



Gadolinium retention in gliomas and adjacent normal brain tissue: association with tumor contrast enhancement and linear/macrocyclic agents

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Abstract

Purpose To quantitate gadolinium deposits in gliomas and adjacent normal brain specimens, and to evaluate their association with tumor contrast enhancement and the type of gadolinium-based contrast agent (GBCA) used.

Methods A total of 69 patients with primary glioma who underwent contrast-enhanced magnetic resonance imaging (MRI) prior to surgery were included in this retrospective study. Gadolinium was measured from histologically viable tumor, normal brain, and necrosis within the sample, when available, using inductively coupled plasma mass spectrometry (ICP-MS). Tumor contrast enhancement was categorized as none, minimal, or noticeable. Differences in gadolinium deposits by contrast enhancement and GBCA type were assessed.

Results Seven patients received linear GBCA and 62 macrocyclic, respectively. At the time of surgery, gadolinium deposits were detected in 39 out of 69 (57%) tumor samples, 8 out of 13 (62%) normal brain, and 12 out of 14 (86%) necrotic specimens. Gadolinium was detected in both enhancing and non-enhancing tumors, but was greatest in gliomas with noticeable enhancement ($p = 0.02$). Administration of linear agents gadodiamide and gadopentetate dimeglumine resulted in significantly higher tumor gadolinium relative to macrocyclic gadoterate meglumine ($p < 0.01$ and $p < 0.05$, respectively). Normal brain and necrosis also showed higher gadolinium after exposure to linear gadodiamide (both $p < 0.05$). In multivariate regression, GBCA type (linear/macrocyclic) was the most powerful predictor of tumor gadolinium retention ($p < 0.001$).

Conclusion Gadolinium can be detected in both enhancing and non-enhancing gliomas, neighboring normal brain, and necrosis. Gadolinium retention is higher after exposure to linear GBCAs compared with the macrocyclic gadoterate meglumine.

Keywords Gadolinium retention · Glioma · Contrast agent · Linear · Macrocyclic

Introduction

Gadolinium is a heavy metal employed by the standard contrast agents used for MRI due to its paramagnetic nature. Free gadolinium ion (Gd^{3+}), however, is highly toxic. To decrease its toxicity and increase elimination from the body, Gd^{3+} is bound to organic chelating agents. Chelators used in gadolinium-based contrast agents (GBCAs) can be classified as either linear or macrocyclic, of which the latter are superior in stability (especially the kinetic stability) [1]. In contrast, linear GBCAs have shown in vitro to release substantial amounts of free Gd^{3+} and are regarded as more unstable [2].

Deposition of gadolinium in the liver, kidney, and bone of mice and rats after exposure to linear GBCAs was reported already in the 1990s [3]. Nevertheless, both linear and macrocyclic GBCAs have been used in routine clinical practice for almost 30 years with no other serious adverse effects

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described than nephrogenic systemic fibrosis in patients with severe renal insufficiency [4].

In 2014, however, Kanda et al. demonstrated increased signal intensities in the dentate nucleus (DN) and globus pallidus (GP), attributed to deposition of gadolinium, on the T1-weighted (T1W) brain MR images of patients who had received multiple doses of linear GBCA and with normal renal function [5]. This association was supported by several other investigators [6–8], whereas administration of macrocyclic GBCAs, even at high doses, was not found to be related to increased signal intensity [9–11]. Finally, gadolinium deposition in the human brain after exposure to both linear and macrocyclic GBCAs was confirmed in autopsy specimens raising concern about the toxicity of the potential free gadolinium in the brain [12–14].

Several pathological conditions of the brain parenchyma such as tumor, infection, autoimmune disease, and ischemia may alter the integrity of the blood–brain barrier (BBB) resulting in contrast enhancement. Whereas gadolinium accumulation is predictable in diseased brain with disrupted BBB and contrast enhancement, gadolinium retention in brain abnormalities without evident BBB disruption or in adjacent normal brain has not previously been studied. Furthermore, despite the routine use of contrast MRI in brain tumor diagnostics, only one previous study has attempted to quantify gadolinium retention in brain tumors. Xia et al. visually detected gadolinium deposits in five out of 28 tumor samples using scanning electron microscopy/energy-dispersive X-ray spectroscopy (SEM/EDS) [15]. However, only linear GBCAs were used in this study and tumor contrast enhancement was not reported.

The purpose of this study was to quantitate gadolinium accumulation in viable tumor tissue and the neighboring normal-appearing brain in both enhancing and non-enhancing gliomas. Also, the aim was to study the association of gadolinium retention with the type and number of GBCA doses administered, tumor subtype, contrast enhancement, and patient renal function.

Materials and methods

This study was approved by the Ethics Committee of Auria Biobank (TYKS-SAPA, Turku University Hospital, Turku, Finland) and the Hospital District of Southwest Finland. All tissue samples were obtained from Auria Biobank, and in accordance with the Finnish Biobank Act (688/2012), a separate informed consent from individual patients was waived.

Patient selection

Adult patients with newly diagnosed supratentorial glioma (brainstem gliomas excluded) surgically resected or biopsied

at Turku University Hospital from January 2005 through December 2013 were retrospectively included. A total of 184 glioma patients were identified out of which 115 were excluded due to insufficient tissue material and/or unavailable pre-operative MR scan. Finally, 69 patients were included. Clinical data was collected from electronic patient records. Plasma creatinine level obtained nearest to the MR scan was used, and glomerular filtration rate (GFR) was calculated using the CKD-EPI equation with creatinine, age, gender, and race taken into consideration.

GBCA administration and tumor contrast enhancement on T1W MRI

Pre-operative MR scans were performed in Turku University Hospital, affiliated hospitals, or private clinics, in case of which all related scans were transferred to University Hospital PACS. Information on the GBCA used was retrieved from the Radiology Information System at University Hospital, PACS, or personal communication with the chief radiologists in affiliated hospitals and private clinics. Only GBCA exposures with evidence of the tumor on brain MRI were included in analyses.

Pre-operative MR images were analyzed by a radiologist with 7 years of experience (A.K.). Tumor contrast enhancement on T1WI was visually categorized into three separate groups: (1) no evidence of contrast enhancement, (2) minimal contrast enhancement defined as one or two small foci of enhancement while the gross majority of the solid tumor was non-enhancing, and (3) distinct/noticeable contrast enhancement.

Tissue samples

Formalin-fixed paraffin-embedded glioma samples were used to determine gadolinium concentration in three distinctive areas: (1) histologically viable tumor, (2) normal-appearing brain tissue when present in the sample, and (3) necrosis. A neuropathologist (M.G.) made annotations with a diameter of 1.5 mm to the most representative areas in the scanned hematoxylin and eosin slides using Panoramic Viewer software (3DHistech, Budapest, Hungary). Corresponding tissue cores from paraffin-embedded samples were then automatically obtained using a dedicated automatic microarrayer (TMA Grand Master, 3DHistech, Budapest, Hungary). Depending on the sample thickness, one to four cores per area were used for analyses. Tissue cores were deparaffinized with xylene and washed in serial dilutions of ethanol which was finally vaporized at room temperature. Deparaffinized tissue samples were weighted and used for gadolinium measurements using ICP-MS.

Gadolinium measurements using ICP-MS

First, 57 samples (42 tumor, 8 normal brain, 7 necrosis) were microwave digested in a mixture of 2.5 ml nitric acid and 0.5 ml hydrogen peroxide and a Teflon vessel was washed out with 50 ml deionized water resulting in relatively low concentrations (average weight of tumor samples 3.3 mg). Therefore, the remaining 40 samples (27 tumor, 6 normal brain, 7 necrosis) were digested by heating the mixture of tissue, 0.5 ml nitric acid, and 0.1 ml hydrogen peroxide up to 100 °C in a glass bottle and washed out with 5 ml deionized water.

Samples were analyzed by ICP-MS (PerkinElmer Sciex Elan 6100 DRC Plus, Waltham, MA, USA) using the following parameters: sweeps/reading = 10, readings/replicate = 1, number of replicates = 7, scan mode = peak hopping, MCA channels = 1, dwell time = 100.0 ms, and integration time = 1000 ms. In addition to gadolinium (mass = 157.924), also rhodium (mass = 102.905) was analyzed and used as an internal standard. Multi-standard 101 was used as a calibration standard for gadolinium (conc. 1, 2.5, 5.0, 10, 25, 50 ppb). The limit of detection was set at 33% relative standard deviation (RSD) to reckon the low gadolinium concentration in the first set of analyses [16]. Measurements with an RSD above 33% were regarded as gadolinium concentration of zero.

The radiologist, neuropathologist, and laboratory personnel were all blinded to the type of GBCA administered at the time of MRI evaluation, tissue analysis, and ICP-MS measurements, respectively.

Glioma classification

The molecular profile of the glioma samples including IDH1 and IDH2 mutation (immunohistochemistry and DNA sequencing), 1p19q codeletion (fluorescent in situ hybridization), and ATRX and p53 mutation (immunohistochemistry) were analyzed, and with all the molecular data available, gliomas were re-assessed by a neuropathologist (M.G.) and diagnosed according to the new WHO 2016 classification.

Statistics

Gadolinium concentration is reported as medians, minimum–maximum range, 25th percentile (P_{25}^{th}), and 75th percentile (P_{75}^{th}) due to the non-normal distribution of the data. Differences on gadolinium concentration by diagnosis, tumor contrast enhancement, and number of GBCA doses administered were assessed with Kruskal–Wallis test. The Mann–Whitney U test was used for pairwise comparisons using the Bonferroni correction when appropriate. Correlations between gadolinium in the tumor and MRI–operation interval, GFR, and gadolinium in normal brain and necrosis were assessed by using the Spearman rank correlation

coefficient. A linear multivariate regression analysis was performed to evaluate the significance of contrast enhancement, GBCA type, and GBCA–operation interval to predict gadolinium content. Two-tailed p values < 0.05 were regarded as significant. All statistical analyses were conducted using the IBM SPSS Statistics version 23.0 for Mac (IBM Corp., Armonk, NY, USA).

Results

Baseline patient, tumor, and MRI characteristics

Primary glioma samples from 69 patients were included (28 glioblastomas, 27 diffuse astrocytomas, and 14 oligodendrogliomas; Table 1). Viable tumor tissue was obtained from all 69 samples, normal brain from 14 samples, and necrosis from 14 glioblastomas. One normal brain sample was excluded since the patient had received three doses of gadopentetate dimeglumine 11 years earlier (without evidence of brain tumor on MRI). This may affect gadolinium deposition in the normal brain and would influence the analyses since at the time of glioma diagnosis the patient received gadoterate meglumine only. Finally, 13 normal brain samples were analyzed.

All glioblastomas showed distinct contrast enhancement whereas in diffuse gliomas the enhancement was more variable. Gadoterate meglumine (Dotarem, Guerbet, Villepinte, France) was used in 60 patients, gadobutrol (Gadovist, Bayer, Whippany, NJ, USA) in two, gadodiamide (Omniscan, GE Healthcare, Chicago, IL, USA) in four, and gadopentetate dimeglumine (Magnevist, Bayer, Whippany, NJ, USA) in three patients, respectively. Linear GBCAs were administered during 2006–2009 and macrocyclic agents 2005–2013. Sixty patients received only one GBCA dose, and nine patients received two to three doses (exclusively gadoterate meglumine) prior to surgery and with evidence of the tumor occurring in the brain MRI. The mean interval between the last GBCA administration and operation was 24 days (range 1–104 days). None of the patients suffered from renal failure.

Gadolinium is detected both in enhancing and non-enhancing gliomas

Gadolinium was detected in 39 out of 69 (57%) tumor samples. Gadolinium retention was most common in glioblastomas, however, without significant difference among diagnoses. In contrast, gadolinium retention associated with contrast enhancement (chi-square $p = 0.04$, Table 2). Gadolinium was significantly higher in gliomas with noticeable contrast enhancement compared to non-enhancing gliomas ($p = 0.02$, Fig. 1). However, it should be noted that 7 out of 21 (33%)

Table 1 Patient, tumor, and MRI characteristics

	Glioblastoma		Astrocytoma		Oligodendroglioma
	IDHwt	IDHmut	IDHwt	IDHmut	1p19q-codeleted, IDHmut
<i>n</i> (total 69)	25	3	7 ^a	20	14 ^b
Age (years) ^c	61	58	62	48	45
Grade					
IV	25 (100%)	3 (100%)			
III			5 (71%)	9 (45%)	4 (29%)
II			2 (29%)	11 (55%)	10 (71%)
Contrast enhancement					
None	0	0	4 (57%)	11 (55%)	6 (43%)
Minimal	0	0	1 (14%)	3 (15%)	3 (21%)
Noticeable	25 (100%)	3 (100%)	2 (29%)	6(30%)	5 (36%)
No. of GBCA MRIs					
1	22 (88%)	3 (100%)	5 (72%)	19 (95%)	11 (79%)
2	2 (8%)	0	1 (14%)	1 (5%)	3 (21%)
3	1 (4%)	0	1 (14%)	0	0
GBCA used ^d					
Gadoterate meglumine	20 (80%)	2 (67%)	7 (100%)	18 (90%)	13 (93%)
Gadobutrol	0	0	0	1 (5%)	1 (7%)
Gadodiamide	3 (12%)	0	0	1 (5%)	0
Gadopentetate dimeglumine	2 (8%)	1 (33%)	0	0	0
Interval GBCA—operation (days) ^c	16	8	25	27	16
GFR, ml/min (range) ^c	91 (60–131)	102 (85–111)	100 (62–140)	107 (70–137)	108 (82–131)

IDH isocitrate dehydrogenase, *IDHwt* IDH-wild type, *IDHmut* IDH-mutant

^a Includes one astrocytoma NOS grade 2

^b Includes two oligodendrogliomas NOS grade 2

^c Expressed as median values

^d Latest preoperative contrast MRI

patients with non-enhancing gliomas showed detectable gadolinium (Fig. 2). Among these, six had received gadoterate meglumine and one gadobutrol, respectively. The routinely

used dosage of GBCAs was 0.2 ml/kg. For four patients with one GBCA MRI, the dosage was 0.1 ml/kg. No difference in gadolinium retention was detected with regard to the dose

Table 2 Gadolinium retention in tumor, normal brain, and necrotic tissue according to tumor contrast enhancement (CE) in T1W MRI (gadolinium concentrations $\mu\text{g}/\text{kg}$ reported as median; min–max range; 25th percentile; 75th percentile)

Gadolinium deposits	No CE <i>n</i> = 21	Minimal CE <i>n</i> = 7	Noticeable CE <i>n</i> = 41
Tumor, <i>n</i>			
Yes	7 (34; 15–824; 32; 373)	5 (54; 9–1648; 20; 983)	27 (123; 12–3549; 68; 349)
No	14	2	14
Normal brain, <i>n</i>			
Yes	2 (32–403)	2 (31–308)	4 (193; 13–447; 16; 425)
No	3	1	1
Necrosis, <i>n</i>			
Yes	na	na	12 (512; 31–15,012; 136; 1819)
No	na	na	2

na not applicable, necrosis only in glioblastomas with noticeable CE

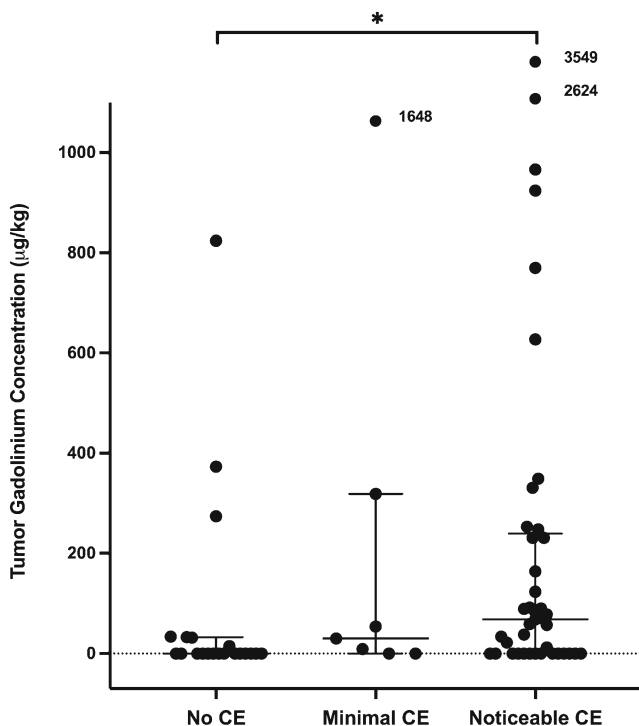


Fig. 1 Levels of tumor gadolinium by contrast enhancement (CE) on T1W MRI. Gadolinium concentration is significantly higher in noticeably enhancing gliomas compared to non-enhancing gliomas ($*p = 0.02$). Three outliers are distinguished with their gadolinium concentration. Data points are shown with medians and interquartile ranges

($p = 0.62$), GFR value ($p = 0.17$), or number of GBCA doses administered ($p = 0.34$; gadoterate meglumine was exclusively used in patients receiving multiple GBCA doses).

Gadolinium retention in gliomas is related to linear GBCAs

As presented in Fig. 3, significantly higher gadolinium concentrations were detected in tumors after administration of linear gadodiamide (median 627 $\mu\text{g}/\text{kg}$, range 319–2624 $\mu\text{g}/\text{kg}$, P_{25}^{th} 322 $\mu\text{g}/\text{kg}$, P_{75}^{th} 2199 $\mu\text{g}/\text{kg}$, $n = 4$; $p = 0.002$) and linear gadopentetate dimeglumine (median 349 $\mu\text{g}/\text{kg}$, range 164–3549 $\mu\text{g}/\text{kg}$, $n = 3$, $p = 0.03$) when compared with the macrocyclic gadoterate meglumine (median 4.5 $\mu\text{g}/\text{kg}$, range 0–1648 $\mu\text{g}/\text{kg}$, P_{25}^{th} 0 $\mu\text{g}/\text{kg}$, P_{75}^{th} 82 $\mu\text{g}/\text{kg}$, $n = 60$). No difference in tumor gadolinium was measured between the two linear agents or gadobutrol (range 34–627 $\mu\text{g}/\text{kg}$, $n = 2$) and other GBCAs. A negative correlation was found between tumor gadolinium concentration and the time interval between MRI and operation (Spearman's $\rho = -0.28$, $p = 0.02$).

For the purpose of linear multivariate regression, GBCA type was analyzed as macrocyclic (gadoterate meglumine and gadobutrol) or linear (gadodiamide and gadopentetate

dimeglumine). Linear regression was calculated to predict tumor gadolinium concentration (dependent variable) based on age, sex, tumor contrast enhancement, GBCA type, and MRI–operation interval (independent variables). Thirty one percent of the tumor gadolinium variance could be explained by the predictors ($R^2 = 0.312$). GBCA type (macrocyclic versus linear) was the only significant predictor of tumor gadolinium concentration, which was 1042 $\mu\text{g}/\text{kg}$ higher with linear compared with macrocyclic agents ($p < 0.001$, unstandardized coefficient 1042 $\mu\text{g}/\text{kg}$, 95% CI 628–1457 $\mu\text{g}/\text{kg}$).

Gadolinium retention in normal brain and necrosis is higher after exposure to linear gadodiamide

Gadolinium was detected in 8 out of 13 (62%) samples of histologically normal appearing brain (Table 2) with a significant correlation between gadolinium concentrations in the tumor and normal brain (Spearman's $\rho = 0.65$; $p = 0.016$; $n = 13$). Of these eight patients with gadolinium detected in the normal brain, two had received linear gadodiamide and six macrocyclic gadoterate meglumine, respectively. As shown in Fig. 4, gadolinium concentration in normal brain was significantly higher after exposure to linear gadodiamide (range 361–447 $\mu\text{g}/\text{kg}$, $n = 2$) compared with macrocyclic gadoterate meglumine (median 13 $\mu\text{g}/\text{kg}$, range 0–403 $\mu\text{g}/\text{kg}$, P_{25}^{th} 0 $\mu\text{g}/\text{kg}$, P_{75}^{th} 32 $\mu\text{g}/\text{kg}$; $n = 11$; $p = 0.04$).

Gadolinium retention was also detected in 12 out of 14 (86%) necrotic tissue samples (Table 2) with a significant correlation between gadolinium concentration in the tumor and necrosis (Spearman's $\rho = 0.66$; $p = 0.01$; $n = 14$). Necrosis gadolinium was significantly higher after exposure to linear gadodiamide (median 2852 $\mu\text{g}/\text{kg}$, range 639–15,012 $\mu\text{g}/\text{kg}$, $n = 3$) compared with macrocyclic gadoterate meglumine (median 118 $\mu\text{g}/\text{kg}$, range 0–1518 $\mu\text{g}/\text{kg}$, P_{25}^{th} 16 $\mu\text{g}/\text{kg}$, P_{75}^{th} 348 $\mu\text{g}/\text{kg}$; $n = 9$) as presented in Fig. 5 ($p = 0.04$). No difference in necrosis gadolinium was measured between gadoterate meglumine and gadopentetate dimeglumine (range 1734–1847 $\mu\text{g}/\text{kg}$, $n = 2$), or the two linear agents.

No significant difference in gadolinium concentrations were detected between tumor and normal brain, or tumor and necrosis, when comparing the concentrations within patients that had either normal brain ($n = 13$) or necrotic tissue samples ($n = 14$) available, respectively. Three patients had all three tissue specimens available. No significant difference, however, was detected in gadolinium concentrations between tumor, normal brain, and necrosis within the three patients.

Discussion

Gadolinium deposited in both enhancing and non-enhancing gliomas with the highest concentrations detected among

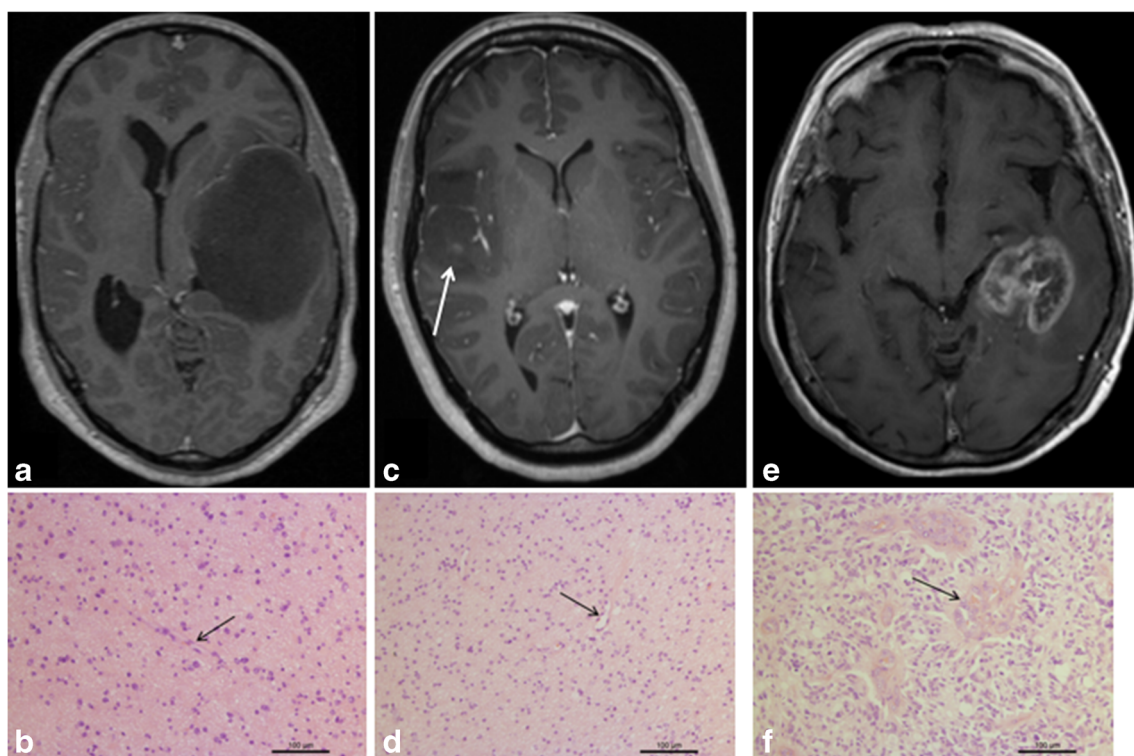


Fig. 2 Representative images of contrast-enhanced T1W MRI and corresponding H&E stainings ($\times 200$ magnification). **a** Astrocytoma, IDH-mutant grade II with no contrast enhancement on MRI and **b** no signs of endothelial proliferation in tumor vessels (black arrow). **c** Oligodendroglioma, IDH-mutant, and 1p19q-codeleted grade II with a minor focus of enhancement (white arrow) but **d** H&E showing thin-

walled tumor vessels and no signs of endothelial proliferation. **(e)** Glioblastoma IDH-wild type with noticeable contrast enhancement and **(f)** tumor vasculature showing endothelial proliferation with multiple layers of endothelial cells and glomeruloid structures within tumor vessels (black arrow). Gadolinium was detected in each of these tumors

tumors with gross enhancement on T1W MRI. Gadolinium was not only found in the viable tumor tissue but also in the normal-appearing adjacent brain and necrotic tissue, with a positive correlation between the amounts deposited in the tumor and normal brain or necrosis. Gadolinium retention was significantly higher after administering linear GBCAs compared with macrocyclic gadoterate meglumine. In multivariate regression analysis, GBCA type (macrocyclic versus linear) was the only significant predictor of tumor gadolinium concentration.

To date, five postmortem studies have demonstrated the pathologic accumulation of gadolinium in the human brain after exposure to linear [12, 13, 17, 18] or macrocyclic [14, 18] GBCAs. None of the studies, however, included decedents who had received gadoterate meglumine that was the most common GBCA used in our cohort of glioma patients. While the highest gadolinium concentrations were detected in DN and GP, two of these studies additionally showed small but measurable concentrations in the brain cortex and white matter suggesting more widespread low-level gadolinium retention in brain parenchyma than just the posterior fossa and basal ganglia [13, 14]. Our results are in line with this and further support the notion of gadolinium retention in small quantities in brain parenchyma

of other regions than DN and GP after administration of both linear and macrocyclic agents.

Autopsy studies have shown that gadolinium deposition in the posterior fossa and basal ganglia is not limited to patients with intracranial abnormalities but can also be detected in patients with normal brains at the time of autopsy [17, 18]. Several mechanisms of this gadolinium transit and retention in brain regions without impaired BBB have been suggested including active metal transporters [19, 20], passage from the cerebrospinal fluid [21–23], and brain glymphatic system [24]. The exact mechanism behind the retention, however, remains unsolved. While the brain tumor provides an obvious explanation for gadolinium retention, we additionally found gadolinium deposits in the adjacent normal brain. Furthermore, a small but significant correlation between the amount of gadolinium in the tumor and normal brain was detected implying passage of gadolinium from the site of pathologic brain lesion. While further studies are needed to confirm this association, an interesting question arises whether gadolinium traverses from the region of brain lesion to neighboring sites in other brain abnormalities such as ischemia, infection, or multiple sclerosis.

Gadolinium concentration was significantly higher in both the tumor tissue and normal brain, as well as in

Drugs Administration requires warning labeling to all GBCAs [32]. Our study elucidates gadolinium retention in brain tumors and surrounding normal tissue with an implication of higher retention associated with linear agents.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent For this type of retrospective study formal consent is not required.

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