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ORIGINAL ARTICLE

# Comparison of Gd-Bz-TTDA, Gd-EOB-DTPA, and Gd-BOPTA for dynamic MR imaging of the liver in rat models

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**Abstract** To evaluate the competitive potential of a new lipophilic paramagnetic complex, Gd-Bz-TTDA [4-benzyl-3,6,10-tri (carboxymethyl)-3,6,10-triazado-decanedioic acid] compared with two other commercially available MR hepatobiliary contrast agents, gadobenate dimeglumine (Gd-BOPTA) and gadoxetic acid (Gd-EOB-DTPA), dynamic MR imaging studies were performed on normal and hepatocellular carcinoma (HCC) rat models using a 1.5-Tesla MR scanner. The results indicate that normal rats that were injected with 0.1 mmol/kg Gd-Bz-TTDA showed significantly more intense and persistent liver enhancement than those that were injected with the same dose of Gd-EOB-DTPA or Gd-BOPTA. All of these agents showed similar enhancement patterns in the implanted HCC. The liver-lesion contrast-to-noise ratios were higher and more persistent in rats that were injected with Gd-Bz-TTDA. These results indicate that Gd-Bz-TTDA is comparable with the commercially available hepatobiliary agents, Gd-EOB-DTPA and Gd-BOPTA, and can result in more intense and prolonged liver enhancement while still providing better liver-lesion discrimination. These results warrant further large-scale studies.


## Introduction

In recent years, three hepatobiliary-specific contrast agents—mangafodipir trisodium (Mn-DPDP, Teslascan, GE Healthcare, Oslo, Norway), gadobenate dimeglumine (Gd-BOPTA, MultiHance, Bracco, Milan, Italy) and gadoxetic acid (Gd-EOB-DTPA, Primovist, Bayer, Berlin, Germany)—have

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been become clinically available for use in magnetic resonance imaging (MRI) [1]. The two gadolium-based agents are able to initially distribute throughout the extracellular fluid spaces as an extracellular contrast agents and are subsequently and selectively taken up by the hepatocytes [1–3]. These contrast agents have proven their usefulness for improving lesion detection in MR imaging of the liver, as well as for characterizing the hepatocellular and non-hepatocellular properties of liver tumors [1,2,4–7].

We have developed and characterized a new lipophilic paramagnetic complex, Gd-Bz-TTDA [4-benzyl-3,6,10-tri (carboxymethyl)-3,6,10-triazado-decanedioic acid], which was designed for use as hepatic MR contrast agent [8,9]. The preliminary results of our previous study showed intense liver enhancement in normal rats lasting from 5 minutes to 3 hours. Gd-Bz-TTDA can also improve tumor conspicuity in late phase images by providing intense liver enhancement [10]. A toxicity study was also conducted that shows that it is safe for these purposes [10]. The R1 relaxivity of Gd-Bz-TTDA is superior to Gd-BOPTA. Its rotational correlation time is longer than Gd-EOB-DTPA, and its water-exchange lifetime is significantly shorter than Gd-EOB-DTPA and Gd-BOPTA [8,9]. To evaluate the competitive potential of this novel contrast agent against Gd-EOB-DTPA and Gd-BOPTA, dynamic MR imaging studies of the livers of normal rats and rats with implanted HCC were performed using these three agents.

## Materials and methods

### Study design

For the MR imaging studies, 12 normal male Wister rats (National Laboratory Animal Breeding and Research Center, Taipei, Taiwan) were used, each weighing 200–250 g. Three rats were randomly assigned to each group. At each MR scan, three rats were immobilized on the same polystyrene board after being anesthetized. Each group received intravenous injection of 0.1 mmol/kg Gd-Bz-TTDA, Gd-EOB-DTPA, or Gd-BOPTA respectively. A marker was administered to each rat, and the type of contrast agent that was given was recorded. During the next study, which occurred at least 3 days later, each rat received a different contrast agent that was administered in the first study. During the third MR imaging study, which also occurred at least for 3 days later, each rat received the remaining contrast agent that they had not received in either of the two previous studies. A total of six rats with implanted HCC (Cheng hepatoma ascites [CHA], AS 30-D; Academia Sinica, Taipei, Taiwan) were also studied. MR imaging studies of the rats with HCC used a similar experimental design as that described above.

### Animal models

The CHA hepatoma model [11] was successfully conducted by percutaneously injecting 0.25 mL ($10^7$–$10^8$ cells/mL) of the CHA suspension into six Wistar rats. A CHA hepatoma usually takes 1–3 weeks to reach its predetermined size. The experiment was performed 3 weeks after implantation, when the tumors measured at least 1 cm in diameter.

### MR imaging

The rats were anesthetized with an intraperitoneal injection of sodium pentobarbital at a dose of 40–50 mg/kg. The tail veins were cannulated using a 1-mL disposable syringe filled with the contrasting agent. The rats were then placed in a head coil in the prone position. MR imaging was performed using a 1.5-T superconductive MR scanner (Gyroscan ACS-NT; Philips Medical Systems, Best, Netherlands). T1- and T2-weighted coronal spin echo (SE) images were acquired as the baseline images. Sequential T1-weighted turbo field-echo (TFE) (TR/TE/flip angle: 15 msec/6.1 msec/25°) coronal images were obtained before and after intravenous injection of the contrasting agents. The following parameters were used: number of excitations, two; field of view, 20 cm; slice thickness, 4 mm; and image matrix, 256 × 128. To assess any dynamic changes in enhancement, postcontrast scans were obtained every 14 seconds for nine continuous scans, every 5 minutes for six subsequent scans, and every 10 minutes for up to 2 hours. Similar protocols with additional T2-weighted images were used on the rats with implanted HCC, both before and after the intravenous injection one of the three contrast agents. During scanning, a glass cylinder containing 2% weight/volume agarose gel was positioned adjacent to the rats as a reference standard.

### Image analysis

Operator-defined regions of interest were selected for the liver parenchyma, away from vessels or artifacts, and from the agarose gel reference standard. Approximately 0.1 $cm^2$ was used for the regions of interest in the liver and the solid and necrotic compartments of the tumors. The operator was blind to information regarding which contrast agents had been injected into the individual rats.

MR images were analyzed in order to evaluate any time-enhancement changes that occurred in the livers of the normal rats that could be identified using the three contrast agents. The signal intensity of each target was normalized by dividing its mean target-signal intensity by that of the agarose gel standard (signal-to-noise ratio, SI/N). The enhancement percentage of the liver was calculated as follows:

$$\text{Enhancement}\,\% = \frac{(\text{SI/N})_t - (\text{SI/N})_{pre}}{(\text{SI/N})_{Dre}} \times 100\%$$

In this equation, $(SI/N)_t$ and $(SI/N)_{pre}$ are the post-contrast and precontrast signal-to-noise ratios of the liver, respectively. The enhancement percentages at different time points were compared for each contrast agent. Results are expressed as the mean ± SD. The Student *t* test was used to compare differences between two of the three groups. A *p*-value $<0.05$ was considered statistically significant. Lesion conspicuity was assessed by the percentage increase in the liver-lesion contrast-to-noise ratio (CNR) using the following formula:

$$\%\ \text{Increase of Liver-Lesion CNR} = \frac{[(SI_{liver} - SI_{lesion})/N]_t - [(SI_{liver} - SI_{lesion})/N]_{pre}}{[(SI_{liver} - SI_{lesion})/N]_{pre}} \times 100\%$$