# Comparison of Dynamic Phase Enhancement of Hepatocellular Carcinoma using Gadoxetate Disodium versus Gadobenate Dimeglumine.

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Disclosure

Dr. Aisen consults for Repligen, Inc, Waltham, Mass, which is developing a formulation of secretin for use in MRCP.

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# Comparison of Dynamic Phase Enhancement of Hepatocellular Carcinoma using Gadoxetate Disodium versus Gadobenate Dimeglumine.

## Abstract

PURPOSE

To determine the differences in enhancement pattern of hepatocellular carcinoma (HCC) during first 5 minutes of post-contrast phases MRI with gadoxetic acid (Gd-EOB-DTPA) versus gadobenate dimeglumine (Gd-BOPTA) using the FDA approved doses.

METHODS AND MATERIALS

95 patients with HCC were examined on 1.5 T scanner; 74 patients with Gd-BOPTA and 21 with Gd-EOB-DTPA. Using the same MRI parameters, post-contrast imaging was performed at pre-contrast, arterial, portal venous, equilibrium, and 5 minute delayed phases. Gd-EOB-DTPA was administered at a dose of 0.025 mmol/kg body weight and Gd-BOPTA at a dose of 0.1 mmol/kg body weight. Both agents were injected at rate of 2 mL/sec and arterial phase was timed by using bolus-triggering software. The contrast-to-noise ratio (CNR) was calculated by $(SI_{lesion} - SI_{liver})/SD_{background}$. (SD=Standard Deviation, SI=signal intensity)

RESULTS

Mean CNRs were not statistically significant different in arterial (p=0.3), portal venous (p=0.1) and 5 minute delayed phases (p=0.73). CNR of lesions scanned with Gd-EOB-DTPA was significantly higher in the equilibrium phase (p=0.006). When pooling the data from all for post-contrast phases, HCCs demonstrated no significant change in enhancement pattern with Gd-EOB-DTPA compared to Gd-BOPTA. CNRs of lesions

scanned with Gd-EOB-DTPA were lower in arterial phase compared to Gd-BOPTA, though this did not reach statistical significance.

CONCLUSION

Gd-EOB-DTPA in HCC imaging resulted in lower CNR during the arterial phase and higher CNR during the portal venous, equilibrium and 5 minute delayed phases compared to Gd-BOPTA using the FDA approved doses, however overall there was no statistical significance (P=0.077).

**Keywords:** Hepatocellular carcinoma, MRI, contrast, Gadoxetate Disodium, Gadobenate Dimeglumine

## Introduction

Gadoxetate Isodium (Gd-EOB-DTPA, Eovist/Primovist®, Bayer) was approved by the FDA for clinical use in 2008 and has emerged as a valuable hepatobiliary phase MRI contrast agent [1,2]. The presence or absence of contrast enhancement in the hepatobiliary phase can be very useful in differentiating previously indeterminate hepatic lesions, such as focal nodular hyperplasia, well-differentiated hepatocellular carcinoma (HCC), adenomas, atypical hemangiomas, and metastases [2-4].

Approximately 50% of Gd-EOB-DTPA undergoes hepatobiliary excretion and 50% is excreted by the kidneys [2]. After being taken up by hepatocytes via the organic anion transport protein, Gd-EOB-DTPA redistributes to the extracellular space and undergoes delayed excretion into bile ducts or sinusoids [5]. Extracellular space redistribution and gradual hepatobiliary phase excretion allows for prolonged dynamic imaging and a progressive increase in enhancement of hepatocytes and hepatocyte-containing lesions. When hepatocellular dysfunction is present, as a result of advanced cirrhosis, Gd-EOB-DTPA is increasingly excreted via the alternate renal pathway [6], which may reduce visibility of lesions on the hepatobiliary phase images. In comparison, Gadobenate dimeglumine (Gd-BOPTA) undergoes 78-96% renal excretion and therefore yields a lower percentage of hepatocyte enhancement in the hepatobiliary phase when compared to Gd-EOB-DTPA [7].

In practical terms, the hepatobiliary phase of scans performed with Gd-EOB-DTPA often provides valuable diagnostic information; for example, most HCC's and almost all metastatic lesions do not take up the agent, and will therefore appear as low signal focal lesions on 20-minute delayed hepatobiliary phase images [2].

There is, however, a possible disadvantage of Gd-EOB-DTPA. Gd-EOB-DTPA is distributed at a molar concentration less than half that of most other agents, including Gd-BOPTA, and the label instructions recommends a lower milliliter dose (Table 1). Thus, the total number of moles of agent is usually 25% of a typical scan performed with Gd-BOPTA. Since arterial phase wash-in and delayed phase relative wash-out are hallmarks of HCC diagnosis, this can be an issue in interpreting Gd-EOB-DTPA enhanced MR scans. For this reason, we investigated and compared the enhancement of HCC with Gd-EOB-DTPA to that of Gd-BOPTA within the first 5 minutes of contrast injection.

**Materials and Methods**

Following FDA approval of Gd-EOB-DTPA in 2008, our institution, a major academic tertiary care center with a large liver transplant service, started using Gd-EOB-DTPA for screening and follow up of HCC in all liver MR exams over a period of 9 months. Patients had chronic liver disease and were scanned on 1.5 T MR scanners (Magnetom Avanto, Siemens Medical Solutions, Malvern, PA USA). Following approval from the institutional review board, a HIPPA compliant retrospective study was performed. Data collection was performed in patients with known HCC that were scanned during this 9-

month time period with Gd-EOB-DTPA (n=21 patients) and from prior cases of known HCC scanned with Gd-BOPTA (n=78).

In both groups, same imaging parameters were used to acquire contrast-enhanced phases using a 3D fat-suppressed, T1-weighted volume interpolated gradient echo sequence (VIBE®, Siemens Medical Solutions, Malvern, PA, USA) (TR: 4.98 ms, TE: 2.27 ms, flip angle:12). FDA approved and manufacturer recommended dose of 0.025 mmol/kg for Gd-EOB-DTPA and 0.1 mmol/kg for Gd-BOPTA were administered intravenously at a rate of 2 ml/sec, followed by a 20 mL normal saline flush. Bolus triggering software was utilized to time the arterial phase scans in both groups. Timing of the arterial phase was approximately 20 seconds, portal venous phase 50 seconds, equilibrium phase 120 seconds and delayed phase 5 minutes after contrast injection. Patients imaged with Gd-EOB-DTPA were additionally imaged at 10 and 20 minutes but these time points are excluded from comparison. K-space was acquired in a linear fashion.

The degree of enhancement of liver lesions was quantified by drawing a circular region of interest (ROI) within the lesion margin ($SI_{lesion}$) and around normal liver parenchyma ($SI_{liver}$). The sensitivity of HCC detection with Gd-EOB-DTPA is decreased in lesions less than 10 mm in diameter [8]; therefore minimum ROI was set at 1 $cm^2$. The standard deviation of background noise was calculated by drawing an ROI outside of the patient ($SD_{background}$) on the same image. The contrast-to-noise ratio (CNR) was calculated using the equation: $CNR = (SI_{lesion} - SI_{liver}) / SD_{background}$.

*Statistical Analysis*

The Mixed-Effect Repeat Measure (MMRM) model with unstructured variance-covariance matrix was used to model the repeated CNR including time, group (Gd-BOPTA or Gd-EOB-DTPA), and the interaction between time and group as fixed effects. The F tests were used to examine the overall difference between the two groups and the difference in mean CNR between the Gd-EOB-DTPA and Gd-BOPTA group at each time point.

## Results

Mean CNRs after administration of Gd-EOB-DTPA and Gd-BOPTA are shown on Figure 1 and Table 2. In the post contrast arterial phase, the mean CNR was 9.7 (±49) in the Gd-EOB-DTPA group and 19 (±36) in the Gd-BOPTA group. In the portal venous phase, the mean CNR was -15.2 (±38) in the Gd-EOB-DTPA group and 4.3 (±55) in the Gd-BOPTA group. In the equilibrium phase, the mean CNR was -25 (±34) in the Gd-EOB-DTPA group and -2.9 (±28) in the gadobenate group. In the 5 minute delayed phase, the mean CNR was -31.4 (±45) in the Gd-EOB-DTPA group and -27.7 (±35) in the Gd-BOPTA group.

The overall difference in CNRs when including all time points did not reach statistical significance (P=0.077). There was greater arterial enhancement on the arterial phase images with Gd-BOPTA than with Gd-EOB-DTPA, but this did not reach statistical significance. However, the contrast reverses on later vascular phase images; lesions are usually hypointense compared to liver on later vascular phases with both agents, a

phenomenon termed "washout" and indicated by negative CNR values. Our data showed greater CNRs and seemingly greater lesion "washout" relative to liver on the later vascular phases on the Gd-EOB-DTPA images compared to the Gd-BOPTA. This difference may be because of progressive enhancement of the liver with Gd-EOB-DTPA, likely due to the combined effects of vascular perfusion and hepatocyte uptake of the contrast agent (Figure 2). Negative CNRs observed beginning with portal venous phase using Gd-EOB-DTPA, compared to equilibrium phase with the Gd-BOPTA.

## Discussion

When compared to Gd-BOPTA, at standard doses Gd-EOB-DTPA demonstrates lower enhancement in normal vasculature and solid abdominal organs [9] and lower dynamic enhancement of the liver vasculature [10]. Frydrychowicz et al compared dynamic post contrast hepatic vasculature signal to noise ratio (SNR) with the higher (non-FDA approved) Gd-EOB-DTPA dose of 0.05 mmol/kg to the standard dose of Gd-BOPTA. Hepatic vascular SNR was lower in the Gd-EOB-DTPA group despite doubling the FDA-approved dose, and it was suggested that this agent be reserved for cases in which hepatobiliary phase imaging is needed [7]. Therefore, it should not be surprising that a hypervascular lesion such as HCC should show relatively lower early dynamic enhancement with Gd-EOB-DTPA compared to Gd-BOPTA.

The sentinel paper by Vogl et al comparing the contrast enhancement in liver tumors with Gd-EOB-DTPA versus Gd-BOPTA was published in 1996 [11]. Patients with a variety

of known liver lesions, including HCC (not all had cirrhosis), focal nodular hyperplasia (FNH), hemangioma, and metastatic disease were scanned with dynamic post contrast T1-weighted FLASH imaging (TR/TE=154/6, 70 degree flip angle, NEX=1) with different doses of Gd-EOB-DTPA (0.0125, 0.025, and 0.05 mmol/kg). Within 1 week, the same patients were scanned using the same dynamic MR pulse sequences with the standard dose of Gd-BOPTA (0.1 mmol/kg). The study included 12 patients with known HCC. Of these 12 patients, 4 were given the highest (0.05 mmol/kg) dose of Gd-EOB-DTPA, only 5 were given the (now FDA-approved) intermediate dose (0.025 mmol/kg), and 3 were given the lowest dose (0.0125 mmol/kg). It should be noted that the first post-contrast image on this study was acquired at 45 seconds following contrast injection which is past the arterial phase and close to the portal venous phase using modern day scanners. The lesions in the 5 patients given the intermediate dose of Gd-EOB-DTPA showed 45 second "wash-in" of contrast media, with subsequent progressive "wash-out" of contrast media throughout the portal venous, equilibrium, delayed, and hepatobiliary phases. When later scanned with Gd-BOPTA, these lesions showed similar characteristic dynamic "wash-in" and "wash-out" of contrast during the first 5 minutes after contrast administration. However, the measured percentage of contrast enhancement of HCC (SI postcontrast – SI precontrast) / SI precontrast in the Gd-BOPTA group was approximately 20-25% higher at all time points in the first 5 minutes when compared to Gd-EOB-DTPA. By ignoring the first 3 minutes of contrast enhancement, the authors concluded that the dynamic enhancement characteristics of HCC with the 0.025 mmol/kg and 0.05 mmol/kg doses of Gd-EOB-DTPA were "similar at 3 minutes" to the 0.1 mmol/kg dose of Gd-BOPTA. Another remote study by Reimer et al published in 1996

concluded that a dose of 0.0125 mmol/kg was sufficient for the detection of liver lesions with significant improvement of lesion detection at 20 and 45 minutes [12]. Conclusions from these studies may have weighed in the FDA decision to focus on the hepatobiliary phase imaging with Gd-EOB-DTPA and approve the intermediate (0.025 mmol/kg) Gd-EOB-DTPA dose for clinical use in 2008.

Our current study has the advantage of a much larger sample size of HCC lesions in the Gd-EOB-DTPA group (n=21) and Gd-BOPTA group (n=74), versus a total sample size of 12 in the 1996 study. However, our study involved retrospective analysis of HCC lesions in different patients, while the 1996 study evaluated known lesions in the same patient with both contrast agents. The relatively small, disproportionate sample size of patients in the Gd-EOB-DTPA group (n=21) may have limited statistical analysis.

The preponderance of evidence in our study and in the literature suggests that Gd-EOB-DTPA offers relatively lower CNR in the liver vasculature, parenchyma, and hepatocellular carcinomas during the first 5 minutes of dynamic imaging when compared to Gd-BOPTA. Given the identical imaging parameters, decreased arterial phase CNRs in the Gd-EOB-DTPA group in our study is probably secondary to using the lower FDA approved and manufacturer recommended dose of Gd-EOB-DTPA (0.025 mmol/kg) which is 25% of the dose administered by Gd-BOPTA (0.1 mmol/kg). Our clinical experiences combined with relatively higher cost of Gd-EOB-DTPA have led our institution to stop using the use of Gd-EOB-DTPA for screening of HCC in suspected patients. It remains a useful agent for problem solving in cirrhotic patients, and other

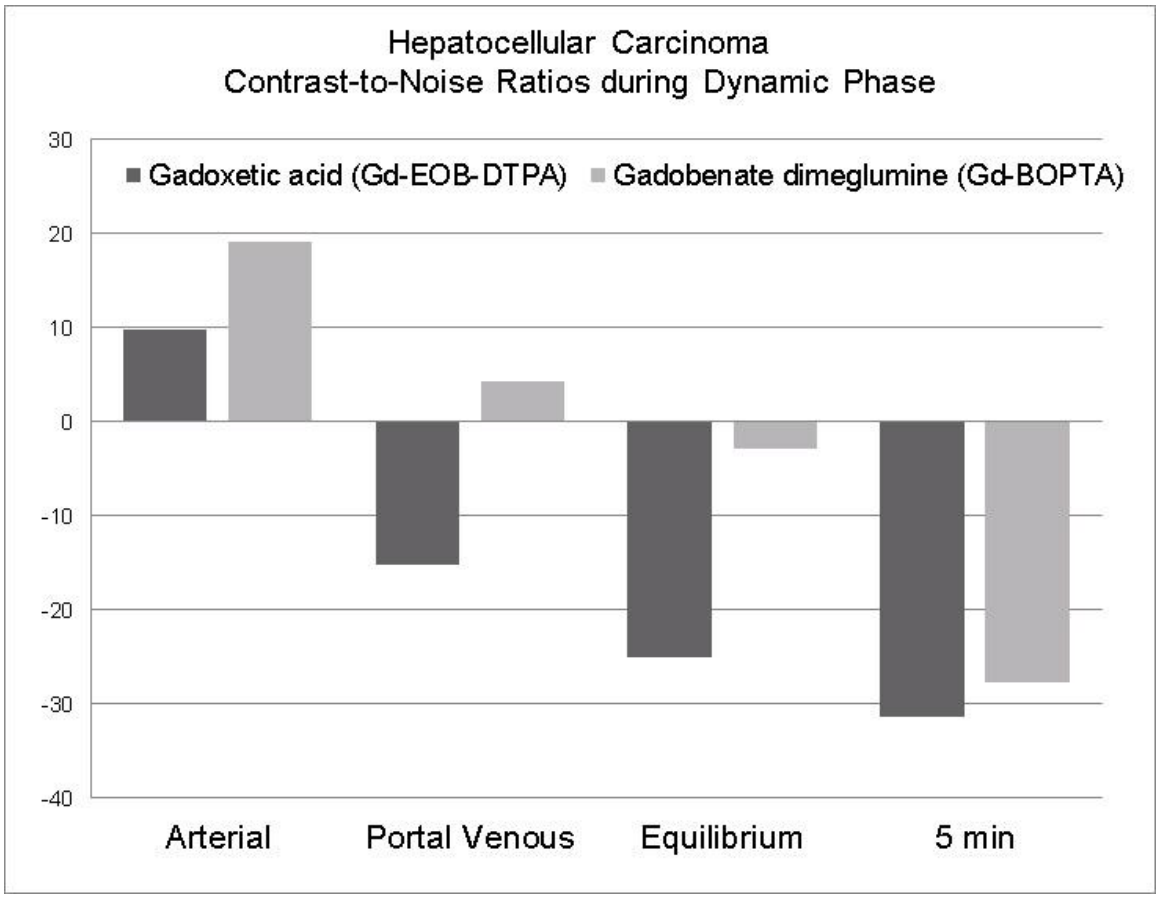
lesions such as metastasis, for which the lower arterial phase enhancement may be less of an issue, and for whom the hepatobiliary phase images may be especially efficacious.

## Conclusion

Using the FDA approved doses of the two contrast agents, Gd-EOB-DTPA yields a lower but not statisically significant CNR for HCC compared to Gd-BOPTA during the arterial phase. Average CNR was higher with Gd-EOB-DTPA during portal venous and 5 minute delayed phases and this advantage is probably secondary to progressive enhancement within the liver parenchyma. The overall difference in CNRs including all time points did not reach statistical significance (P=0.077).

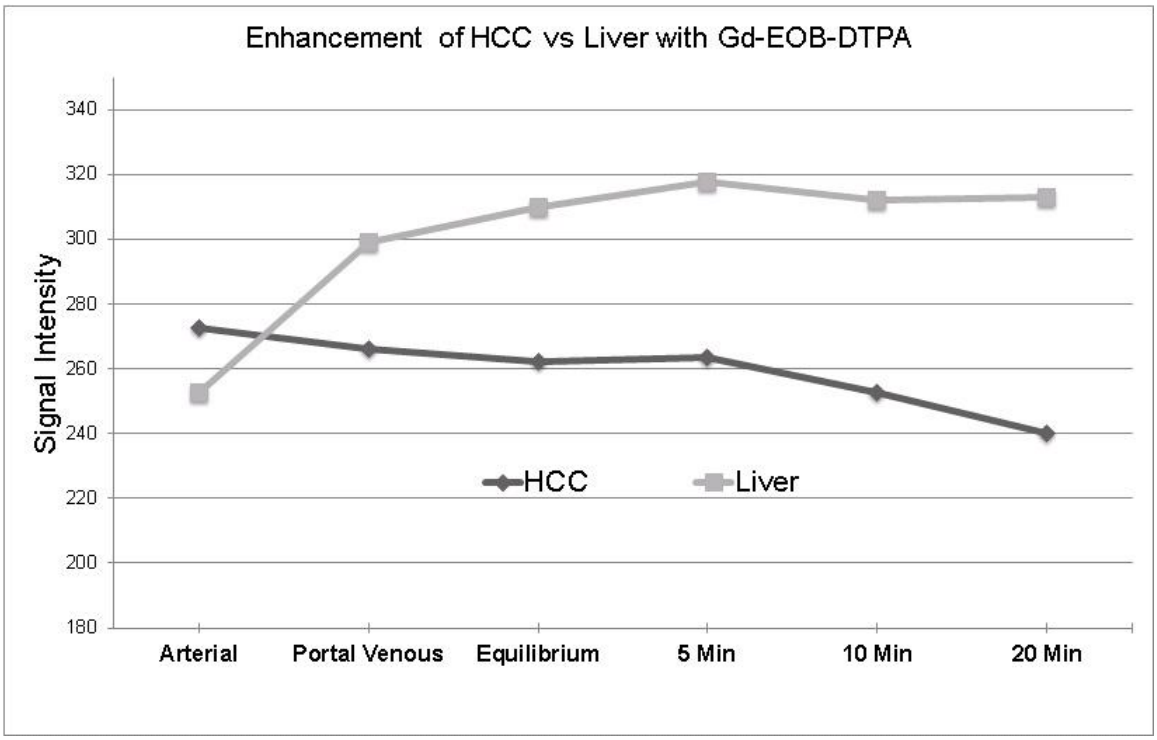
## Figures

**Figure 1**. Comparison of the CNRs during the first 5 minutes with Gd-EOB-DTPA versus Gd-BOPTA.




Bar plot of least square mean of the Gd-EOB-DTPA and Gd-BOPTA group at each time point. Mean CNR of HCC lesions in the arterial (20 sec), portal venous (50 sec), equilibrium (120 secs), and 5 minute delayed post contrast sequences. Gd-BOPTA yields approximately twice the CNR of Gd-EOB-DTPA during the arterial phase. Gd-EOB-DTPA shows washout earlier than the Gd-BOPTA, beginning with the portal venous phase. $CNR = (SI_{lesion} - SI_{liver}) / SD_{background}$.

**Figure 2.** Comparison of enhancement curves of HCC and liver with GD-EOB-DTPA.




Linear plot chart of average signal intensity curves of HCC and liver parenchyma at all time points. There is progressive enhancement of the liver with Gd-EOB-DTPA, likely due to hepatocyte uptake of the contrast agent. HCC shows higher signal intensity compared to the liver parenchyma during the arterial phase and rapidly starts loosing its signal intensity over 20 minutes. Progressive enhancement of the liver parenchyma compared to the HCC is probably one of the reasons of relatively higher CNRs during the portal venous, equilibrium and 5 minute delayed phases of the GD-EOB-DTPA.

## Tables

**Table 1.** Comparison of Gd-EOB-DTPA and Gd-BOPTA dosage based on FDA and manufacturer recommendations.

| **Contrast agent** | **Concentration** | **FDA recommended dose** |
|---|---|---|
| **Gd-EOB-DTPA** | 181 mg/ml | 0.025 mmol/kg |
| **Gd-BOPTA** | 529 mg/ml | 0.1 mmol/kg |

**Table 2**. Comparison of mean CNR in Gd-EOB-DTPA and Gd-BOPTA groups at the arterial, portal venous, equilibrium, and 5 minute delayed time points.

| | **CNR Gd-EOB-DTPA** | **CNR Gd-BOPTA** | **Least Square Mean Difference** | **P value** |
|---|---|---|---|---|
| Arterial | 9.7 ± 49 | 19.5 ± 36 | -9.8 | 0.3 |
| Portal Venous | -16.3 ± 38 | 4.3 ± 55 | -20.6 | 0.1 |
| Equilibrium | -25 ± 34 | -4.2 ± 28 | -20.9 | 0.006 |
| 5 min Delayed | -31.4 ± 45 | -28.2 ± 35 | -3.1 | 0.73 |
| Overall CNR difference including all time points | | | | 0.08 |

CNR data are expressed as mean ± SD. Only statistically significant difference in CNRs of two groups was during equilibrium phase ($p=0.006$). When including all time points, there was no statistical significance ($p=0.08$).

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Figure 1

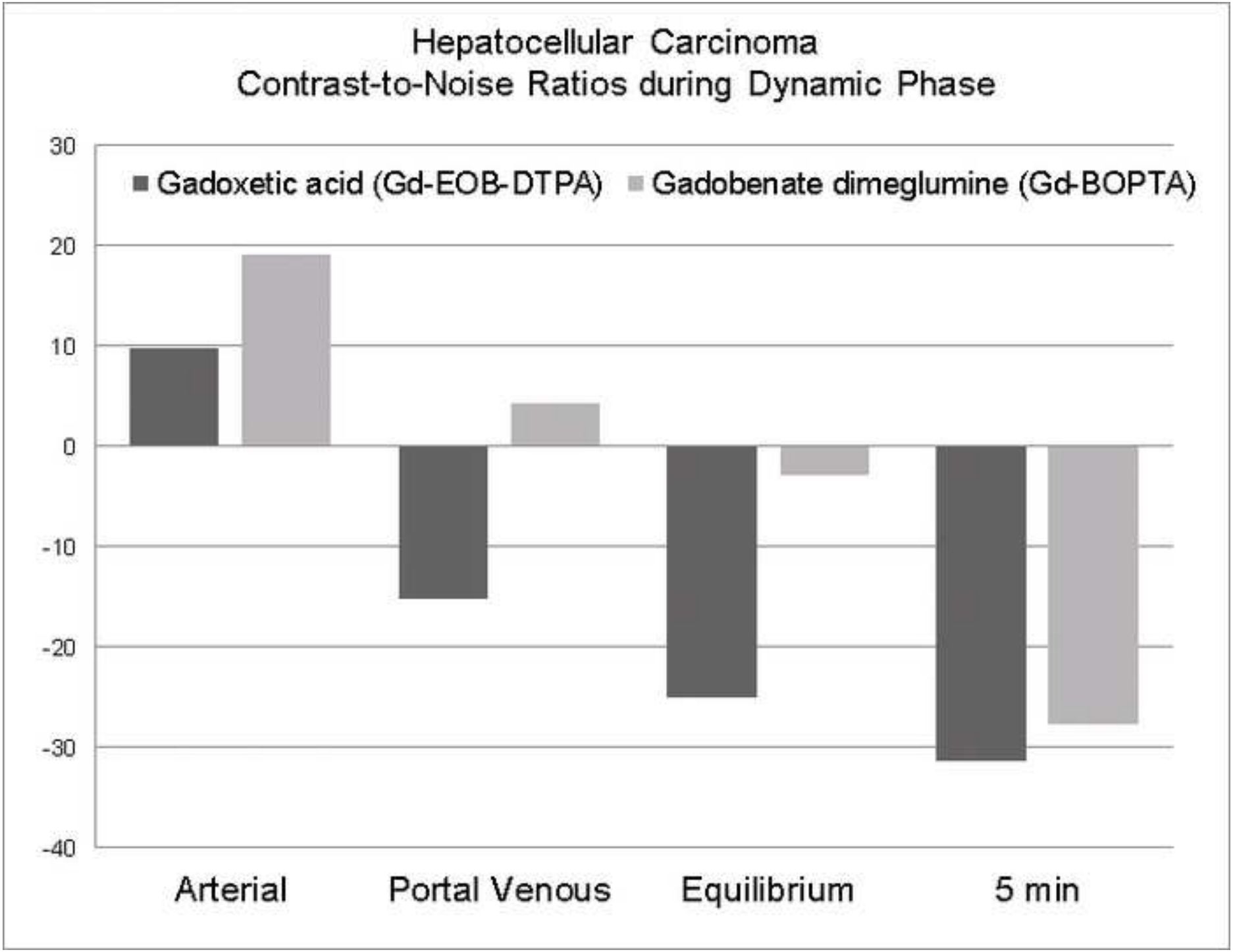
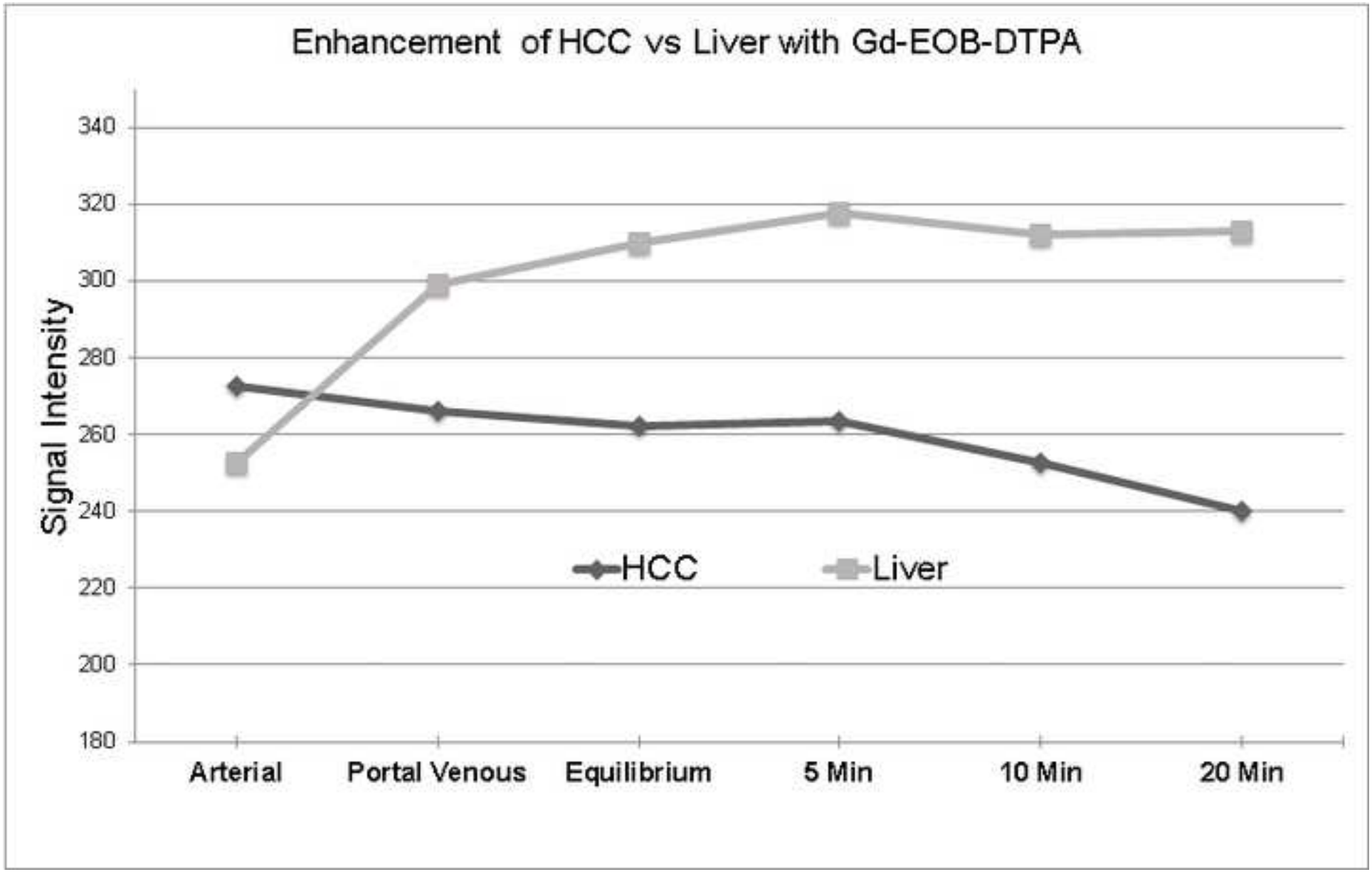

Hepatocellular Carcinoma
Contrast-to-Noise Ratios during Dynamic Phase
Gadoxetic acid (Gd-EOB-DTPA)
Gadobenate dimeglumine (Gd-BOPTA)
30
20
10
0
-10
-20
-30
-40
Arterial
Portal Venous
Equilibrium
5 min

Figure 2


Enhancement of HCC vs Liver with Gd-EOB-DTPA
Signal Intensity
340
320
300
280
260
240
220
200
180
HCC
Liver
Arterial
Portal Venous
Equilibrium
5 Min
10 Min
20 Min