chemical species generated by transmetallation. Phosphate- and carbonate-bound gadolinium is thought not to have a T1 shortening effect [29]. This means that the increased T1 signal intensity visible on MRI does not reflect the actual amount of retained gadolinium in human tissue [5]. If we determine the chemical speciation of retained gadolinium in brain, we can understand the pathophysiology of gadolinium deposition and its clinical significance.

In our study, R_{change} (DN:pons) appears to be similar or slightly more prominent for gadopentetate dimeglumine than for gadodiamide in plotted graphs (Fig. 3). This is not consistent with a previous animal study in rats, which reported a higher T1 signal intensity change of deep cerebellar nuclei after injection of gadodiamide compared with gadopentetate dimeglumine [21]. Also, gadodiamide has been reported as the most commonly implicated agent of NSF, with approximately 1.5 times more cases of NSF compared to gadopentetate dimeglumine [30]. Gadopentetate dimeglumine, the linear ionic agent, is known to be more resistant to dechelation than gadodiamide, the linear nonionic form [31]. The slightly longer elimination half-life of gadopentetate dimeglumine (94 ± 11 min [standard deviation]) than gadodiamide (77.8 ± 16 min) might have contributed to this conflicting result [32, 33]; however, this small difference with overlapping confidence intervals is insufficient to explain the result. Difference in saturation effect after high-dose administration, which was recently reported by Robert et al. [34], could be another reason. Further comparison studies between groups exclusively administered high doses of each agent would reveal the different deposition rate between the two linear agents.

R_{change} (GP:TH) did not show a significant correlation with exposure to any GBCA in our study. Several previous studies reported increased signal intensity in the GP, but to a lesser degree than the DN [6, 12, 16, 20]. Postmortem studies reported that GP contained a lower concentration of gadolinium than DN [7, 19], and in an animal study with rats no elevated signal intensities were observed in GP for any GBCA [21]. Reduced deposition of gadolinium in GP might result in the statistically insignificant signal change observed in our study. Further study with a larger sample size and higher doses of exposure might reveal different regional vulnerabilities to gadolinium deposition in the brain.

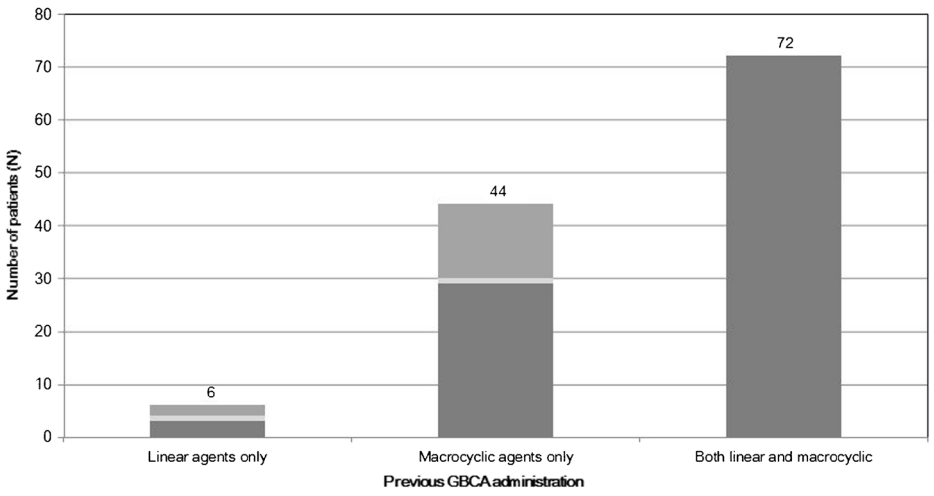
Table 1 Characteristics of the 122 patients

Parameter	Result
Age (years)*	59.0 ± 9.7
Sex	
Men	67 (54.9%)
Women	55 (45.1%)
Interval between baseline and final exams (days)*	1323.3 ± 687.2
History of neurosurgery	23 (18.9%)
History of chemotherapy	121 (99.2%)
Platinum-based chemotherapy	94 (77.0%)
Molecularly-targeted therapy	42 (34.4%)
Other therapy	37 (30.3%)
History of radiation therapy	111 (91.0%)
Whole brain	41 (33.6%)
Tumour selective	70 (57.4%)
Diagnosis	Lung cancer (n = 91), breast cancer (n = 20), stomach cancer (n = 2), ovarian cancer (n = 1), cervical cancer (n = 1), colon cancer (n = 1), hemangioblastoma (n = 1), hepatocellular carcinoma (n = 1), malignant thymoma (n = 1), prostate cancer (n = 1), renal cell carcinoma (n = 1), thyroid cancer (n = 1)
Brain metastasis	120 (98.4%)
At the beginning	96 (78.7%)
Developed during interval	24 (19.7%)
eGFR	
≥60 ml/min per 1.73 m^2	117 (96.0%)
<60 ml/min per 1.73 m^2	5 (4.1%)
Abnormal liver function	0 (0%)

Note. Unless otherwise noted, data are number (%) of patients

* Data are means ± standard deviations

eGFR estimated glomerular filtration rate



Mean No. of administration (range)	20.8 (15-30)	26.1 (14-51)	31.5 (12-65)
Type of GBCAs; No. of patients (No. of administration)[a] or (Mean No. of administration, range)[b]	Gadodiamide only; 2 (15, 19)[a]	Gadobutrol only; 14 (24.6, 16-37)[b]	72
	Gadopentetate dimeglumine only; 1 (18)[a]	Gadoterate meglumine only; 1 (22)[a]	
	Both; 3 (gadodiamide, 21; gadepentetate dimeglumine, 1)[a], (3; 18)[a], (10; 20)[a]	Both; 29 (27.0, 14-51)[b]	

Fig. 2 Distribution of patients according to the types of previously administered GBCAs. *GBCA* gadolinium-based contrast agent, *No* number

Table 2 Results of nonparametric regression models: R_{change} (DN:pons)

Parameter	Estimated value of parametric coefficients*	Standard error*	Estimated degrees of freedom*‡	P value*
Sex	0.015	0.015		0.317
Neurosurgery	0.004	0.018		0.822
Chemotherapy	−0.028	0.057		0.623
Radiation therapy	0.020	0.026		0.448
Renal function	−0.006	0.037		0.874
Age (y)			1.000	0.318
Interval (d)			1.165	0.168
Number of GBCAs				
Gadodiamide			1.611	0.006
Gadopentate dimeglumine			1.822	<0.001
Gadobutrol			1.000	0.404
Godoterate meglumine			2.250	0.326

* Data were calculated using the GAM

‡ Degrees of freedom refers to the curvature of the fitted GAM line relative to a simple straight line. Some variables were automatically forced to a linear relationship (df = 1)

R_{change} relative change, *DN:pons* dentate nucleus−to−pons ratio, *GBCA* gadolinium−based contrast agents, *GAM* generalized additive model

In our study, many patients had metastatic lesions in the brain (98.4%), a history of radiotherapy (91.0%), chemotherapy (99.2%) and surgery (18.9%). A previous study reported increased blood-brain barrier (BBB) permeability in the tumour area by about 20% [35]. Also it has been reported that ionizing radiation can disrupt the BBB and may enhance the delivery of the drugs to the brain [36, 37]. The association between the permeability status of the

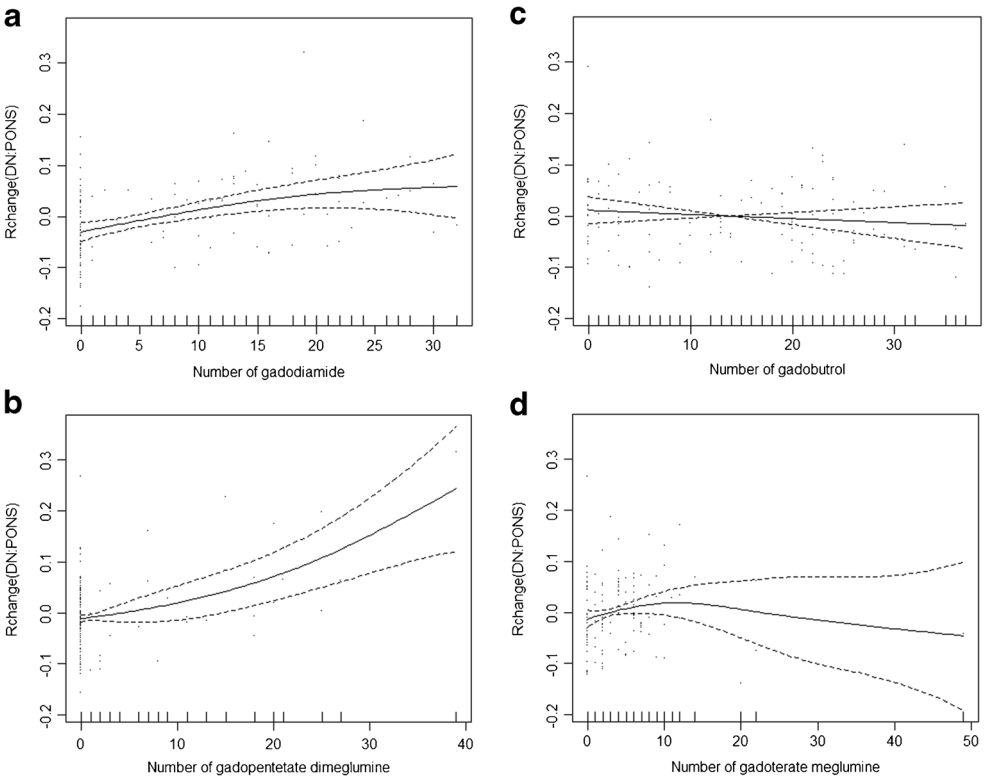


Fig. 3 Graphs of R_{change} (DN:pons) according to various GBCAs. Graphs of R_{change} for DN:pons between the baseline and final MRI according to the number of administrations of (**a**) gadodiamide, (**b**) gadopentetate dimeglumine, (**c**) gadobutrol and (**d**) gadoterate meglumine. *R_{change}* relative change, *DN:pons* dentate nucleus-to-pons ratio, *GBCA* gadolinium-based contrast agent

Table 3 Results of nonparametric regression models: R_{change} (GP:TH)

Parameter	Estimated value of parametric coefficients*	Standard error*	Estimated degrees of freedom*‡	P value*
Sex	0.008	0.011		0.495
Neurosurgery	0.004	0.015		0.804
Chemotherapy	−0.015	0.045		0.749
Radiation therapy	0.022	0.020		0.278
Renal function	−0.054	0.029		0.062
Age (y)			1.949	0.289
Interval (d)			1.000	0.684
Number of GBCAs				
Gadodiamide			1.523	0.080
Gadopentate dimeglumine			1.000	0.136
Gadobutrol			1.000	0.388
Godoterate meglumine			1.000	0.944

* Data were calculated using the GAM

‡ Degrees of freedom refers to the curvature of the fitted GAM line relative to a simple straight line. Some variables were automatically forced to a linear relationship (df = 1)

R_{change} relative change, *GP:TH* globus pallidus-to-thalamus ratio, *GBCA* gadolinium-based contrast agent, *GAM* generalized additive model

BBB and the deposition of gadolinium has not been revealed yet; however, postmortem brain specimen showed 18–42% of deposited gadolinium crossed the BBB [7]. Compromised BBBs in our patients might influence the delivery and deposition of gadolinium in the neuronal tissue. Chemotherapy can also interact with other drugs by physiochemical interactions or by competing for binding sites [38, 39]. Surgery and postoperative status affect

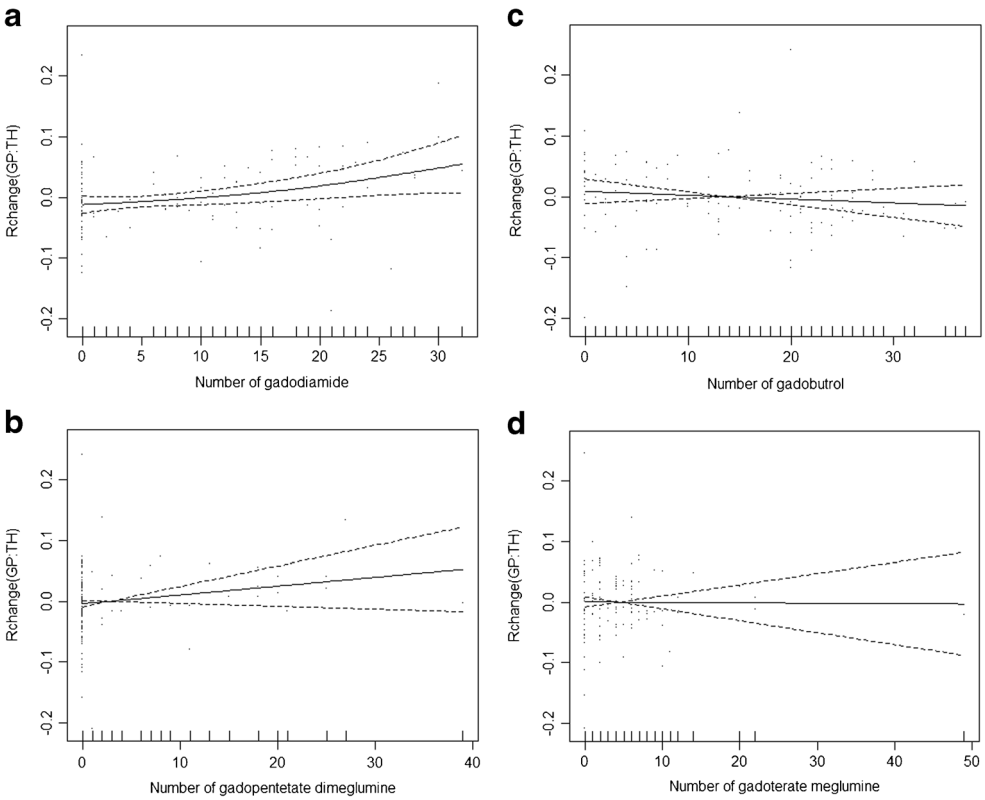


Fig. 4 Graphs of R_{change} (GP:TH) according to various GBCAs. Graphs of R_{change} for GP:TH between the baseline and final MRI according to the number of administrations of (**a**) gadodiamide, (**b**) gadopentetate dimeglumine, (**c**) gadobutrol and (**d**) gadoterate meglumine. *R_{change}* relative change, *GP:TH* globus pallidus-to-thalamus ratio, *GBCA* gadolinium-based contrast agent

perfusion, blood volume, drug metabolism and renal or biliary drug excretion [40]. The large proportion of patients with underlying brain lesions and treatment history in our study might have affected the distribution and deposition of gadolinium, even though these factors were not statistically significant.

Our study has several limitations. First, it is retrospective study from patients who were administered different types of GBCAs. The ideal study design would be to randomly assign patients to the different agents to exclude the effect of other confounding variables, though this would be unethical and impractical. Also it would have been better to select and compare patients who were exclusively administered one agent multiple times; however, only a small number of patients received one type of agent in our institution. Instead, we tried to reveal the impact of each GBCA by statistical analysis. However, the possibility of an interaction between effects of various GBCAs remains [41]. Second, MRI was performed with eight different 3 T MRI units and we did not consider the different MRI vendors, models and coils, which could affect the measured signal intensity; however, a study reported that measured signal-to-noise ratio and contrast-to-noise ratio were fairly uniform across scanners at the same field strength [42]. We hypothesized that the measured signal intensity ratio of two structures would be comparable between different vendors of same strength. Third, we calculated the DN:pons and GP:TH to indirectly reflect gadolinium deposition in the brain. However, the pons and TH are also sites of gadolinium deposition, as reported in an autopsy study [7], and therefore may be inappropriate as a reference. However, even the cerebrospinal fluid (CSF) space showed an increase in signal intensity after gadolinium injection in an animal model [21]. We could not find a better candidate as a reference. Further study using absolute T1 value or R1 relaxivity would be useful to assess absolute signal change in the brain. Last, the clinical significance of gadolinium deposition in the brain cannot be evaluated in this study. Many patients in our study showed neurological symptoms such as cognitive impairment, focal neurological deficit, delirium or ultimately seizure, but it was impossible to establish one cause in patients with underlying malignancy, brain metastatic lesions and poor general condition. Further studies without confounding factors are required to reveal the clinical significance of brain deposition of gadolinium.

In conclusion, our study suggests that previous administration of the linear GBCAs gadodiamide and gadopentetate dimeglumine may be associated with increased T1 signal intensity in the DN under high-dose accumulation conditions. Conversely, no association was noted in our study with the macrocyclic GBCAs, gadobutrol and gadoterate meglumine.

Compliance with ethical standards

Guarantor The scientific guarantor of this publication is Seung-Koo Lee.

Conflict of interest The authors of this manuscript declare no relationships with any companies, whose products or services may be related to the subject matter of the article.

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Statistics and biometry One of the authors has significant statistical expertise.

Ethical approval Institutional Review Board approval was obtained.

Informed consent Written informed consent was waived by the Institutional Review Board.

Methodology Retrospective, diagnostic or prognostic study, performed at one institution.

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