

ORIGINAL ARTICLE

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Comparison of gadoxetic acid and gadobenate dimeglumine, liver-specific contrast agents used in magnetic resonance imaging in differential diagnosis of liver masses**Mehmet Akcicek¹, Serkan Unlu¹, Mehtap Ilgar¹, Tamer Baysal²**¹Malatya Training Research Hospital, Department of Radiology, Malatya, Turkey²Istanbul Kartal Dr. Lutfi Kirdar Education and Research Hospital, Department of Radiology, Istanbul, Turkey

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Abstract

To compare Gadoxetic acid and Gadobenate dimeglumine in the detection and characterization of liver masses. In this study, 59 lesions in 28 patients are included in which were dynamic MRI that had been used Gadoxetic acid (Gd-EOB-DTPA) and Gadobenate dimeglumine (Gd-BOPTA). Observers recorded the liver lesions and adjacent parenchymal signal intensities (SI) in precontrast, arterial and hepatocyte phase by using the ROIs for the quantitative analysis. All statistical analyzes were performed with SPSS 22 software. $p < 0.05$ was considered significant. In the cases of hemangiomas Gd-BOPTA applied, the SI of the lesions increased by 7.46% in the transition to the arterial phase, and 74.6% in the transition to the hepatocyte phase. In the cases of Gd-EOB-DTPA applied, the SI of the lesions increased by 16.01% in the transition to the arterial phase, and 99.76% in the transition to the hepatocyte phase. Compared two agents in the arterial and the hepatocyte phases there were no statistically significant differences. In the cases of metastases Gd-BOPTA applied, the SI of the lesions increased by 28.10% in the transition to the arterial phase, and 90.48% in the transition to the hepatocyte phase. In the cases of Gd-EOB-DTPA applied, the SI of the lesions increased by 12.68 % in the transition to the arterial phase, and 47.72% in the transition to the hepatocyte phase. Compared two agents in the hepatocyte phase the p-value was 0.006 and found a statistically significant difference. The difference in parenchymal-lesion contrast is more prominent for metastatic liver lesions in the hepatocellular phase in patients administered Gd-EOB-DTPA.

Keywords: Gadoxetic acid, gadobenate dimeglumine, contrast agents, liver metastasis, liver hemangiomas**Introduction**

Intravenous contrast agents on liver MRI improve the contrast between the lesion and the liver, facilitating the detection and characterization of disease [1]. Firstly, Gadopentetate dimeglumine (Gd-DTPA) has been approved for clinical use; its practical use has increased, and new agents have been produced [2]. The ideal contrast medium to be used in liver MRI should be an agent with a strong magnetic effect, low side effects and biodistribution differentiation [3]. The contrast agents have been used in liver MRI can be grouped into five main categories: nonspecific extracellular gadolinium chelators, hepatocyte-specific contrast agents, reticuloendothelial system-specific contrast agents, blood pool agents and combined contrast agents [4]. Gadolinium

chelates are the most commonly used agents [4,5]. All contrast agents except superparamagnetic iron oxides that are used clinically in liver MRI act by shortening the T1 and T2 durations of the liver parenchyma. The liver signal is increased in T1-weighted sequences (T1W) because of the shortening of T1 time in gadolinium- and manganese-containing agents [1,6]. In recent years, hepatocyte-specific contrast agents have been developed for lesion characterization. Compared with classical gadolinium chelates, these agents increase the contrast between the lesion and the liver [6,7]. Gadoxetic acid is a hepatocyte-specific agent with gadolinium that has been commonly used in clinical practice [8,9]. In many studies, the efficacy of this contrast agent in detecting focal liver lesions due to high hepatocyte specificity was compared with that of nonspecific gadolinium chelates [10].

This study compared Gadoxetic acid disodium (Gd-EOB-DTPA) and Gadobenate dimeglumine (Gd-BOPTA) agents, which are both extracellular and hepatocyte-specific gadolinium chelates, in detecting and characterizing of liver masses.

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Materials and Methods

The study was carried out at Istanbul Kartal Dr. Lutfi Kırdar Education and Research Hospital Radiology Department. This study received approval from the hospital ethics committee. Contrast-enhanced dynamic MR images had been performed at the hospital imaging center in two years were investigated retrospectively. The patients' images were selected in which the gadolinium-based contrast agents Gd-EOB-DTPA and Gd-BOPTA had been administered and masses had been detected in the liver. A total of 59 lesions were identified as hemangiomas and metastases in 28 patients under follow-up who met these criteria. Except for hemangiomas and metastases we did not detect any other lesions. Two groups were formed according to the contrast media used, and the contrast ratios were evaluated in the obtained images. Studies that were not complete for any reason, images with artifacts and the examinations in which liver lesions had not been detected were not included.

MRI examination of all patients was performed using a 1.5 T MRI device (Siemens Avanto, Germany) using an 8-channel phased array coil. Routine pre-contrast upper abdominal images, coronal T2W, axial T2W, axial fat-suppressed T2W and T1W, axial T1W in-phase/out-of-phase sequences and pre-contrast DWI images had been obtained. Then IV contrast agents had been administered, and axial fat-suppressed T1W images had been taken in the early (0 s, 25 s, 60 s, and 90 s), late (5 m) and hepatocyte (15 m for Gd-EOB-DTPA, 60 m for Gd-BOPTA) phases. The contrast medium had been administered at the manufacturers' recommended dose of 0.1 ml/kg (0.025 mmol/kg Gd-EOB-DTPA; 0.05 mmol/kg Gd-BOPTA) as indicated in the package inserts, followed by 20 ml of serum at 2 ml/sec with an automatic pump injector system. Spectral Adiabatic Inversion Recovery (SPAIR) was used as the fat suppression technique in all sequences.

All images were transferred to the picture archiving and communications system workstation at a resolution of 2,048 × 2,060 pixels and evaluated randomly by two experienced radiologists. Radiologists were blinded to the contrast agent used and recorded the degree of enhancement of the liver lesion and parenchyma of the same or adjacent segment by measuring the ROI (region of interest) on the pre-contrast, arterial and hepatocyte phases images. Observers described each lesion according to size and localization to avoid confusion during data analysis in the case of patients with multiple lesions in the same segment. Additionally, in evaluations of the parenchyma, vascular structures were not measured. As ROIs were measured in homogenous locations at heterogeneous lesions, intratumoral necrosis or hemorrhage was excluded from this field. To protect against a partial volumetric effect, 59 lesions larger than 1 cm in diameter and visible in all sequences in 28 patients were used. Radiologists evaluated each case independently, for cases with measurement differences they re-evaluated together and agreed jointly.

All statistical analysis was performed with the SPSS 22 (Statistical Package for Social Sciences) program. Differences were considered

significant at $P < 0.05$. As the data distribution was not normal and the variance homogeneous, to calculate enhancement in the arterial and hepatocyte phases as a percentage (%), the nonparametric Mann-Whitney U test was applied.

Results

Gd-BOPTA had been used on 9 patients who had a total of 23 lesions. Eight lesions were hemangiomas and the others were metastases. Half of 36 lesions in 19 patients who had been administered Gd-EOB-DTPA were hemangiomas and the others were metastases.

In the dynamic contrast-enhanced MRI series, the difference in signal intensity (SI) from second 0 to the arterial phase and from second 0 to the hepatocyte phase were calculated in cases of hemangiomas. Eight hemangiomas in which had been administered Gd-BOPTA as a contrast agent in MRI were evaluated. The average SI in the transition to the arterial phase was calculated as 7.46% in this group. The median value was 0.78%. On the other hand, 18 hemangiomas were also evaluated in which Gd-EOB-DTPA had been used. The average SI in the transition to the arterial phase was calculated as 16.01% in this group. The median value was 8.80%. The difference between the two groups in the transition to the arterial phase in hemangioma cases was not statistically significant ($P = 0.437$; Figure 1 and 2).

The average SI in the transition to the hepatocyte phase was calculated as 74.60% in the first group, and the median value was 60.05%. The average SI in the transition to the hepatocyte phase was calculated as 99.76% in the second group, and the median value was 96.38%. The difference between the two groups in the transition to the hepatocyte phase in the hemangioma cases was not statistically significant ($P = 0.505$; Figure 1).

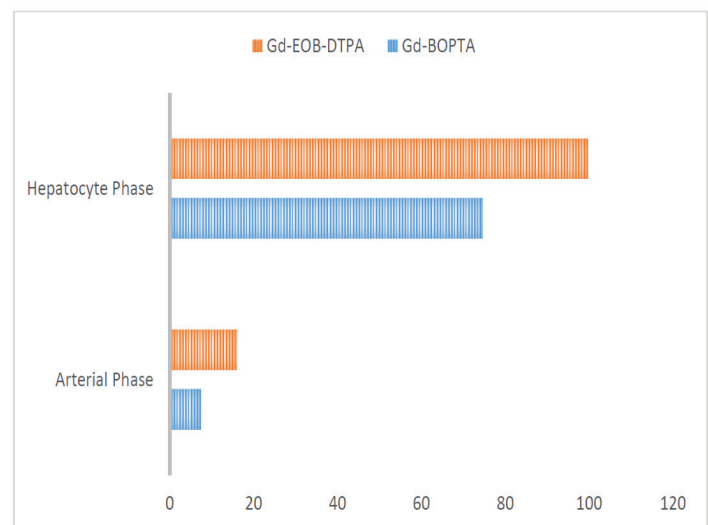


Figure 1. The enhancement ratios in hemangiomas in which Gd-BOPTA and Gd-EOB-DTPA had been administered.

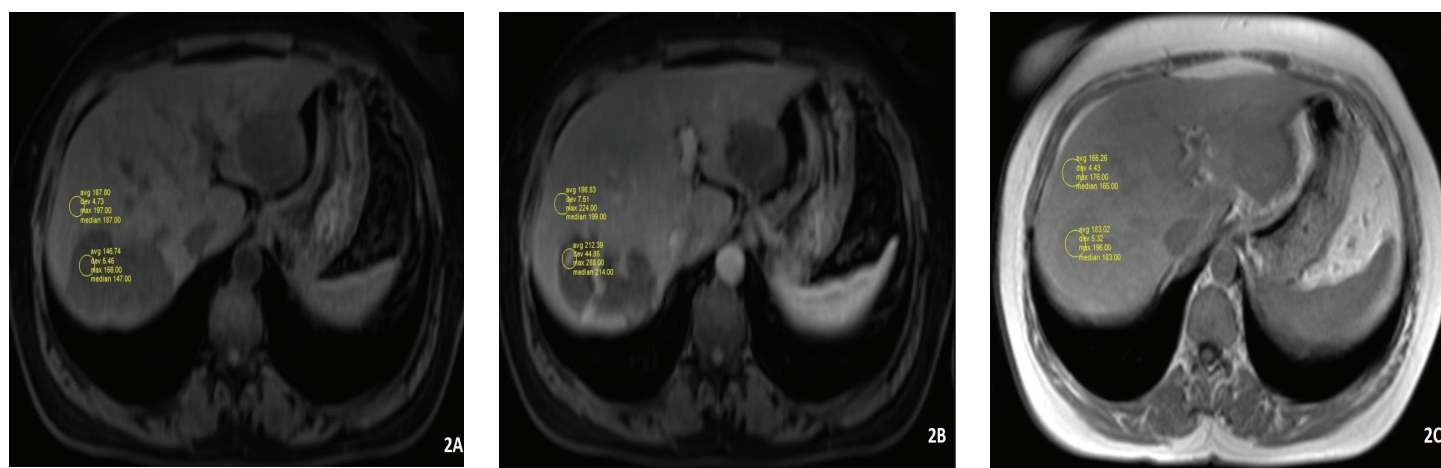


Figure 2. A 50-year-old female patient who had had a radical nephrectomy because of a malignant neoplasm in the left kidney. Dynamic MR images applied Gd-BOP-TA. a. pre-contrast b. arterial phase c. hepatocyte phase. The signal intensity of both the hemangioma in segment 7 and the liver parenchyma were calculated by measuring the respective ROIs.

The average differences in SI in the transition to the arterial and hepatocyte phases for metastatic lesions were also calculated. In patients with metastases had been administered with Gd-BOPTA, the SI of 15 metastatic lesions were increased by an average of 28.10% in the arterial phase, and the median value was calculated as 27.62%. In the group had been administered with Gd-EOB-DTPA, the SI of a total of 18 metastatic lesions were found to increase by an average of 12.68% in the arterial phase shift, and the median value was calculated as 7.47%. The difference in percentage increment of the SI in the arterial phase between metastases cases which had been administered with Gd-BOPTA or Gd-EOB-DTPA was not statistically significant ($P = 0.112$; Figure 3).

The signal SI of the metastatic lesions in Gd-BOPTA-administered patients increased by an average of 90.48% in the hepatocyte phase transition, and the median value was calculated as 93.50%. The metastatic lesions in Gd-EOB-DTPA-administered patients showed a 47.72% increase in the hepatocyte phase transition, and the median value was 34.38%. The difference in percentage increase of SI in the hepatocyte phase transition between metastasis cases administered with Gd-BOPTA or Gd-EOB-DTPA was statistically significant ($P = 0.006$; Figure 3 and 4).

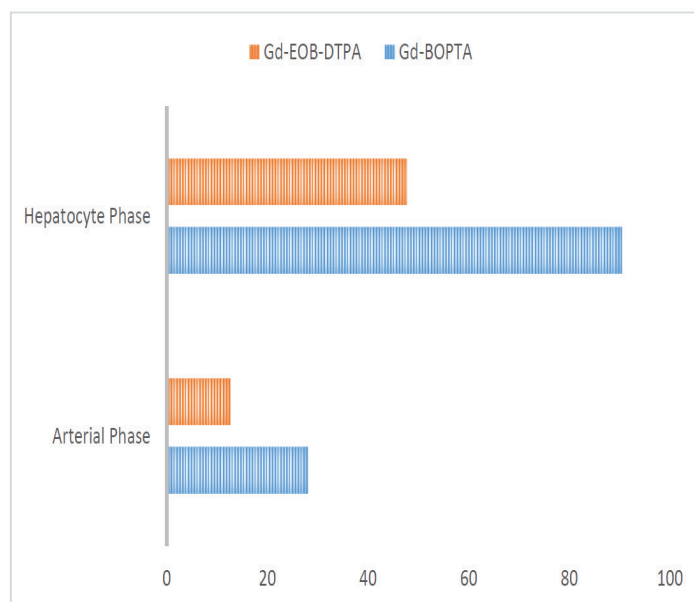


Figure 3. The enhancement ratios in metastasis in which Gd-BOPTA and Gd-EOB-DTPA had been administered.

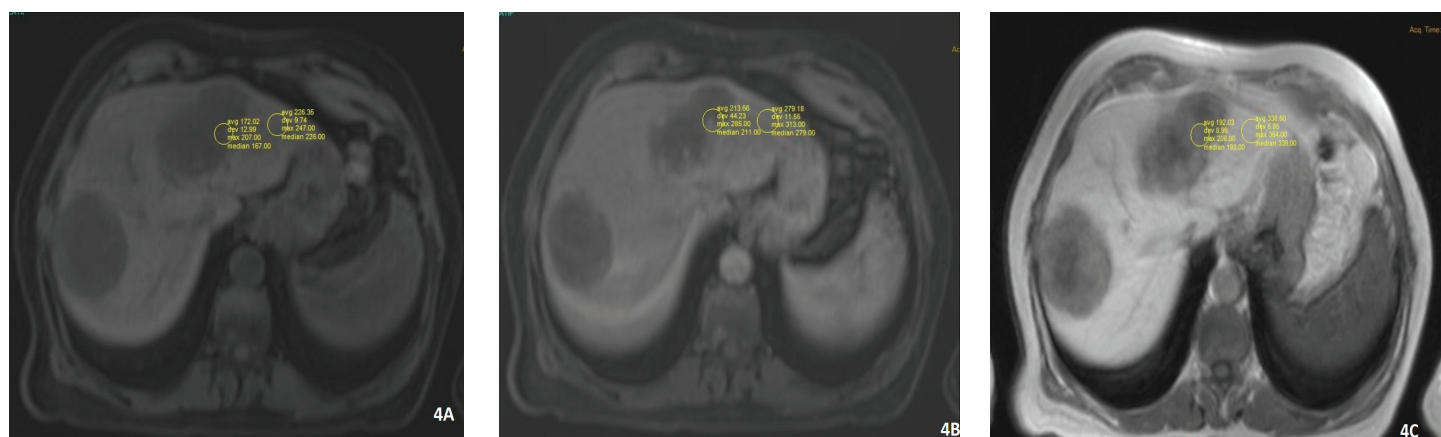


Figure 4. Gd-EOB-DTPA enhanced dynamic MRI images of a 64-year-old male patient followed-up for lung cancer a. pre-contrast b. arterial phase c. hepatocyte phase. The signal intensity of metastatic lesions in segment 4 and liver parenchyma were calculated by measuring the respective ROIs.

The increase of liver parenchyma SI in the hepatocyte phase as a percentage were also calculated in all patients. In 9 cases had been administered Gd-BOPTA, the parenchymal SI in the hepatocyte phase increased by 54.04%, and the median value was 58.14%. In 19 cases had been used Gd-EOB-DTPA, the increase of parenchymal SI in the hepatocyte phase was calculated as 80.63%. The median value was 67.48%. The difference in the increase of SI of hepatic parenchyma in the hepatocyte phase between two agents was not statistically significant ($P = 0.157$; Figure 5).

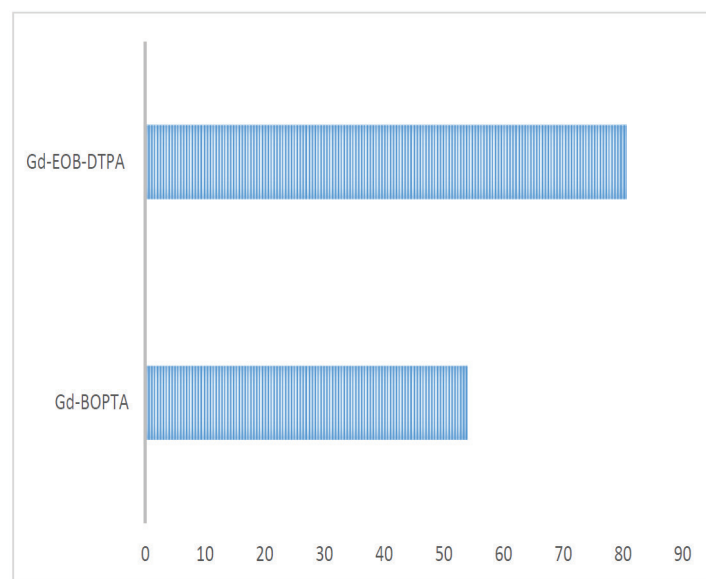


Figure 5. Percentage increases in SI values of the liver parenchyma in the hepatocyte phase in cases of Gd-BOPTA and Gd-EOB-DTPA administration

Discussion

Optimal detection of liver lesions can alter the patient's treatment protocol and, in some cases, prevent costly procedures such as unnecessary laparotomy [4,6]. Intravenous contrast materials given in liver MRI facilitate the detection and characterization of diseases by increasing the contrast between the lesion and the liver [4,11]. Gadolinium chelates developed for this purpose are the most commonly used agents [1,5,9]. In recent years, hepatocyte-specific contrast agents have been developed to provide additional lesion characterization. These agents increase the contrast between the lesion and the liver compared with classical gadolinium chelates [6,7]. These agents may be used in the pre-operative evaluation of patients under consideration for curative liver resection [12].

Gd-EOB-DTPA is a hepatobiliary specific gadolinium agent that has been used in clinical practice. The ability to take hepatobiliary phase images 10–20 minutes after contrast injection is a significant advantage whereas images in the hepatocyte phase are taken between the first and third hours in the use of Gd-BOPTA, another gadolinium-based hepatobiliary specific contrast agent [8,13]. Previous studies have shown that Gd-EOB-DTPA is well-tolerated and non-reactive and has a minor side-effect ratio [14,15]. Our study reported no serious side effects in the patients. Gd-EOB-DTPA is given in low doses compared with Gd-BOPTA, and the majority is excreted by biliary excretion. This facilitates its use especially in patients at risk for nephrogenic systemic fibrosis [8,16]. In many studies, the effectiveness of this contrast agent, due to its

high hepatocyte specificity, in detecting focal liver lesions was compared with that of nonspecific gadolinium chelates [17*19]. In this study, we compared Gd-EOB-DTPA and Gd-BOPTA, both extracellularly distributed and as a part of hepatocyte-specific gadolinium chelates, in detecting and characterizing liver masses.

In a study in which quantitative analysis was performed, it was shown that the contrast enhancement of intra-abdominal solid organs and the aorta in the arterial phase was higher with Gd-DTPA administered [10]. That is, on dynamic MRI, the contrast enhancement of the abdominal solid organs and aorta in the arterial phase and that of the portal vein and inferior vena cava in the portal phase were found to be less with Gd-EOB-DTPA than with Gd-DTPA [10]. Liver parenchyma has a strong contrast enhancement because of the high rate of biliary excretion of Gd-EOB-DTPA, and the diagnostic accuracy with a high contrast noise ratio (CNR) increases when detecting lesions such as HCC. However, this is similar for MRI applied Gd-BOPTA [8]. A prospective study of 22 lesions in 18 HCC patients by Park and colleagues showed that dynamic contrast-enhanced MR scans with Gd-BOPTA and Gd-EOB-DTPA had similar diagnostic accuracy, sensitivity and positive predictive values [8]. In a retrospective study of Park and colleagues in 47 patients with HCC lesions, because of the hypointense properties of these lesions in the hepatocyte phase, Gd-EOB-DTPA contrast studies were superior to Gd-BOPTA in the detection of HCC [20].

Intravascular enhancement of Gd-EOB-DTPA is less likely due to the recommended dose difference between Gd-BOPTA and Gd-EOB-DTPA [21]. In a prospective study of ten healthy volunteers by Brismar et al., Gd-BOPTA 0.1 mmol/kg and Gd-EOB-DTPA 0.025 mmol/kg were applied, and the contrast enhancement between the liver parenchyma and hepatic artery, as well as between the portal vein and middle hepatic artery was measured as an intensity. In conclusion, Gd-BOPTA showed higher contrast enhancement in the arterial and portal phases compared with Gd-EOB-DTPA, and there was no difference in liver parenchymal enhancement in the late phase [22]. We found an increase in the signal intensities of the liver parenchyma in the hepatocyte phase with both agents was not found to be statistically significant.

Huppertz reported in a meta-analysis that the hepatocyte phase of Gd-EOB-DTPA enhanced MR examinations did not provide an additional benefit in the differential diagnosis of metastases, hemangiomas, and cysts, three types of lesions that appear hypointense at this phase because they do not show selective enhancement of hepatocytes. On the other hand, the hepatocyte phase is highly prevalent in the differential diagnosis of metastases and FNH or adenomas [21]. In our study, when the contrast ratios of Gd-BOPTA and Gd-EOB-DTPA were compared in metastases in the hepatocyte phase transition from second 0, the difference in percentage increase of the signal intensities between two agents was statistically significant. In contrast, there was no significant difference between hemangioma cases with Gd-BOPTA and Gd-EOB-DTPA. Since hemangiomas do not contain hepatocytes like metastases, we would expect them to have less contrast with Gd-EOB-DTPA as in metastases in the hepatocellular phase. However, we believe that the absence of statistically significant differences may have been due to the contrast medium pooling in hemangiomas.

Conclusion

In the detection and characterization of liver masses, the difference in parenchymal-lesion contrast is more prominent for metastases in the hepatocellular phase in patients administered Gd-EOB-DTPA. Given this result, Gd-EOB-DTPA may be preferred in the MRI of liver hemangiomas and metastases because of its lower dosage, lower risk of nephrogenic systemic fibrosis and shorter time to reach the hepatocyte phase.

Competing interests

The authors declare that they have no competing interest.

Financial Disclosure

There are no financial supports

Ethical approval

This study received approval from Dr Lütfi Kırdar Kartal Training and Research Hospital ethics committee by number 89513307/1009/208.

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References

- Agostini A, Kircher MF, Do R, et al. MR imaging of the liver (including biliary contrast agents): Part 1: technical considerations and Contrast Materials. In: Seminars in roentgenology. NIH Public Access, 2016;p. 308.
- Lohrke J, Frenzel T, Endrikat J, et al. 25 years of contrast-enhanced MRI: developments, current challenges and future perspectives. Adv Ther. 2016;33:1-28.
- Karabulut N, Elmas N. Contrast agents used in MR imaging of the liver. Diagn Interv Radiol. 2006;12:22-30.
- Seale MK, Catalano OA, Saini S, et al. Hepatobiliary-specific MR contrast agents: role in imaging the liver and biliary tree. Radiographics. 2009;29:1725-48.
- Gandhi S, Brown M, Wong J, et al. MR Contrast agents for liver imaging: what, when, how. Radio Graphics. 2006;26:1621-36.
- Namasivayam , Martin DR, Saini S. Imaging of liver metastases: MRI Cancer Imaging. 2007;7:2-9.
- Thian YL, Riddell AM, Koh DM. Liver-specific agents for contrast-enhanced MRI: role in oncological imaging. Cancer imaging. 2013;13:567.
- Park Y, Kim SH, Kim SH, et al. Gadoteric acid (Gd-EOB-DTPA) – enhanced MRI versus gadobenate dimeglumine (Gd-BOPTA)-enhanced MRI for preoperatively detecting hepatocellular carcinoma: an initial experience. Korean J Radiol. 2010;11:433-40.
- Pietryga JA, Burke LM, Marin D, Jaffe TA, Bashir MR. Respiratory motion artifact affecting hepatic arterial phase imaging with gadoterate disodium: examination recovery with a multiple arterial phase acquisition. Radiology. 2014;271:426-34.
- Tamada T, Ito K, Sone T, et al. Dynamic contrast-enhanced magnetic resonance imaging of abdominal solid organ and major vessel: comparison of enhancement effect between Gd-EOB-DTPA and Gd-DTPA. J Magn Reson Imaging. 2009;29:636-40.
- Filippone A, Blakeborough A, Breuer J, et al. Enhancement of liver parenchyma after injection of hepatocyte specific MRI contrast media: a comparison of gadoteric acid and gadobenate dimeglumine. J Magn Reson Imaging. 2010;31:356-64.
- Albiin N. “MRI of focal liver lesions.” Current medical imaging reviews 8.2. 2012;107-16.
- Morana G, La Torre E, Fuser M, et al. Optimal imaging of focal liver lesions. Imaging in Medicine. 2010;2:497–518.
- Endrikat J, Schwenke C, Vogtlaender K, et al. Safety profile of gadoteric disodium in elderly patients (≥ 65 years). Acta Radiologica. 2018;59:81-8.
- Endrikat JS, Dohanish S, Balzer T, et al. Safety of gadoteric disodium: results from the clinical phase II–III development program and postmarketing surveillance. J Magn Reson Imaging. 2015;42:634-43.
- Ringe K, Husarik D, Sirlin C, et al. Gadoteric disodium-enhanced MRI of the liver: part 1, protocol optimization and lesion appearance in the noncirrhotic liver. AJR. 2010;195:13-28.
- Frydrychowicz A, Nagle, SK, D’Souza SL, et al. Optimized high resolution contrast enhanced hepatobiliary imaging at 3 tesla: a cross over comparison of gadobenate dimeglumine and gadoteric acid. J Magn Reson Imaging. 2011;34:585-94.
- Zech CJ, Herrmann KA, Reiser MF, et al. MR imaging in patients with suspected liver metastases: value of liver-specific contrast agent Gd-EOB-DTPA. Magn Reson Med Sci. 2007;6:43-52.
- Caraiani CN, Dan M, Fenesan DI, et al. Description of focal liver lesions with Gd-EOB-DTPA enhanced MRI. Clujul Med. 2015;88:438.
- Park G, Kim YK, Kim CS, et al. Diagnostic efficacy of gadoteric acid - enhanced MRI in the detection of hepatocellular carcinomas: comparison with gadopentetate dimeglumine. Br J Radiol. 2010;83:1010-6.
- Huppertz A. Gadoteric acid-enhanced MRI compared with unspecific extracellular contrast media for differential diagnosis of metastasis and benign liver lesions. EJCMO. 2010;1-7.
- Brisman TB, Dahlström N, Edsberg N, et al. Liver vessel enhancement by Gd-BOPTA and Gd-EOB-DTPA: a comparison in healthy volunteers. Acta Radiol. 2009;50:709-15.