

## Original Research Article

# Enhancing contrast of magnetic resonance imaging in patients with liver cirrhosis: Conveyance times of Primovist in hepatobiliary system

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### Abstract

**Purpose:** To determine transit times for excretion of gadoxetic acid (Gd-EOB-DTPA), a recent magnetic resonance imaging (MRI) contrast agent, in hepatobiliary system of patients with liver cirrhosis.

**Methods:** Liver cirrhosis patients that underwent contrast MRI examination at Renai Hospital, Taipei City, Taiwan were included. The patients who have experienced contrast-enhanced abdominal MR examination after injection of 10 mL Gd-EOB-DTPA at 1.5-T MR from December 2009 to March 2011, were included retrospectively. The images were evaluated for the presence of contrast agent in intra-hepatic bile ducts (IHD), common bile duct (CBD), gall bladder and duodenum.

**Results:** The optimal time for arterial phase was from 15 s after injection while the optimal time for portal venous imaging was from 40 s after injection. Furthermore, the optimal time to observe changes was 20 min after contrast initiation of Gd-EOB-DTPA in 39 patients (83 %) in IHD and 37 patients (78.5 %) in CBD. Gall bladder reflux was visible in 26 patients (43 %), and duodenal excretion in 17 patients (36 %). After 30 min of contrast injection, Gd-EOB-DTPA could still be detected in 6 patients (13 %) in IHD and 7 patients (15 %) in CBD, while gall bladder reflux was visible in 10 patients (21 %), and duodenal excretion in 20 patients (55 %).

**Conclusion:** The excretion of Gd-EOB-DTPA can be observed in liver cirrhosis patients.

**Keywords:** Hepatocellular carcinoma, Magnetic resonance imaging (MRI), Gadoxetic acid, Common hepatic duct

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## INTRODUCTION

The liver is the most metabolically complex organ in human body. It is large and complex organ with diverse functions, many of them are critical for survival [1]. The approaches for medical diagnosis and disease characterization of the liver and the biliary system via non-invasive methods have greatly improved over the previous decades due to the unending development of

computed tomography (CT), sonography or ultrasound (US), nuclear medicine (NM) and magnetic resonance imaging (MRI) [2]. Contrary to CT and NM, Magnetic Resonance imaging does not expose the patient to any ionizing radiation [3]. MRI of superior body soft-tissue contrast was believed to provide enough diagnostic information for most needs, without the use of contrast media [4]. Gadolinium-based and other contrast media were, however, soon

considered to be of significant importance in disease detection and characterization [5].

Gd-EOB-DTPA (gadolinium ethoxybenzyl diethylenetriaminepentaacetic acid, Primovist® 0.25 mmol/ml, Bayer Schering Pharma, Berlin, Germany) is a more recently approved liver-specific contrast agent [5,6]. It combines hepatocellular specificity with T1-relaxivity and extracellular behavior [7]. After intravenous injection, Gd-EOB-DTPA is first distributed into the extracellular space and then taken up by the hepatocytes.

It is excreted un-metabolized form in equal proportions by the kidneys and ATP-dependent active transport in the hepatocytes to the biliary system. Due to which, the hepatobiliary excretory proportion is approximately ten times greater than for Gd-BOPTA. Renal excretion of Gd-EOB-DTPA can be substituted by the hepatobiliary elimination and vice versa [8].

## METHODS

### Study design

This is a retrospective study analyzing data from the hospital database as the study material. We collected all the patients' baseline information including the Child Pugh scores, bilirubin level, and liver function. We followed guidelines given by American Association of study of liver diseases [22].

### Patient population

Institutional Review Board of Taipei City Hospital - Renai Branch approved the study and informed consent was waived. Patients with liver cirrhosis but with normal glomerular filtrate rate (GFR) were included in the analysis. All the patients underwent Gd-EOB-DTPA contrast-enhanced abdominal MR examination at Taipei City Hospital-Renai Branch from January 2011 to August 2012. Dataset of patient with ages equal or greater than 20 years were included in the study as the safety and effectiveness of Gd-EOB-DTPA has not been established in pediatric patients.

A total of 47 patients were enrolled in this study. Clinical and demographic information of the patients in the present study is illustrated in Table 1.

Patients younger than 18 years or with abnormal glomerular filtration rate were excluded from the study. Also Patients who had any contra-indication to MRI (cardiac pacemaker,

ferromagnetic implants, etc.) were excluded as well.

**Table 1:** Patient demographic data and clinical information of the patients

Age range (mean age)	22–80 years (57.3years)
Sex (M/F)	32/15
Total bilirubin	2.11mg/dL
AST/ALT	46/40 IU/L
Creatinine	0.98 mg/dL
CBD diameter	4.84 mm (2.91- 10.86)
Hepatitis (n)	B (40) C (4)
	Alcoholic (2) B +Alcoholic (1)
Child-Pugh class (n)	A (40) B (5) C (2)

### Imaging Methods

All MRI examinations of the liver of the enrolled patients were performed with Achieva 1.5T A-Series MRI Scanner from Philips phased-array body coil. Prior to contrast agent administration, turbo spin-echo (TSE) T2WI (TR/TE: 1000 – 1800/110 milliseconds; Slice thickness 8mm; Gap 0.8 mm; Matrix, 192x256; TSE factor, 24; number of average [NEX], 2; Flip angle 90°; FOV, 38-40 cm) without and with fat saturation, and coronal T2WI were obtained under respiratory trigger. Dual T1WI (TR/TE: 180/2.3/4.6; Slices thickness 8mm; Matrix, 192x256; NEX, 1; Flip angle 10°; FOV, 38-40 cm) and fat sat T1WI were performed during one breath hold. Automatic shimming has been used for fat suppression imaging to maximize magnetic field homogeneity. Flow compensation is also used for the same purpose.

For the contrast-enhanced MRI, all the patients received a dose of 0.025 mmol/kg or 10 ml of Gd – EOB-DTPA (Primovist; Bayer Schering Pharma, Osaka, Germany). The contrast agent was injected as a bolus at a speed of nearly 2 ml/s through peripheral veins. Dynamic 3D T1-weighted fast field echo (FFE) sequence (TR/TE: 5 - 10/3.3 ms; Slice thickness 5 mm; Matrix, 192 x 256; NEX, 1; Flip angle 10°; FOV, 38 - 40 cm) was carried out before, 18 - 20 s (arterial phase, AP), 50 ~ 55 s (portal venous phase, PP), 85 ~ 90 s (venous phase, VP) following the contrast agent injection. In addition, three delay phase images (180 s, 20 min and 30 min after the injection of contrast agent) were acquired.

### Imaging analysis

The images were evaluated for the presence of

contrast agent in the intra-hepatic bile ducts (IHD), the common bile duct (CBD), the gallbladder and the duodenum in AP, PP, VP and three delayed phases. The images were evaluated by the same radiologist. He had to record the phase in which the Gadoteric acid appeared.

### Statistical analysis

The data has been presented as mean  $\pm$  standard deviation (SD). Each experiment was repeated at least 3 times. Statistical analysis was performed using SPSS version 19 for one-way analysis of variance (ANOVA) with  $p < 0.05$  being significant, was used to determine whether there was significant difference in time of first appearance of contrast agent in the individual segments of the hepatobiliary tract, with the cirrhotic degree (according to Child-Pugh score) and the bilirubin level (according to mean value of bilirubin and the level of bilirubin data).

## RESULTS

The demographic patient data and clinical indications for the abdominal MR examinations are provided in Table 1. Out of the 47 patients, gall bladder (GB) was not visible in 9 patients, 4 out of 9 patients had cholecystectomy. The GB might have been removed due to complications associated with the gall bladder i.e. gall stones, and gall bladder cancer etc. The mean CBD diameter was 4.84 mm.

The optimal time of arterial phase was from 18 - 20 s after injection, while for the portals, 50 - 55 s after injection for the venous phase. The mean time for opacification was after 20 min contrast injection in 39 patients (39/47, 83 %) at the IHD

in 37 patients (37/47, 78 %) at the CBD. Gall bladder reflux was visible in 26 (26/47, 43 %) and 17 patients (17/47, 36 %) at the duodenal. After 30 min, Gd – EOB-DTPA could still be detected in 6 patients (6/47, 13 %) at the IHD and in 7 patients (7/47, 15 %) at the CBD. Gallbladder reflux was visible in 10 patients (10/47, 21 %), duodenal excretion in 26 patients (26/47, 55 %) respectively as shown in Table 2.

On visualization of the biliary tree, the distribution was not statistically significant ( $p < 0.05$ ) between bilirubin level and visualization of the biliary tree as shown on Table 3.

On Visualization of Gd – EOB-DTPA contrast in IHD and CBD for Patients with different bilirubin level, the excretion of Primovist in the biliary tree is affected by the bilirubin level. After 30 min, the  $p$  value was significant ( $p=0.043$ ) in comparison with group 1 and group 3. The  $p$  value was not significant, between group 1 and 2 ( $p=0.27$ ) after 30 min of injection. The  $p$ -value was not statistically significant between group 2 and group 3, after 30 min post injection ( $p=0.226$ ) as provided in Table 4.

In group three, where the bilirubin level is more than 2 mg / dl 30 minutes' post injection, the visualization level is 40 % as shown in Figure 1. This illustrates the severity of liver cirrhosis can influence the uptake and excretion of the contrast agent. Dahlqvist et al, demonstrated that impaired hepatobiliary function severely influences the hepatic uptake of Gd – EOB - DTPA when they did a study on 31 patients on how to quantify the hepatocyte specific uptake of Gd - BOPTA and Gd – EOB - DTPA using dynamic contrast enhanced (DCE) MRI [19].

**Table 2:** Transit times in various segments of the biliary excretion route

Biliary excretion segment	AP	PP	VP	3min	20min	30min
IHD	0	0	*2/0/0	0	*36/3/0	*2/2/2
CBD	0	0	*3/0/0	0	*34/3/0	*3/2/2
GB	0	0	*1/0/0	0	*24/2/0	*5/3/2
Duodenum	0	0	0	*1/0/0	*17/0/0	*19/5/2

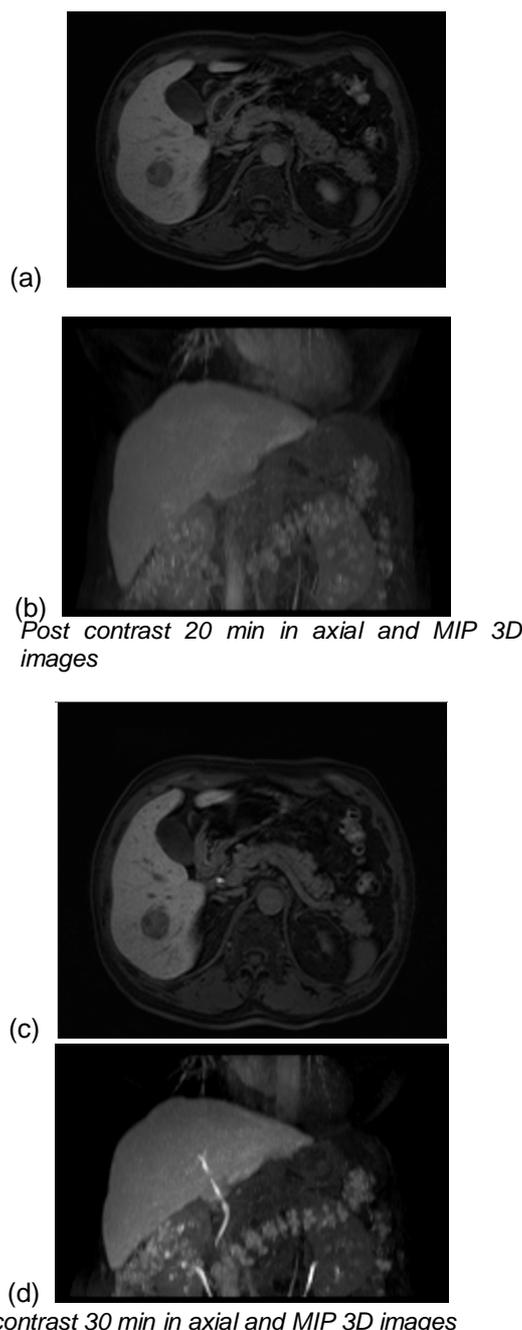
**Table 3:** Bilirubin levels on visualization of the biliary tree

Phase	IHD		CBD		GB		Duodenum	
	No.	Bilirubin	No.	Bilirubin	No.	Bilirubin	No.	Bilirubin
	2	0.75 $\pm$ 0.35	3	0.79 $\pm$ 0.26	1	0.87	0	VP
3 min	0	0	0	0	0	0	1	0.87
20 min	39	2.07 $\pm$ 5.59	37	2.13 $\pm$ 5.74	26	2.44 $\pm$ 6.86	17	3.11 $\pm$ 8.48
30 min	6	2.85 $\pm$ 3.69	7	2.58 $\pm$ 3.44	10	2.16 $\pm$ 2.91	26	1.57 $\pm$ 1.85
P-value		0.885		0.888		0.964		0.653

No. indicates number of patients

**Table 4:** Visualization of Gd – EOB-DTPA contrast in IHD and CBD for patients with different bilirubin level

Variable		Group 1 (27) (>1.2 mg/dl)	Group 2 (15) (1.2 - 2.1 mg/dl)	Group 3 (5) (>2 mg/dl)
Venous phase	IHD	2	-	-
	CBD	3	-	-
3 min	IHD	-	-	-
	CBD	-	-	-
20 min	IHD	23	12	3
	CBD	21	12	3
30 min	IHD	2(2/27) 7.4%	3(3/15) 20%	2(2/5) 40%
	CBD	3(3/27) 11%	3(3/15) 20%	2(2/5) 40%



**Figure 1:** Appearance of Gd-EOB-DTPA in the hepatobiliary System after 20 and 30 min in Subfigure a, b, c and d

## DISCUSSION

Currently, data regarding transit times of Gd-EOB-DTPA via the biliary excretion route in the patients is limited, as most of the 'delayed imaging time course data' have been gathered from healthy volunteers. Our analysis which was performed on the patients with liver cirrhosis showed no difference in terms of transit times when compared to the other studies conducted on patients with normal liver. Kristina I. Ringe *et al* evaluated the hepatobiliary transit times of Gd-EOB-DTPA in 61 patients with normal liver function [14]. After 20 min of contrast initiation, Gd-EOB-DTPA was visible in the IHD and CBD in all patients.

In our study, 40 out of 47 patient were Child Pugh A. This might be the reason that there is no difference between our study and Kristina's study. In a phase I clinical evaluation, Hamm *et al* detected enhancement of the CBD as early as 10 min after contrast administration in 44 healthy volunteers [10]. Dahlström *et al*, who also evaluated the biliary excretion of Gd-EOB-DTPA in healthy subjects, later on confirmed these findings [15]. Bollow *et al* investigated the time course of contrast enhancement in the bile ducts in 16 healthy volunteers at 4 different doses of Gd-EOB-DTPA. Initial enhancement of the CBD was seen at a mean time of  $10 \pm 4$  min post contrast [11]. Our results are in line with the previously reported transit times for the intrahepatic bile ducts and the CBD but in patients with normal liver function which basically means that Gd-EOB-DTPA is not affected by liver disease. The number of patients in our study is small and the majority of the patients represented were only mildly affected by the disease. Patients with child Pugh C seemed to influence liver excretion of the contrast media. This confirms previous studies which indicate a tendency towards decreased diagnostic capability with the severity of cirrhosis.

Frank *et al* compared the quality of biliary duct

visualization using Gd-EOB-DTPA enhanced magnetic resonance cholangiography in 40 adults with liver cirrhosis and 20 adults with normal liver parenchyma [18]. The overall quality was rated as sufficient for anatomical visualization of the biliary tree in all individuals of the control group 20 min after Gd-EOB-DTPA administration, but in only 16/40 patients (40 %) of the cirrhosis group within 30 min after administration. Analysis revealed non-sufficient visualization of the biliary tree 20 min after Gd – EOB-DTPA administration, were total serum bilirubin levels  $\geq 30 \mu\text{mol/l}$ .

The excretion of Primovist in the biliary tree is affected by bilirubin level in group 3 where the bilirubin level is more than 2mg/dl 30 minutes post injection. The visualization level is 40 percent. This illustrates that the severity of liver cirrhosis can influence the uptake and excretion of the contrast agent. Dahlqvist *et al* demonstrated that impaired hepatobiliary function severely influences the hepatic uptake of Gd-EOB-DTPA when they did a study on 31 patients on how to quantify the hepatocyte-specific uptake of Gd-BOPTA and Gd-EOB-DTPA using dynamic contrast-enhanced (DCE) MRI [19].

Primovist can be detected in most of the patients after 20 minutes with child Pugh A/B/C in this study. In the venous phase we can detect Primovist in patients 2/3/1, IHD, CBD, GB respectively early in the phase. It is important to note that all these patients have child Pugh A. Patients with child Pugh B and C seemed to influence the liver excretion of the contrast media. Our results were pretty similar to a study by Tsutomu Tamada that showed similar results after the MR image obtained in an 80-year-old woman with cirrhosis (Child-Pugh C) acquired 20 min after Gd-EOB-DTPA administration[20,21].

### Study limitations

One weakness of this study is the different distribution of the number of the study population in Child-Pugh class (A, B and C) with a high number of population in (A) compared with very low population number in (B and C). This may have led to failure in having an insignificant *p*-value. As this was a retrospective study, the exact point of time for acquisition of the delayed images was not standardized.

### CONCLUSION

It can be concluded that liver cirrhosis patients show no significant changes with regards to transit times when compared to normal patients.

Despite the difficulties in quantification of liver function, GD – EOB- DTPA enhanced MR imaging (MRI) offers a unique opportunity to combine qualitative and quantitative morphological and functional information that may improve the assessment of focal liver lesions and diffuse liver diseases and probe liver function.

### DECLARATIONS

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#### Conflict of Interest

No conflict of interest associated with this work.

#### Contribution of Authors

The authors declare that this work was done by the authors named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by them.

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