Are there differences between macrocyclic gadolinium contrast agents for brain tumour imaging? Results of a multicenter intra-individual crossover comparison of gadobutrol with gadoteridol (The TRUTH study)

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Authors: E. Bültmann¹, K. R. Maravilla², M. P. Smith³, S. Bastianello⁴, T. Hirai⁵, T. Frattini⁶, C. Colosimo⁷, G. Pirovano⁸; ¹Hannover/DE, ²Seattle, WA/US, ³Boston, MA/US, ⁴Pavia/IT, ⁵Kumamoto/JP, ⁶Como/IT, ⁷Rome/IT, ⁸Monroe, NJ/US
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Aims and objectives

Gadobutrol (Gadovist/Gadavist; Gd-BT-DO3A; Bayer Healthcare) and gadoteridol (ProHance; Gd-HP-DO3A; Bracco Imaging) are nonionic macrocyclic gadolinium-based contrast agents (GBCAs) approved and widely utilised throughout the world for enhanced MR imaging of the CNS at a dose of 0.1 mmol/kg bodyweight.

Structurally, the two agents differ only in that a hydroxypropyl ("HP") group on the gadoteridol molecule is replaced by a trihydroxybutyl ("BT") group on the gadobutrol molecule (1).

The published r1 relaxivity values at 1.5T are 4.7-5.2 L•mmol⁻¹•sec⁻¹ for gadobutrol and 4.1-4.3 L•mmol⁻¹•sec⁻¹ for gadoteridol (2,3).

The principal difference between the agents is that gadobutrol is formulated at a 1.0M concentration while gadoteridol is formulated at a 0.5M concentration.

The purpose of this multicenter, multinational study was to determine whether 1.0M gadobutrol has any benefits over 0.5M gadoteridol for morphologic imaging of brain tumors when these agents are administered at identical 0.1 mmol/kg doses in two identical MR examinations performed at 1.5T.
Methods and materials

This was a rigorously controlled double-blind, randomised, intra-individual crossover clinical trial in which 229 adult patients enrolled in a consecutive manner at 19 participating centers each underwent two identical MR examinations (one with gadobutrol, one with gadoteridol) within a two-week period (4).

The study was HIPAA-compliant, was conducted according to Good Clinical Practice standards and was registered at www.clintrials.gov (ref. NCT01613417). All patients signed an approved informed consent form before enrollment.

The 229 enrolled patients (98 male, 131 female; 55.3±14.4 years; range: 19-86 years) were prospectively randomized to receive contrast agent according to one of two administration orders: gadoteridol was administered first to patients in group A (n=113) while gadobutrol was administered first to patients in group B (n=116).

MR Imaging

MR imaging was performed on 1.5T systems from several vendors using a multi-channel head coil.

The imaging protocol comprised T1-weighted spin-echo (T1SE), T2-weighted fast spin-echo (T2FSE) and T2-weighted FLAIR acquisitions before contrast injection, and T1SE and 3-dimensional T1-weighted high-resolution gradient-echo (T1GRE) acquisitions after injection. The same MR scanner, imaging planes, slice prescriptions, and sequence parameters were used for both examinations in each patient.

IV contrast agent administration was performed identically in both examinations at 0.1 mmol/kg bodyweight (0.2 mL/kg for gadoteridol and 0.1 mL/kg for gadobutrol) using either manual bolus injection (n=207) or power injector (n=22). All injections were followed by a saline flush of up to 30 mL.

Post-contrast image acquisition began at a pre-specified time between 3-10 minutes after injection, but could vary within this range depending on the site-specific protocol. However, the timing and order of post-contrast sequences were identical for both exams within each patient.

Image Evaluation
All images were evaluated by three independent, neuroradiologists who were unaffiliated with the study centers and blinded to the contrast agent used, to patient clinical and radiological information, and to interpretations by on-site investigators. Each reader evaluated all patient images separately and independently on a multi-monitor workstation. The reading consisted of two sessions.

Diagnostic performance

In the first session, each reader evaluated images presented in unpaired, randomized order to determine the extent of anatomical coverage (complete or partial) and to rate the overall quality of visualization (non-diagnostic, poor, fair, good, excellent). Any images rated non-diagnostic would be excluded from subsequent evaluation.

Next, assessments of diagnostic performance were performed by each offsite reader separately for lesions detected in each of the two examinations. For this assessment each reader assigned a diagnosis to each detected lesion from a list of 99 possible diagnoses ratified by the World Health Organization (WHO; 5) that covers the range of non-tumor and tumor diagnoses.

For each lesion readers assigned either a single diagnosis or could choose to assign differential diagnoses (i.e. 2, 3, or >3 diagnoses). Using this approach a confidence score for correct lesion diagnosis was determined using a 5-point scale as follows: 5 (single diagnosis, correctly matched with final truth standard diagnosis); 4 (2 differential diagnoses; the first or second correctly matched); 3 (3 differential diagnoses; the first, second or third correctly matched); 2 (>3 differential diagnoses; the first, second or third correctly matched) or 1 (no match or non-diagnostic images or lesions confirmed at final diagnosis but not detected at MRI).

Subsequent comparisons of diagnostic performance (lesion detection rate, accuracy for tumor characterization, i.e., the distinction between benign and malignant tumors based on WHO brain tumor classification) and confidence for lesion characterization were performed for patients with histologically-confirmed brain tumors after biopsy or surgical resection. For these evaluations, patients with only follow-up diagnostic data from alternative imaging procedures were excluded.

Qualitative and quantitative assessment of diagnostic information

In the second reading session, qualitative and quantitative assessment of images from each patient was performed with images presented in global matched-pairs fashion. For
each randomized patient number, all images from Exam 1 were displayed simultaneously with the images from Exam 2. Each reader was able to perform all routine interactive image manipulation functions (e.g. window/level, zoom, pan) on both image sets. If the post-injection images from either examination were considered technically inadequate by any of the three readers (e.g. if artifacts compromised interpretability), no further assessment was performed for that patient by that reader.

Qualitative assessment:

Technically adequate images were evaluated qualitatively for diagnostic information and scored in terms of: a) overall diagnostic preference b) lesion border delineation, c) disease extent, d) visualization of lesion internal morphology and e) lesion contrast enhancement compared to surrounding normal tissue. All assessments were performed using 3-point scales from -1 (Exam 1 superior) through 0 (exams equal) to +1 (Exam 2 superior). For the various endpoints, superiority for one exam was recorded if it allowed better separation of one or more lesions from surrounding tissue, structures or edema, better definition of lesion extent, clearer depiction of intra-lesion features, better difference in SI between lesion(s) and surrounding normal tissue, or depiction of one or more lesions seen only on that exam.

Quantitative assessment:

Quantitative evaluation was also performed by each reader, independently using a simultaneous matched-pairs approach. Signal intensity (SI) measurements were made using regions-of-interest (ROIs) positioned on areas of normal brain parenchyma, and on up to three enhancing lesions per patient identified on post-contrast images from both examinations. A multi-monitor imaging workstation (TeraRecon AquariusNet server version 4.4.1.4; San Mateo, CA) was utilized to determine SI values on a pixel-by-pixel basis and to calculate the percent enhancement (E%) of lesions and the lesion-to-background ratio (LBR).

Safety Assessments

Monitoring for adverse events was performed from the time the patient signed the informed consent form until 24 hours after administration of the first study agent, and then from the moment the second study agent was administered until 24 hours after administration of the second agent. Decisions on event severity and its relationship to the study agent (has reasonable possibility or not) were made by the investigating radiologist.

Statistical Analysis
Power determination was based on the primary efficacy assumption that a 0.1 mmol/kg dose of gadoteridol is non-inferior to an equivalent dose of gadobutrol in terms of global diagnostic preference. Sample size was calculated (nQuery v. 6.01; Statistical Solutions Ltd., Cork, Ireland) using the Newcombe-Wilson score method which is based upon the lower confidence limit for the difference in paired proportions; an estimated enrolment of 185 subjects was deemed necessary for the lower limit of the observed 2-sided 95% confidence interval for the difference to exceed #5% with 85% power. Assuming a patient dropout rate of 10%, a minimum enrolment of 206 subjects was planned.

Analysis of blinded reader evaluations was performed using the statistical software package SAS version 9.2 (SAS Institute Inc., Cary, NC, USA). The distribution of reader preferences for the diagnostic information endpoints was tested using the Wilcoxon signed rank test. Altman's general approximate normal method was used to estimate the 2 sided 95% confidence interval for the difference in matched paired proportion.

Differences in quantitative enhancement between gadoteridol and gadobutrol were analyzed using a mixed effects model. The change from pre-dose was the response variable and factors included in the model were patient, period, sequence, study agent and pre-dose score, where patient nested within sequence was the random effect.

Determinations of diagnostic performance including 95% confidence intervals were performed for patients with histologically-confirmed tumors from biopsy or surgery in terms of lesion detection rate and accuracy for tumor characterization. Comparison of detection rate and accuracy was performed using McNemar's test. Inter-reader agreement was presented as percentage agreement and assessed using generalized kappa (#) statistics. Agreement was classified as excellent (# values >0.8) good (#=0.61-0.8), moderate (#=0.41-0.6), fair (#=0.21-0.4) or poor (#<0.2). An overall mean confidence score ± SD for lesion characterization was determined from the individual lesion confidence scores assigned to each patient. Comparison of mean confidence scores was performed using paired t-test. Fisher's Exact test was used to compare incidence of adverse events for the two agents and overall quality of visualization. All statistical tests were conducted at a significance level of p<0.05.
**Results**

**Patients**

All 229 enrolled patients underwent at least one contrast-enhanced MRI examination and were included in the overall safety population. Twenty patients discontinued after the first examination (13/113 [11.5%] after gadoteridol; 7/116 [6.0%] after gadobutrol; p=0.165). Reasons for discontinuation included withdrawal of consent (n=11), surgical intervention (n=3), mild adverse event (n=2), claustrophobia (n=1), change of hospital (n=1), inability to obtain intravenous access (n=1), and lack of enhancing lesion (n=1). Of the remaining 209 (91.3%) patients, 11 were excluded from the efficacy population because of protocol violations (study agent doses missing or differed by >15%, n= 9; differences of >2 minutes between injection and post-dose acquisition start times, n=2). The final efficacy analysis population therefore comprised 198 patients (Fig. 1), of which 93 (43 male, 50 female; 54.4±14.4 years; range: 19-79) were randomized to group A and 105 (47 male, 58 female; 55.9±14.3 years; range: 25-82 years) to group B. There were no significant between-group differences in sex (p=0.835), age (p=0.463), age group (18-64 years, #65 years; p=0.184), weight (p=0.071), height (p=0.503), or race (p=0.150) distribution.

Anatomical coverage was considered complete for all 198 patients by readers 1 and 3 and for 197/198 patients by reader 2. All images from both agents were considered diagnostic by all readers and no images were excluded due to motion degradation. Readers 1, 2 and 3 considered the overall quality of visualization to be good or excellent for 91.4%, 89.9% and 98.5% of patients, respectively, after gadoteridol and for 92.9%, 90.4% and 100% of patients after gadobutrol with no significant differences noted (p=0.709, p=1.0, p=0.248; readers 1, 2 and 3, respectively). A total of 444 lesions were identified on-site in these 198 patients (Fig. 1). Of these lesions, 373/444 (84%) in 181 patients were diagnosed as tumors (293 [66%] malignant; 80 [18%] benign) while 71/444 (16%) were non-tumors (Table 1). Among these 198 patients, 139 had at least one lesion that was confirmed histologically after biopsy or surgery. A total of 308 lesions (tumors and non-tumors) were present in these 139 patients, which were included in subsequent analysis of lesion detection rate. Among these 139 patients, 128 had a total of 246 lesions that were confirmed histologically as tumors while the remaining 11 patients had lesions confirmed histologically as non-tumors. All 246 histologically-confirmed tumors were included in assessments of accuracy for tumor characterization (i.e. benign versus malignant tumors based on WHO brain tumor classification) and for confidence in brain tumor characterization (Fig. 1).

**Qualitative Image Evaluation**
Figures 2, 3, 4, 5 and 6 graphically display the results of the 3 blinded readers for global diagnostic preference, lesion border delineation, disease extent, internal morphology and qualitative assessment of contrast enhancement, respectively. No significant differences between gadoteridol and gadobutrol were noted by any reader for any parameter. The small number of cases in which one agent was preferred was nearly equally distributed for gadobutrol vs. gadoteridol. The 95% confidence intervals for all qualitative assessments confirmed that gadoteridol is not inferior to gadobutrol. Agreement between the three blinded readers was high for all assessments, ranging from 82.5% of patients for assessment of lesion contrast enhancement to 97.9% of patients for definition of disease extent.

Examples of comparative enhancement between gadoteridol and gadobutrol are shown in Figs. 7, 8, and 9.

**Quantitative Enhancement**

The mean percent signal enhancement of lesions on T1SE images was similar for gadoteridol and gadobutrol for all three readers (Reader 1: 97.3% vs. 96.9% [p=0.620]; Reader 2: 95.6% vs. 98.8% [p=0.451]; Reader 3: 92.8% vs. 95.3% [p=0.772]).

No significant differences between gadoteridol and gadobutrol were noted by any reader for pre- to post-dose changes in LBR on T1SE images (Fig. 10). Similar findings were noted for assessments of T1GRE images.

**Diagnostic performance**

Lesion Detection:

No significant differences between agents were noted by Readers 1 and 2 in the numbers of patients with brain lesions while only minimal differences were noted by Reader 3 (Table 2). Similarly, no significant differences were noted by Readers 1 and 2 in the numbers of lesions detected. Based on 308 lesions included in the analysis, all three readers agreed for 70.8% (#=0.39) of lesions after gadoteridol administration and for 72.4% (#=0.47) of lesions after gadobutrol administration. At the patient level, based on 139 subjects with histopathological disease confirmation, all three readers agreed in 95.7% (#=0.44) of patients after gadoteridol administration and in 95.0% (#=0.48) of patients after gadobutrol.

Accuracy for Tumor Characterization:
No significant differences were noted among Readers 1 and 2 between gadoteridol and gadobutrol for characterization of detected tumors either at the patient level or at the lesion level (Table 3). Conversely, improved lesion characterization with gadoteridol was noted by Reader 3. Based on 128 subjects with histologically-confirmed brain tumors, all three readers agreed in their assessments for 70.3% (#=0.45) of patients after gadoteridol and for 66.4% (#=0.43) of patients after gadobutrol.

Confidence for Brain Tumor Diagnosis:

Of 128 patients with histologically-confirmed brain tumors, slightly higher mean confidence scores were assigned in the gadoteridol group (Reader 1: 3.6±1.8 vs. 3.3±1.9, p=0.016; Reader 2: 3.6±1.5 vs. 3.4±1.6, p=0.011; Reader 3: 3.5±1.6 vs. 3.3±1.7, p=0.119) indicating more single diagnoses and fewer differential diagnoses with gadoteridol. Similar findings were noted for 246 histologically-confirmed tumors (Reader 1: 3.5±1.8 vs. 3.2±1.9, p=0.001; Reader 2: 3.7±1.6 vs. 3.4±1.7, p<0.001; Reader 3: 3.3±1.7 vs. 3.2±1.8, p=0.033).

Safety

There was no significant difference in the incidence of adverse events between the two agents (p=0.199). No serious adverse events were reported for either agent.
Images for this section:

Fig. 1: Flow chart outlining patient enrollment, dropout rates and lesion study populations

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<table>
<thead>
<tr>
<th>Tumor/ Non-tumor</th>
<th>Specific Diagnosis</th>
<th>n=444 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Malignant tumor diagnoses</strong></td>
<td>Anaplastic astrocytoma (grade III)</td>
<td>12 (2.7)</td>
</tr>
<tr>
<td></td>
<td>Glioblastoma multiforme (grade IV)</td>
<td>55 (12.4)</td>
</tr>
<tr>
<td></td>
<td>Anaplastic oligodendroglioma (grade III)</td>
<td>4 (0.9)</td>
</tr>
<tr>
<td></td>
<td>Anaplastic oligoastrocytoma (grade III)</td>
<td>8 (1.8)</td>
</tr>
<tr>
<td></td>
<td>Ependymo-astrocytoma</td>
<td>2 (0.5)</td>
</tr>
<tr>
<td></td>
<td>Malignant Lymphoma</td>
<td>1 (0.2)</td>
</tr>
<tr>
<td></td>
<td>Metastatic Tumors</td>
<td>211 (47.5)</td>
</tr>
<tr>
<td><strong>Benign tumor diagnoses</strong></td>
<td>Astrocytoma (grade II)</td>
<td>2 (0.5)</td>
</tr>
<tr>
<td></td>
<td>Pilocytic astrocytoma (non-invasive, grade I)</td>
<td>1 (0.2)</td>
</tr>
<tr>
<td></td>
<td>Oligodendroglioma (grade II)</td>
<td>1 (0.2)</td>
</tr>
<tr>
<td></td>
<td>Ependymoma (grade II)</td>
<td>1 (0.2)</td>
</tr>
<tr>
<td></td>
<td>Mixed oligoastrocytoma (grade II)</td>
<td>1 (0.2)</td>
</tr>
<tr>
<td></td>
<td>Pineocytoma (grade I)</td>
<td>1 (0.2)</td>
</tr>
<tr>
<td></td>
<td>Pituitary adenoma</td>
<td>5 (1.1)</td>
</tr>
<tr>
<td></td>
<td>Craniopharyngioma (grade I)</td>
<td>1 (0.2)</td>
</tr>
<tr>
<td></td>
<td>Meningioma (grade I)</td>
<td>38 (8.6)</td>
</tr>
<tr>
<td></td>
<td>Atypical meningoMA (grade II)</td>
<td>9 (2.0)</td>
</tr>
<tr>
<td></td>
<td>Benign Mesenchymal Tumor</td>
<td>1 (0.2)</td>
</tr>
<tr>
<td></td>
<td>Melanocytoma</td>
<td>1 (0.2)</td>
</tr>
<tr>
<td></td>
<td>Hemangioblastoma (grade I)</td>
<td>1 (0.2)</td>
</tr>
<tr>
<td></td>
<td>Schwannoma (neurinoma, neurilemmoma) (grade I)</td>
<td>16 (3.6)</td>
</tr>
<tr>
<td></td>
<td>Cysts and tumor-like lesions (Epidermoid)</td>
<td>1 (0.2)</td>
</tr>
<tr>
<td><strong>Non-tumor diagnoses</strong></td>
<td>White matter disease</td>
<td>1 (0.2)</td>
</tr>
<tr>
<td></td>
<td>Vascular lesion</td>
<td>10 (2.3)</td>
</tr>
<tr>
<td></td>
<td>Infective/inflammatory disease</td>
<td>2 (0.5)</td>
</tr>
<tr>
<td></td>
<td>Infarct</td>
<td>1 (0.2)</td>
</tr>
<tr>
<td></td>
<td>Hemorrhage</td>
<td>1 (0.2)</td>
</tr>
<tr>
<td></td>
<td>Post-operative/post-treatment changes</td>
<td>56 (12.6)</td>
</tr>
</tbody>
</table>

**Table 1:** Truth standard lesion diagnoses

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Fig. 2: Bar graph shows reader preference and diagnostic results from 3 independent blinded readers for global diagnostic preference

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**Fig. 3:** Bar graph shows reader preference and diagnostic results from 3 independent blinded readers for lesion border delineation

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**Fig. 4:** Bar graph shows reader preference and diagnostic results from 3 independent blinded readers for lesion internal morphology

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Fig. 5: Bar graph shows reader preference and diagnostic results from 3 independent blinded readers for lesion extent

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Fig. 6: Bar graph shows reader preference and diagnostic results from 3 independent blinded readers for qualitative contrast enhancement

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**Fig. 7:** 61-year old male with brain metastases from primary lung cancer. A-C Images acquired before (A: unenhanced T1wSE) and after (B: T1wSE; C: High resolution T1wGRE) administration of gadoteridol. D-E Images acquired before (D: unenhanced T1wSE) and after (E: T1wSE; F: High resolution T1wGRE) administration of gadobutrol. Two lesions clearly seen in both exams show no differences in contrast enhancement or in the size of lesions.

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Fig. 8: 51-year old female with glioblastoma multiforme. A-C Images acquired before (A: unenhanced T1wSE) and after (B: T1wSE; C: High resolution T1wGRE) administration of gadoteridol. D-E Images acquired before (D: unenhanced T1wSE) and after (E: T1wSE; F: High resolution T1wGRE) administration of gadobutrol. Rim-enhancing mass in right thalamus with extension into the posterior interhemispheric region is clearly seen in both examinations. No differences in contrast enhancement or in the size of lesions are apparent.

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Fig. 9: 49-year old female with meningioma, grade I. A-C Images acquired before (A: unenhanced T1wSE) and after (B: T1wSE; C: High resolution T1wGRE) administration of gadoteridol. D-E Images acquired before (D: unenhanced T1wSE) and after (E: T1wSE; F: High resolution T1wGRE) administration of gadobutrol. No differences in contrast enhancement or in the size of the lesion are apparent.

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**Fig. 10:** Blinded reader comparison of mean post-contrast # pre-contrast LBR on T1SE sequences after 0.1 mmol/kg doses of gadoteridol and gadobutrol. No significant differences were noted by any reader.

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### Table 2: Detection of histologically-confirmed brain tumors on MR images acquired after administration of 0.1 mmol/kg gadoteridol or 0.1 mmol/kg gadobutrol in 139 patients with 308 brain lesions subsequently confirmed at biopsy or surgery

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<table>
<thead>
<tr>
<th>Lesion Detection</th>
<th>READER 1</th>
<th>READER 2</th>
<th>READER 3</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Gadoteridol</td>
<td>Gadobutrol</td>
<td>Gadoteridol</td>
</tr>
<tr>
<td>No. patients with tumors detected at MRI</td>
<td>133 (95.7%)</td>
<td>135 (97.1%)</td>
<td>137 (98.6%)</td>
</tr>
<tr>
<td>p-value</td>
<td>0.317 (−4.2, 1.4)</td>
<td>0.564 (−1.7, 3.2)</td>
<td>0.046 (0.1, 5.7)</td>
</tr>
<tr>
<td>No. tumors detected at MRI</td>
<td>240 (77.9%)</td>
<td>236 (76.6%)</td>
<td>269 (87.3%)</td>
</tr>
<tr>
<td>p-value</td>
<td>0.480 (−2.3, 4.9)</td>
<td>0.239 (−1.3, 5.2)</td>
<td>0.018 (0.6, 5.9)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Lesion Characterization</th>
<th>READER 1</th>
<th>READER 2</th>
<th>READER 3</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Gadoteridol</td>
<td>Gadobutrol</td>
<td>Gadoteridol</td>
</tr>
<tr>
<td>No. patients with tumors correctly characterized at MRI</td>
<td>94 (73.4%)</td>
<td>96 (75.0%)</td>
<td>106 (82.8%)</td>
</tr>
<tr>
<td>p-value</td>
<td>0.695 (−9.4, 6.2)</td>
<td>0.132 (−1.1, 8.9)</td>
<td>0.012 (1.8, 13.8)</td>
</tr>
<tr>
<td>No. tumors correctly characterized at MRI</td>
<td>169 (68.7%)</td>
<td>164 (66.7%)</td>
<td>198 (80.5%)</td>
</tr>
<tr>
<td>p-value</td>
<td>0.492 (−3.8, 7.8)</td>
<td>0.059 (−0.1, 8.3)</td>
<td>0.001 (3.0, 11.6)</td>
</tr>
</tbody>
</table>
Table 3: Accuracy for brain tumor characterization on MR images acquired after administration of 0.1 mmol/kg gadoteridol or 0.1 mmol/kg gadobutrol in 128 patients with 246 histologically confirmed brain tumors

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Conclusion

A previous Phase III clinical trial, which is unpublished, found no differences between a 0.1 mmol/kg dose of gadobutrol and an equivalent 0.1 mmol/kg dose of gadoteridol for enhanced MR imaging of the CNS (6, 7). In that study, blinded readers found no differences between the two agents in terms of qualitative visualization endpoints (contrast enhancement, lesion border delineation, and visualization of lesion internal morphology), numbers of lesions detected or accuracy for lesion diagnosis.

Our findings from this study confirm that no major differences between gadoteridol and gadobutrol are apparent when single 0.1 mmol/kg doses of each agent are administered to patients with confirmed brain lesions.

Specifically, three blinded, expert neuroradiologists who evaluated images from #194 patients in matched-pairs for qualitative visualization endpoints expressed no preference for either agent in the vast majority of cases. In the few cases in which a reader expressed a preference, the number of cases in which gadobutrol was preferred was approximately equal to the number of cases in which gadoteridol was preferred.

Similar findings were noted for quantitative enhancement measurements: no significant differences between gadobutrol and gadoteridol were noted either for mean percent signal enhancement or for pre- to post-dose changes in LBR.

Two conclusions can be derived from this study:

• First, findings demonstrate that the two-fold higher concentration of gadobutrol in the commercially-available formulation provides no advantage for morphologic imaging of brain lesions. This conclusion is not unexpected given that image acquisition for morphologic imaging of brain tumors typically begins at least 3-5 minutes following contrast administration by which time contrast equilibration will have occurred, which would obviate any potential benefits of a higher administered concentration (8, 9).

• Second, although r1 relaxivity is a major factor for contrast efficacy (9), the slightly different r1 relaxivity values reported for gadobutrol and gadoteridol are insufficient to show any discernable clinical effect, either for qualitative or quantitative lesion enhancement or for diagnostic performance.

These conclusions are supported by other intra-individual crossover studies performed at 1.5T comparing these agents with other GBCAs for brain tumor imaging. Thus, Greco et al (10) compared gadoteridol with gadopentetate dimeglumine (Magnevist; r1: 3.9-4.1
L•mmol⁻¹•s⁻¹; 2, 3) in 80 subjects for presence of disease, degree of enhancement, number of lesions, and additional information gained (lesion border delineation, improved visualization, distinction of edema, disease classification, determination of recurrent tumor) and found no significant GBCA preference as determined by two blinded readers.

More recently, separate prospective multicenter intra-individual crossover studies have compared gadobutrol with gadoterate meglumine (Dotarem: r1: 3.6 L•mmol⁻¹•sec⁻¹; 2) in 136 patients (11) and gadobenate dimeglumine (MultiHance; r1: 6.3-7.9 L•mmol⁻¹•s⁻¹; 2, 3) in 123 patients (12), respectively.

- In the former study (11) significant preference for gadobutrol over gadoterate meglumine was noted by 2 of 3 blinded readers for overall reader preference. However, none of the 3 readers considered gadobutrol superior to gadoterate meglumine for lesion delineation while only one blinded reader noted minimally significant preference for gadobutrol for the definition of lesion internal structure. Quantitatively, the percent lesion enhancement following gadobutrol was approximately 9% higher than that following gadoterate meglumine but this yielded no significant difference between the two agents for measured contrast-to-noise ratio and no differences in number of lesions detected with either agent were observed.

- In the latter study (12) all 3 blinded readers demonstrated highly significant (p<0.0001) preference for the higher-relaxivity 0.5M gadobenate dimeglumine over 1.0M gadobutrol for all qualitative end-points (lesion border delineation, definition of disease extent, visualization of lesion internal morphology, lesion contrast enhancement, global diagnostic preference) with good inter-reader agreement for all evaluations. In addition, significant superiority was noted for all quantitative assessments with a mean difference of approximately 22% in percent lesion enhancement between gadobenate dimeglumine and gadobutrol.

Together with our findings, these studies suggest that only r1 differences of a certain magnitude are sufficient to elicit discernable clinical differences in GBCA performance. Thus, intra-individual studies that have compared GBCAs with similar r1 relaxivity have generally demonstrated similar image quality and diagnostic performance (6, 7, 10) while studies that have compared GBCAs with higher r1 have demonstrated measurable differences in image preference and diagnostic performance [12].

In summary, the overriding conclusion of our study is that gadoteridol and gadobutrol confer similar image enhancement and diagnostic performance when administered under identical conditions at an approved dose of 0.1 mmol/kg bodyweight. The similar performance of these two GBCAs support the fact that the small difference in r1 values between the two agents does not confer any diagnostic advantage. Further, our study confirms the findings of a previous unpublished multicenter study (6, 7) in showing that the
two-fold higher gadolinium concentration of the gadobutrol formulation has no significant impact on routine morphologic imaging of brain lesions.
References

11. Anzalone N, Scarabino T, Venturi C, et al. Cerebral neoplastic enhancing lesions: Multicenter, randomized, crossover intraindividual comparison between gadobutrol (1.0M) and gadoterate meglumine (0.5M) at 0.1mmolGd/kg body weight in a clinical setting. Eur J Radiol. 2013; 82:139-45.