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Brain tumours at 7T MRI compared to 3T—contrast effect after half and full standard contrast agent dose: initial results

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Abstract

Objectives—To compare the contrast agent effect of a full dose and half the dose of gadobenate dimeglumine in brain tumours at 7 Tesla (7T) MR versus 3 Tesla (3T).

Methods—Ten patients with primary brain tumours or metastases were examined. Signal intensities were assessed in the lesion and normal brain. Tumour-to-brain contrast and lesion enhancement were calculated. Additionally, two independent readers subjectively graded the image quality and artefacts.

Results—The enhanced mean tumour-to-brain contrast and lesion enhancement were significantly higher at 7T than at 3T for both half the dose (91.8 ± 45.8 vs. 43.9 ± 25.3 [$p=0.010$], 128.1 ± 53.7 vs. 75.5 ± 32.4 [$p=0.004$]) and the full dose (129.2 ± 50.9 vs. 66.6 ± 33.1 [$p=0.002$], 165.4 ± 54.2 vs. 102.6 ± 45.4 [$p=0.004$]). Differences between dosages at each field strength were also significant. Lesion enhancement was higher with half the dose at 7T than with the full dose at 3T ($p=.037$), while the tumour-to-brain contrast was not significantly different. Subjectively, contrast enhancement, visibility, and lesion delineation were better at 7T and with the full dose. All parameters were rated as good, at the least.

Conclusion—Half the routine contrast agent dose at 7T provided higher lesion enhancement than the full dose at 3T which indicates the possibility of dose reduction at 7T.

Keywords

7 Tesla MRI; Contrast media; Brain tumour; Gadolinium effect; High-field MRI

Introduction

Contrast-enhanced magnetic resonance imaging (CE-MRI) is the accepted method of choice for diagnostic imaging of primary brain tumours and cerebral metastases [1], with a standard intravenous dose of 0.1 mmol/kg gadolinium-based contrast agents for MR systems up to 3 Tesla (3T) [2].

The introduction of clinical MRI operating at a static magnetic field of 7 Tesla (7T) [3, 4], with increasing availability in the near future, mandates the adjustment of MR protocols for these ultra-high-field units. This includes optimization of contrast-enhanced MR imaging.

Several studies at various field strengths [5–8] have reported an increase in contrast agent effects at higher field strength in brain tumours, compared to a lower field [5–8]. A better tumour-to-brain contrast following gadolinium administration in a higher magnetic field is

of clinical importance for routine examinations of brain tumours: studies on MR systems up to a static magnetic field of 3T indicate that a reduction of the contrast agent dose might potentially be possible at high field strength [7]. To the best of our knowledge, no studies have been published comparing contrast enhancement of primary brain tumours or metastases on 7T MRI images with 3T MRI images.

The present study was, therefore, designed to evaluate the contrast agent effect of half the standard dose (0.05 mmol/kg body weight) and a standard dose (0.1 mmol/kg) of MRI contrast agent in the evaluation of brain tumours, using a clinical research-oriented, whole-body 7T MR unit, with special attention to the value of this ultra-high-field strength relative to 3T as a standard of reference.

Materials and methods

Institutional ethical committee approval was obtained, and, after written, informed consent, ten consecutive patients were included (six males, and four females), with a mean age of 54 ± 15.8 years (range, 28-74 years). Patients were included in the prospective study if they fulfilled the following criteria: they were adult, had a suspected primary brain tumour or metastasis, and they were scheduled for resection or biopsy at the department of neurosurgery and needed a presurgical MRI of the brain. Furthermore, included patients had no contraindications against MRI or intravenous contrast agent administration (including renal function, with a glomerular filtration rate (GFR) of >60 ml/min in all patients, assessed by calculation from an actual blood creatinine value), and they were clinically stable. Exclusion criteria were impaired compliance during the examination or if the two different MR investigations could not be performed before the scheduled neurosurgical procedure. All included patients finished the protocol. Final histology revealed meningioma ($n=2$), grade IV glioblastoma ($n=2$), lymphoma ($n=2$), and metastases ($n=2$), an anaplastic astrocytoma ($n=1$), and a hemangiopericytoma ($n=1$).

All patients were examined on both a 7 Tesla (Magnetom Siemens Healthcare, Erlangen, Germany) and a 3 Tesla (TIM TRIO, Siemens Healthcare, Erlangen, Germany) MR whole-body system, with a time interval of at least 24 hours between the examinations. A dedicated 32-channel head coil was used at 7T (In Vivo, Gainesville, FL, USA) and at 3T (Siemens, Healthcare, Erlangen, Germany). The protocol included isotropic 3D GRE sequences with magnetization preparation (MP-RAGE), acquired in sagittal, but reconstructed in axial slices. The measurement sequence parameters at 3T were as follows: orientation sagittal, TR/TE/TI 2190/3.02/1300 ms; FOV 250×250 mm; matrix size 320×307 pixels; phase encoding 96 %; a nominal in-plane resolution of 0.78×0.81 mm; slice thickness 0.8 mm; number of slices 192; pixel bandwidth 180 Hz/pix; no parallel imaging acceleration; number of averages 1; and measurement duration 11 min 16 sec. Data were subsequently reconstructed in the axial orientation with a slice thickness of 2 mm, and the number of slices was 65.

The measurement sequence parameters for 7T were: TR/TE/TI 3800/3.55/1700 ms; FOV 230×230 mm; matrix size 320×307 pixels; a nominal in-plane resolution 0.71×0.75 mm; slice thickness 0.7 mm; number of slices 224; pixel bandwidth 96 Hz/pix; parallel imaging

using GRAPPA [9] with a factor of 2 with phase encoding reference lines 24; number of averages 1; and a measurement duration of 7 min 58 sec. Subsequently, data were reconstructed in the axial orientation, with a slice thickness of 2 mm, and the number of slices was 71.

Gadobenate dimeglumine (Gadolinium- BOPTA, Multihance, Bracco Diagnostics, Inc., Princeton, NJSpA, Milan, Italy) was administered intravenously in a bolus fraction of 0.05 mmol/kg body weight (“half dose”) twice, which resulted in a final cumulative standard dose of 0.1 mmol/kg (“full dose”). The sequences were performed before, and were repeated ten minutes after, the administration of half the dose, and immediately after the cumulative full contrast agent dose. After each examination, the images were observed for potential immediate clinical consequences, and results for the 3T MRI were routinely reported immediately after the examination and independent of the study evaluation.

Study evaluation

For quantitative evaluation, signal intensities by region of interest (ROI) measurements in the lesion and the contralateral normal white matter were assessed, with ROIs placed identically on all series of images in each of the patients.

The tumour-to-brain contrast ($R_{L,B}$) on the unenhanced and the enhanced images, and the enhancement of the lesion (E_L), were calculated with the following equations:

$R_{L,B} [\%] = \frac{S_L - S_B}{S_B} \cdot 100$, and $E_L [\%] = \frac{S_L - S_{L0}}{S_{L0}} \cdot 100$, with S_{L0} and S_L taken as the signal intensity of an ROI assessed over a lesion before (S_{L0}) and after (S_L) contrast agent administration, and S_B taken as the signal intensity assessed over the contralateral white matter.

Qualitative assessment was performed on-screen by two independent readers (S.T., 25 years of experience; N-H. I-M., 16 years of experience), who were blinded to the patient name, field strength, and contrast agent dose. The evaluation included parameters concerning the lesion (visibility, delineation, contrast agent enhancement of the lesion), and general image quality of the sequence (grey-white-differentiation, homogeneity, and overall quality of the sequence), rated on a ten-point scale, from 0 (non-diagnostic), to 10 (excellent). The presence of artefacts (motion, susceptibility, and pulsation artefacts) was also assessed on a ten-point-scale, with 0 (non-diagnostic images), to 10 (no artefacts). In image sets for which different points were assigned, mean values were calculated. One reader performed the grading twice, with a time interval of six weeks between gradings.

For statistical analysis, all computations were performed using IBM SPSS Statistics version 19.0. Metric data are presented using mean $\pm$ standard deviation. In order to compare average tumour-to-brain contrast, the lesion enhancement, and the subjective evaluation for the full and half dose, as well as for 3T and 7T, two-way ANOVAs for repeated measures were performed. For comparison between each group at each scanner, additional Wilcoxon matched-pairs signed ranks tests were performed. In order to avoid an increasing error of the second type, no multiplicity corrections were performed. A p -value of .05 was considered

to indicate statistically significant results. The inter-rater and intra-rater agreements were assessed by calculation of kappa coefficients.

Results

Quantitative assessment was performed in all patients. The tumour-to-brain contrast values after a half and a full contrast agent dose are demonstrated in Fig. 1. Overall, the differences between 3T and 7T were significant; as well as the differences between half the dose and the full dose. As shown in Table 1, the Wilcoxon matched-pairs signed ranks tests showed pairwise significant differences. At each field strength, the mean values differed significantly for the half (0.05 mmol/kg) vs. the full (0.1 mmol/kg) dose, with higher tumour-to-brain contrast after the administration of a full dose ($p=.001$ at 3T, and $p=.002$ at 7T). In addition, significantly higher tumour-to-brain ratios were found after half the dose at 7T, compared to half the dose at 3T ($p=.010$). The same was true for the full routine dose ($p=.002$). The tumour-to-brain contrast after the application of 0.05 mmol/kg at 7T was not significantly different from that achieved by 0.1 mmol/kg at 3T ($p=.386$). The significant interaction ($p=.037$) indicates that the difference in average tumour-to-brain contrast between a full and a half dose is larger for 7T than for 3T.

Similar results were found for the Gd-enhancement of the lesion, as shown in Fig. 2. The mean lesion enhancement after half the contrast agent dose was higher at 7T, compared to 3T, as well as after the full dose (Table 2). Also, at both field strengths, the full dose led to significantly higher enhancement than half the dose. The lesion enhancement after the application of 0.05 mmol/kg at 7T was significantly higher than 0.1 mmol/kg at 3T ($p=0.037$). Examples are provided in Figs. 3 and 4.

Qualitative assessment was performed in 9/10 patients. In 1/10 patients, motion artefacts due to compliance reasons during the first examination did not allow a reliable, subjective comparison.

The subjective impression of contrast enhancement, and the visibility and delineation of the lesion were rated higher after the application of the full contrast agent dose, compared to half the dose, on both field strengths. The same parameters were rated better at 7T, compared to 3T, at each given contrast agent dose. All parameters concerning either the lesion or the overall image quality were rated six or higher. Susceptibility and pulsation artefacts were considered worse at 7T, compared to 3T. Apart from one patient, in whom motion and susceptibility artefacts were considered moderate, all artefacts were graded mild or absent. None of the other parameters were statistically significantly different. Apart from rating of pulsation artefacts, the inter-rater agreement was good to excellent (ICC 0.7). The intra-rater agreement was good or excellent for all parameters. Mean values are provided in Table 3.

Discussion

To date, contrast-enhanced MRI is the recommended state-of-the art method for brain tumour imaging [1], with MR protocols optimized for systems up to 3T. The increasing availability of clinical 7T MR units in the future mandates the need for protocol adjustments

for ultra-high field strength. Comparing the contrast effect of a Gd-based contrast agent in patients with brain tumours at 3T and 7T MRI, we found both significantly higher tumour-to-brain contrast and lesion enhancement at 7T, compared to 3T. These objective results were confirmed by blinded subjective image evaluation. Our in vivo results are in line with previous studies comparing lower field strengths. In a brain tumour animal model [10], higher contrast efficacy was found at 3T compared to 1.5T. The contrast effect of Gd in patients with brain tumours was also greater at 1.5T vs. 0.3T [5], at 2T vs. 0.5T. [6], and at 3T vs. 1.5T [7, 8], using either Gd-DTPA [6, 7] or Gd-DTPA-BMA [5, 8].

A greater contrast effect of Gd at the higher field strength can be explained by the fact that, on contrast-enhanced images, the T1 relaxation of a given tissue is influenced by multiple parameters. Two essential factors are the intrinsic T1 relaxation rate of the tissue and the relaxivity r_1 of the gadolinium-based contrast agent. For semisolid tissues, the intrinsic longitudinal (or spin-lattice) relaxation rate ($R_1=1/T_1$) decreases with increasing field strength. An R_1 reduction of 20 % to 30 % has been observed at 3.0T compared to 1.5T [11]. This corresponds to an increase in the T1 relaxation time of between 35 % and 40 % [12]. On the other hand, the nuclear magnetic relaxation dispersion or relaxivity r_1 of paramagnetic gadolinium-based contrast agents, described by the Solomon-Bloembergen-Morgan equation, is also lower at higher magnetic field strengths [13, 14], which was well-known in vitro for field strengths up to 4.7T [15–17] and has been recently demonstrated for 7T, compared to 3T [18].

It has been assumed that, although both the relaxation rate (R_1) of the tissue and the relaxivity (r_1) of the contrast agent decrease with increasing field strength, this correlation is not linear [7, 8, 19]. The additional shortening by contrast agent application seems to produce lower contrast at 3T than at the higher magnetic field of 7T.

As expected, in our study, the contrast effect was also higher for the full routine dose, compared with half the dose at both field strengths in both objective and subjective evaluations. In the past, several studies have assessed the diagnostic performance of contrast-enhanced brain tumour MR imaging with different contrast agent doses. To date, a standard contrast agent dose of 0.1 mmol/kg is recommended at field strengths up to 1.5T [2], although favourable results have been found with double (0.2 mmol/kg) or even triple doses [4, 6, 20–23]. It is also known that higher contrast agent doses are required at low-field MRI, such as 0.2T [24].

Conversely, several studies assessed whether it was possible to reduce the contrast agent dose at higher field strengths. Promising results were reported for 3T, compared to 1.5T [7], where half the standard dose of Gd-DTPA produced even higher contrast at 3T as compared to that obtained by the full standard dose at 1.5T. In our study, the application of half the dose (0.05 mmol/kg) of contrast agent at 7T also led to a contrast effect that was not significantly different from that obtained at the full routine dose (0.1 mmol/kg) at 3T. The lesion enhancement even was higher after half the dose at 7T ($p=0.037$) than after the full dose at 3T.

In our small patient series, subjective lesion visibility and delineation, as well as contrast enhancement, were rated “good” or better for both the half dose and the full standard dose at both field strengths.

Our preliminary results, therefore, indicate that a reduction of the contrast agent dose is potentially possible at ultra-high field strength. This must be further tested in larger patient studies.

Limitations

Our study should be classified as preliminary, with a small number of patients, in which none suffered from a tumour of the skull base or brain stem. Further studies are necessary to assess the clinical utility of 7T brain tumour imaging in larger patient populations.

Another issue to be addressed is the fact that the ROIs were placed subjectively in the quantitative evaluation. However, the ROI assessment of the different sequences within one examination could be kept identical by use of the copy and paste function. For the second examination, identical ROI placement was attempted by visual comparison with the first examination.

Due to imaging time availability, all but one patient was first examined at 7T. Such an order of examinations could potentially lead to better results, i.e., higher tumour-to brain contrast, at 3T. However, a time interval of one day has been found to be sufficient to allow excretion of >95 % of the agent [25].

In addition, in our study, the full dose imaging was performed after the cumulative application of two half doses, raising a question about the potential influence of the prolonged time interval of the first half dose. However, several studies have shown that, even with primary full dose injection, after an immediate signal intensity increase, only minor quantitative changes are observed on delayed images [2, 26, 27]. Our measurement times are within the time range before the signal decrease that was reported to occur no earlier than 45 min post injection [26, 27].

Another limitation is the fact that we tested one contrast agent only. We used gadobenate dimeglumine for the following reasons. Several studies have shown the superior relaxivity of Gd-chelates with higher protein binding capacity, relative to other Gd-chelates both in vitro [16–18], including one study on 3T and 7T [18], and in vivo, including in animal models [10, 28] and brain tumour patients [29, 30].

The clinical utility of contrast-enhanced 7T MRI in brain tumours with only minor contrast enhancement was not specifically tested. Especially for those tumours, future studies have to show whether and to what extent a reduction in the contrast agent dose at high-field MRI is also possible, or whether improved detectability can be achieved by the use of a higher static magnetic field strength.

In summary, we could show that the tumour-to-brain contrast and the lesion enhancement after the administration of Gd-BOPTA was significantly higher at 7T than at 3T. Half the

standard contrast agent dose at 7T led to a contrast effect comparable to that obtained with the full standard dose at 3T.

Our results, thus, show that a standard contrast agent dose can be implemented at 7T. As brain tumour patients require repetitive MR examinations, a contrast agent dose reduction would be desirable, and our results suggest that even halving the dose without loss of tumour-to-brain contrast is potentially possible with 7T.

Future studies with larger patient numbers must determine (1) to what extent the dose can be reduced at 7T without the loss of diagnostic information, or (2) whether there are indications where it would be advantageous to maintain a standard dose and to gain better visibility of lesions with minor contrast enhancement.

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Institutional Review Board approval was obtained. Written informed consent was obtained from all subjects (patients) in this study. Study subjects or cohorts have not been previously reported. Methodology: prospective, experimental, performed at one institution.

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Key Points

- The contrast effect of gadobenate dimeglumine was assessed at 7T and 3T.
- In brain tumours, contrast effect was higher at 7T than at 3T.
- Tumour-to-brain contrast at 7T half dose and 3T full dose were comparable.
- 7T half dose lesion enhancement was higher than 3T full dose enhancement.
- Our results indicate the possibility of contrast agent dose reduction at 7T.

Fig. 1.

The tumour-to-brain contrast values [%] after a half and a full contrast agent dose, at 3T and at 7T (patients and means)

Fig. 2.
The signal enhancement of the lesion [%] after a half and a full contrast agent dose, at 3T and at 7T (patients and means)

Fig. 3.

A 53-year-old female patient with a meningioma in the left temporal lobe. A-C show T1w MRI at 3T: **a** before the application of contrast agent; **b** after the application of contrast agent at a dosage of 0.05 mmol/kg (« half dose »); and **c** after 1 mmol/kg (« full dose ») of the agent. The enhancement and lesion-to-brain contrast were more pronounced after 1 mmol/kg of the agent. The same was true for 7T: **d** pre-contrast T1w image; **e** after 0.05 mmol/l; and **f** after 1 mmol/kg. For each dose, the enhancement was higher at 7T compared to 3T, whereas the results for half the dose at 7T and the full dose at 3T were not significantly different

Fig. 4.

A 51-year-old female patient with anaplastic astrocytoma. 3T MRI (**a-c**) and 7T MRI (**d-f**) showed an enhancing lesion in the right frontal lobe after half the routine contrast agent dose (**b, e**) and after a full dose (**c, f**), compared to the precontrast series (**a, d**). The lesion-to-brain contrast and enhancement were more pronounced after the full dose, and at the higher field strength

Table 1The tumour-to-brain-contrast post $Gd(R_{L,B})$

Contrast agent dose	3 Tesla	7 Tesla	
0.05 mmol/kg	43.9 (± 25.3)	91.8 (± 45.8)	p=0.010
0.1 mmol/kg	66.6 (± 33.1)	129.2 (± 50.9)	p=0.002
	p=0.004	p=0.002	

Values are means $\pm$ standard deviation [%]

Table 2The signal enhancement of the lesion (E_L %)

Contrast agent dose	3 Tesla	7 Tesla	
0.05 mmol/kg	75.5 (± 32.4)	128.1 (± 53.7)	p=0.004
0.1 mmol/kg	102.6 (± 45.4)	165.4 (± 54.2)	p=0.004
	p=0.020	p=0.002	

Values are means $\pm$ standard deviation [%]

Table 3

Subjective grading

		3 Tesla		7 Tesla		p	
Contrast agent dose (mmol/kg)		0.05	0.1	0.05	0.1	Field strength	dose
lesion related parameters *	contrast agent enhancement	8.1±1.1	8.9±0.7	9.1±0.6	9.7±0.4	.009	.001
	visibility	8.6±0.9	9.1±0.6	9.1±0.7	9.7±0.4	.001	.002
	delineation	8.6±0.8	9.1±0.6	9.2±0.6	9.7±0.3	.002	.003
image quality *	gray-white-differentiation	7.9±0.7	7.9±0.6	7.8±0.8	8.3±0.7	.415	.258
	homogeneity	9.1±0.5	8.9±0.7	8.7±0.4	8.8±0.4	.213	.523
	overall sequence quality	9.2±0.4	8.9±0.7	8.4±1.1	8.7±0.6	.089	.787
artifacts °	motion	9.0±0.4	8.6±0.9	7.8±1.8	8.4±1.1	.149	.409
	susceptibility	9.0±0.6	9.1±0.5	7.9±1.4	8.1±1.0	.016	.428
	pulsation	9.4±0.2	9.4±0.3	8.7±1.0	8.8±0.9	.041	.412

* 10-point scale (from 0 = non-diagnostic, to 10 = excellent)

° 10-point scale for artifacts (from 0 = non-diagnostic images, to 10 = no artifacts)