

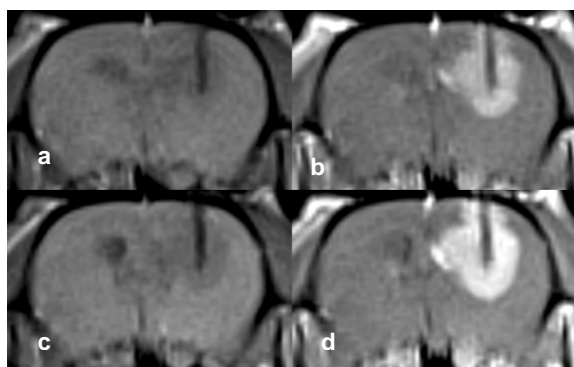
## Lesion Enhancement in a Rat Brain Tumor Model: Evaluation of 1 M Gadobutrol vs Two Conventional Gadolinium Chelates, all injected at a Dose of 0.1 mmol/kg at 3T.

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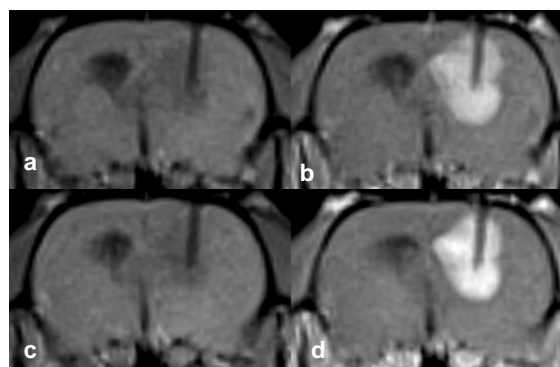
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**Introduction:** Contrast enhanced (CE) magnetic resonance imaging (MRI) of the brain is a well evaluated method at 1.5 and 3 T for the detection of primary brain tumors as well as metastatic spread. After intravenous injection, gadolinium based contrast agents may only pass to the brain parenchyma in areas of disrupted blood-brain barrier (BBB), and specifically not to areas with normal blood-brain barrier (BBB). The leakage of a gadolinium chelate through the disrupted BBB demarcates pathologic from normal brain tissue, leading to both increased sensitivity and specificity. Seven gadolinium chelates have been approved in countries across the world for CE MRI of the brain. These contrast agents are, with one exception, formulated at a concentration of 0.5 mmol/mL. Gadobutrol is a double concentrated non-ionic macrocyclic gadolinium chelate, with high in vivo stability. Combining a 1.0 M, high relaxivity, gadolinium chelate and 3 T offers multiple opportunities for further improvement of lesion enhancement. The aim of this study is to compare the differences in contrast enhancement using 0.1 mmol/kg body weight 1 M gadobutrol vs two standard gadolinium chelates, both formulated at 0.5 M, (gadopentetate dimeglumine and gadoterate meglumine) in a standardized rat glioma model at 3 T.

**Material and Methods:** 19 rats divided into two groups were evaluated. Group 1 (n=10) was examined applying gadobutrol and gadopentetate dimeglumine at a dose of 0.1 mmol/kg; Group 2 (n=9) was examined applying gadobutrol and gadoterate meglumine at a dose of 0.1 mmol/kg. The time between intraindividual injections was 24 hr or greater. Contrast agent injections were performed in a randomized order. Image acquisition was performed using a T1-weighted 2D TSE technique (TR/TE 500/16, FA 180°) with an acquisition time of 1:47 min:sec. At a field-of-view of 75x75 mm<sup>2</sup> and a matrix size of 320x320 the voxel size achieved was 0.2x0.2x2.0 mm<sup>3</sup>. Data acquisition was performed before and at 5 consecutive time points every 2 minutes following contrast agent injection. A region-of-interest analysis was performed to measure the signal-to-noise ratio (SNR) and contrast-to-noise-ratio (CNR) of tumor and normal contralateral brain.



*Illustrated are pre- (a, c) and 3 min. (b, d) post-contrast scans at 3 T of an implanted glioma. The magnitude of contrast enhancement was substantially greater after the administration of gadobutrol (d) as compared to gadoterate meglumine (b), with both agents injected at the same dose level of 0.1 mmol/kg.*



*Illustrated are (a, c) pre- and (b, d) 3 min. post-contrast scans at 3 T, acquired in the same animal, prior to and following administration of 0.1 mmol/kg (b) gadopentetate dimeglumine as compared to (d) gadobutrol. Note the greater magnitude of contrast enhancement (in this implanted glioma) with gadobutrol.*

**Results:** Tumor SNR post-contrast was significantly higher for gadobutrol in both groups. The lowest SNR values were consistently noted at time point 1 and the highest SNR values at time point 3. SNRmean specifically ranged (assessing all time points post-contrast) from 78.7 to 89.1 vs 74.3 to 80.8 in group 1 (gadobutrol vs gadopentetate dimeglumine) and from 79.9 to 88.9 vs 74.2 to 80.8 in group 2 (gadobutrol vs gadoterate meglumine). Tumor SNR was statistically significantly different at all measured time points in group 2 ( $P < 0.05$ ), and for all but one time point in group 1.

CNR was statistically significantly higher for gadobutrol in both groups ( $P < 0.0001$ ); the CNR mean values for gadobutrol were  $25.5 \pm 8.2$  in group 1 and  $27.1 \pm 8.3$  in group 2. CNR mean values were  $18.6 \pm 5.6$  for gadopentetate dimeglumine and  $19.2 \pm 5.3$  for gadoterate meglumine. The difference in tumor SNR was statistically significant at all measured time points in group 2 ( $p < 0.05$ ). For the gadobutrol/gadopentetate dimeglumine comparison in group 1 the difference of tumor SNR was also statistically significant different ( $p < 0.05$ ) with the exception of the time point at 9 min post-contrast ( $p = 0.07$ ). Tumor contrast enhancement (CE) showed a percentage increase between 19.6% and 35.9%, depending upon time post-injection, for the gadobutrol vs gadopentetate dimeglumine comparison in group 1 and between 23.2% and 27.8% for gadobutrol vs gadoterate meglumine in group 2.

**Conclusion:** The results of this study show statistically significantly higher brain tumor SNR and CNR for gadobutrol compared to gadopentetate dimeglumine and gadoterate meglumine at 3 T. Injecting the same gadolinium chelate dose on a weight basis, tumor mean SNR gains were superior for gadobutrol at all acquired post contrast time points. These findings are in concordance with the T1 relaxivity of the 3 agents, as evaluated in plasma at 3 T. Use of gadobutrol may thus facilitate improved brain tumor detection at 3T, in particular for very small lesions, in the presence of BBB disruption.