Focal liver lesion detection in gadoxetic acid-enhanced liver MRI: Effects of scan delay, hepatic function, and magnetic field strength

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Directed by Professor Myeong-Jin Kim

The Master′s Thesis submitted to the Department of Medicine,

the Graduate School of Yonsei University

in partial fulfillment of the requirements for the degree of

Master of Medical Science

Hua Sun Kim

December 2011

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December 2011

ACKNOWLEDGEMETS

First and foremost, I would like to thank Professor Myeong-Jin Kim for his guidance and support. This thesis would simply not be possible without his warm advice and encouragement.

I am deeply grateful to Professor Jae-Joon Chung and Professor Joon Suk Lim for generously providing his knowledge and guidance throughout the course of the clinical study for this thesis.

Last but not least, I thank my family for their unfailing love and support.

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ABSTRACT

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Purpose : To determine the effects of scan delay, hepatic function, and magnetic field

strength on the performance of gadoxetic acid disodium enhanced magnetic resonance

imaging in diagnosing focal liver lesions.

Materials and Methods : Gadoxetic acid disodium enhanced MRI conducted in 72

patients with two sets of hepatobiliary phase images obtained at 10 minutes and 20

minutes were reviewed retrospectively. For quantitative analysis, liver-to-lesion signal

difference ratio (SDR) was measured and compared between precontrast, 10-minute

delay, and 20-minute delay images. SDRs were compared between 1.5-T and 3.0-T and

also between cirrhotic patients and non-cirrhotic patients. For qualitative analysis, two board-certificated radiologists reviewed 10-minute delay and 20-minute delay images. The sensitivity and specificity of each reader was compared.

Conclusion : An increase in the liver-to-lesion signal difference ratio on 10- and 20-min delay images was dependent on the patients' hepatic function but not dependent on the magnetic strength of the imaging system. There was no significant difference in sensitivity or specificity between the 10-minute and 20-minute delay images.

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I. INTRODUCTION

Gadolinium ethoxybenzyl diethylenetriaminepentaacetic acid (Gd-EOB-DTPA, gadoxetic acid;

Primovist, Bayer Schering Pharma, Berlin, Germany) is a new hepatobiliary magnetic

resonance (MR) contrast agent with a unique capacity as an extracellular contrast agent and

hepatocyte-specific agent for use in double phase imaging. It requires only a single bolus

injection[1, 2] and results in higher hepatocyte uptake and biliary excretion than previous

hepatocyte-specific agents[3]. Gd-EOB-DTPA is actively taken up by hepatocytes with

subsequent biliary excretion[4-6]. Previous studies showed that the uptake and biliary excretion of

Gd-EOB-DTPA is dependent on liver function[7, 8]. This property is of particular interest in

practice because many patients suspected of having a focal liver lesion also have impaired liver function. In this study, for quantitative analysis, we compared 10-minute and 20-minute delay images to examine liver-to lesion signal difference ratios (SDRs), defined as (the signal intensity of the liver minus the signal intensity of the focal lesion)/the signal intensity of the liver. For qualitative analysis, we compared sensitivity and specificity in 10-minute and 20-minute delay images.

II. MATERIALS AND METHODS

1. Patient population

Between May, 2007 and January, 2008, 92 patients suspected of having focal hepatic lesions underwent liver MRI using gadoxetic acid as a contrast agent.

2. MRI examination

MR imaging was performed with a 1.5-T (Intera Achieva; Philips Medical Systems, Best, Netherlands) in 47 patients and a 3.0-T (TrioTim; Siemens, Erlangen, Germany or Intera Achieva; Philips Medical systems, Best, Netherlands) system in 45 patients with phased-array coils. All of the images were obtained in the transverse plane with a rectangular field of view of 22-24 x 38 cm, which was adjusted for each patient. Dynamic T1-weigted MR imaging was performed using a transverse breath-hold three-dimensional T1-weighted fat-suppressed spoiled gradient-recalled-echo sequence with a bolus injection of 10 mL of Gd-EOB-DTPA followed
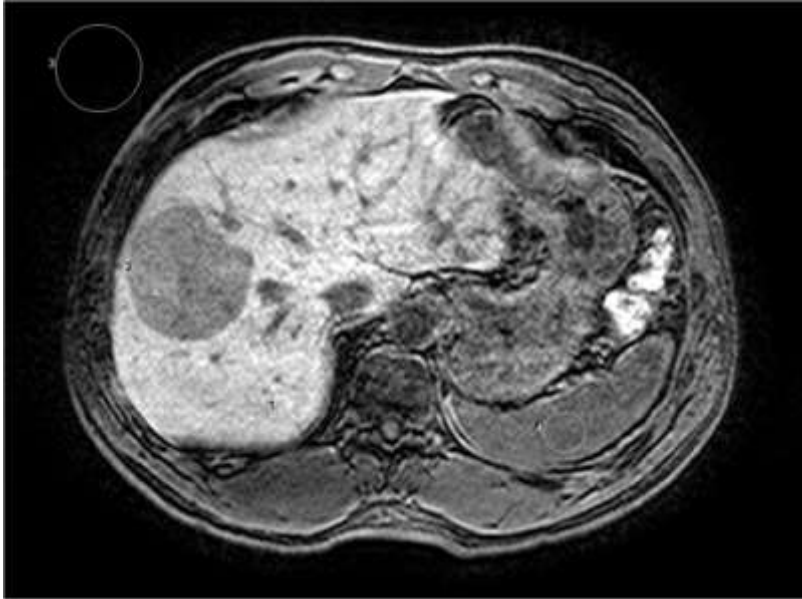
by a 30-mL saline flush.

Hepatobiliary phase images were obtained at 10 minutes and 20 minutes after injection of Gd-

EOB-DTPA. Images were obtained using the same pulse sequence for dynamic MR imaging.

Imaging parameters for the 1.5-T MRI were as follows: 4 repetition time msec/echo time msec

4.44/2.17; flip angle, 15°; acquisition matrix size 256 x 256; and interpolated section thickness,

2.2 mm. Imaging parameters for the 3.0-T MRI were as follows: repetition time msec/echo time

msec 2.54/0.95; flip angle, 13°; acquisition matrix size 192 x 256; and interpolated section

thickness, 2 mm.3. Image analysis

For quantitative analysis, a region of interest (ROI) was drawn at each of four different locations

including the background liver, focal lesion, spleen, and background noise. The ROI on the liver

was drawn on the right lobe posterior segment to avoid artifacts from the aorta. The minimum

area of ROI for liver was 100 mm^2 and was drawn to avoid visible ducts or vessels as much as

possible. The ROI on the lesion was drawn with a minimum ROI of 50 mm^2 and on the largest

lesion present in cases with multiple lesions. Focal lesions less than 1 cm were excluded from

this study. In cases with necrotic masses, the ROI was drawn on the solid portion of the lesion.

The ROI on the spleen was drawn to avoid visible vessels as much as possible with a minimum

ROI of 200 mm^2. The background noise signal was measured on the right anterior quadrant in

an oval shape with a minimum ROI of 400 mm^2 (Figure 1).

Figure 1. An example of the ROI measurement

1) Liver: ROI on the right lobe posterior segment with minimum area of 100 mm^2

2) Lesion: minimum ROI area of 50 mm^2, avoiding necrotic areas

3) Background noise signal: ROI on right anterior quadrant in oval shape with minimum ROI of 400 mm^2

4) Spleen: minimum ROI area of 200 mm^2

For patients with focal lesions, liver-to-lesion signal difference ratio (SDR) was defined as (the signal intensity of the liver minus the signal intensity of the focal lesion)/the signal intensity of the liver. This ratio was measured and compared between pre-contrast, 10-min delay, and 20-min delay images for each patient. SDRs were compared between 1.5-T and 3.0-T and also

between cirrhotic patients and non-cirrhotic patients. To assess a patient's hepatic function, the Child-Pugh score and the Model for End-Stage Liver Disease (MELD) score were calculated and compared, together with the SDR, with the scores and ratios of clinically diagnosed cirrhotic patients and non-cirrhotic patients. For qualitative analysis, two board-certificated radiologists with 1 and 2 years of consecutive experience in abdominal imaging reviewed two sets of blinded image series composed of 10-minute delay and 20-minute delay images. One set of images contained a mixture of randomly chosen 10-minute and 20-minute delay images from each of the patients and the complementary set had the remaining images. The location and number rating as determined by a four-tiered confidence scale (1: probably not present, 2: possibly present, 3: probably present, 4: definitely present) of every detected focal lesion was documented by the readers. In cases of potential false-positive or false-negative lesions, a senior reviewer with more than 10 years of experience in liver MR imaging participated as a referee and examined the EOB-delay images as well as other image sequences T2 weighted image and dynamic enhancement image together with the patients' clinical data and past history and follow exam studies. Each detected lesion was categorized into false-negative (FN), false-positive (FP), true-negative (TN), or true-positive (TP) groups. The sensitivity and specificity of each reader was compared between the 10-minute delay and 20-minute delay images.

4. Statistical analysis

Statistical analysis was performed using the MedCalc program (version 6.15.000; MedCalc

Software, Mariakerke, Belgium). A P value of less than 0.05 was considered to be indicative of a statistically significant difference. SDRs for the 10-minute delay and 20-minute delay images were compared using the 'the paired sample t-test. The diagnostic capability of each reviewer was determined by calculating the area under the receiver operating characteristic (ROC) curve (Az) for each reviewer. Calculations of statistical significance for the differences between the areas under the ROC curves of the 10-minute delay and 20-minute delay images were performed using the univariate z score test using the same software. To analyze the relationship between liver function and SDR, Pearson correlation analysis was also performed using the MedCalc program. Sensitivity of analysis was calculated as the number of true-positive lesions/ (the number of true-positive lesions + the number of false-negative lesions) and specificity was calculated as the number of true-negative lesions/ (number of true-negative lesions + the number of false-positive lesions).

III. RESULTS

Among the 92 patients enrolled in the study, 18 patients were excluded from the comparison of SDR because they had no focal lesion in the liver or had focal lesions of less than 1 cm. Therefore, a total of 72 patients were included in this study. There were fifty-two male patients and twenty female patients with an average age of 56 years (maximum 83, minimum 20, and standard deviation of 12). MRI was performed on a 3-T system in 35 patients, and on a 1.5-T

system in the remaining 37 cases. Fifty-three patients had no evidence of chronic liver disease,

while the remaining thirty-nine patients had clinically diagnosed cirrhosis. Among the 39

patients with cirrhosis, 30 patients had hepatocellular carcinoma (HCC), 5 patients had

dysplastic nodules, two patients had focal nodular hyperplasia, one patient had hemangioma,

and one patient showed no focal lesion of the liver on MRI. Patients without cirrhosis were

diagnosed with various diseases including metastasis, cyst, eosinophilic infiltration,

angiomyolipoma, and others.

Seventy-two patients had at least one focal liver lesion larger than 1 cm in diameter. Eight

patients were excluded for SDR measure because their largest lesion was less than 1 cm. Ten

patients had no focal lesion in the liver. The final MRI diagnosis for each patient is shown in

Table 1.

Table 1. Final MRI Diagnosis for Each Patient

Final MRI Diagnosis	Number of patients
HCC	46
metastasis	16
Focal nodular hyperplasia	5
Dysplastic nodule	4
Cysts	4
Hemangioma	3
Angiomyolipoma	2
AP shunt	2
Eosinophilic infiltration	1
No focal lesion on MRI	10

A total of 195 focal lesions not smaller than 1 cm were detected in the 72 patients by the two

reviewers. Among the identified lesions, 145 were found to be true-positive lesions and 50 were

determined to be false-positive lesions. The numbers of false-negative, false-positive, true-

positive and true-negative diagnoses when using 10-minute and 20-minute delay images are

shown in Table 2 for reader 1 and Table 3 for reader 2.

Table 2. Results of Reader 1

20-minute delay images	10-minute delay images				
	FN	FP	TN	TP	
FN	10	0	0	14	24 (12.4%)
FP	0	1	11	0	12 (6.2%)
TN	0	7	31	0	38 (19.6%)
TP	13	0	0	107	120 (61.9%)
	23	8	42	121	194
	(11.9%)	(4.1%)	(21.6%)	(62.4%)	

FN: false-negative, FP: false-positive, TP: true-positive, TN: true-negative

Table 3. Results of Reader 2

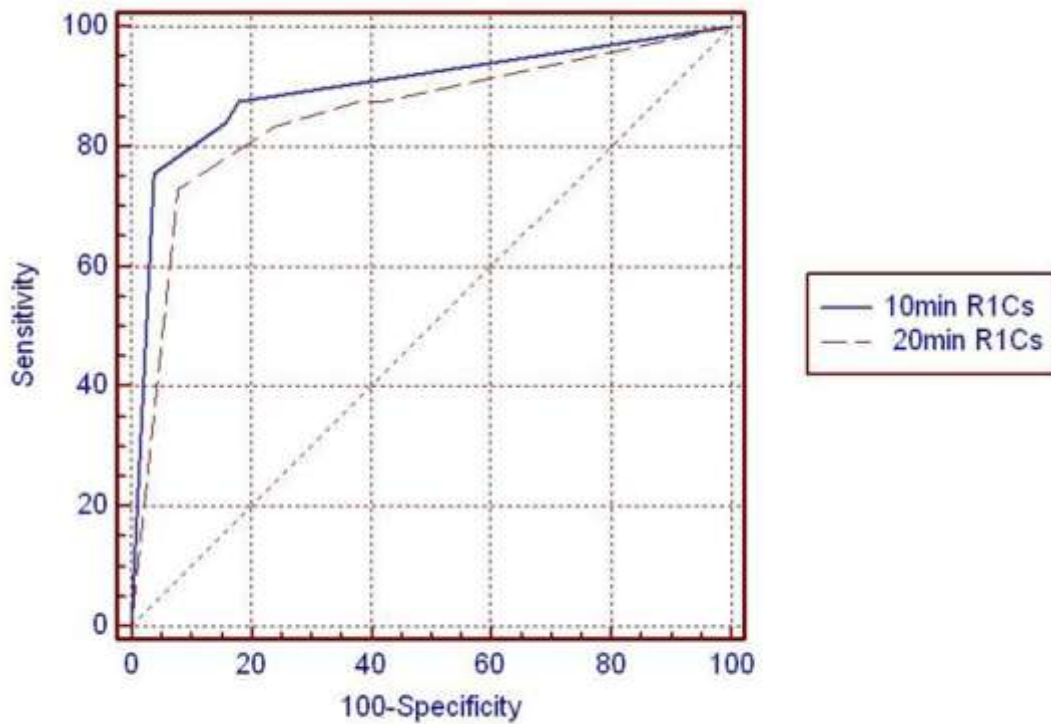| 20-minute delay images	10-minute delay images				
	FN	FP	TN	TP	
FN	11	0	0	10	21 (10.8%)
FP	0	0	7	0	7 (3.6%)
TN	0	4	39	0	43 (22.2%)
TP	12	0	0	111	123 (63.4%)
	23 (11.9%)	4 (2.1%)	46 (23.7%)	121 (62.4%)	194

FN: false-negative, FP: false-positive, TP: true-positive, TN: true-negative

The sensitivity and specificity of each reader with 10-minute and 20-minute delay images are
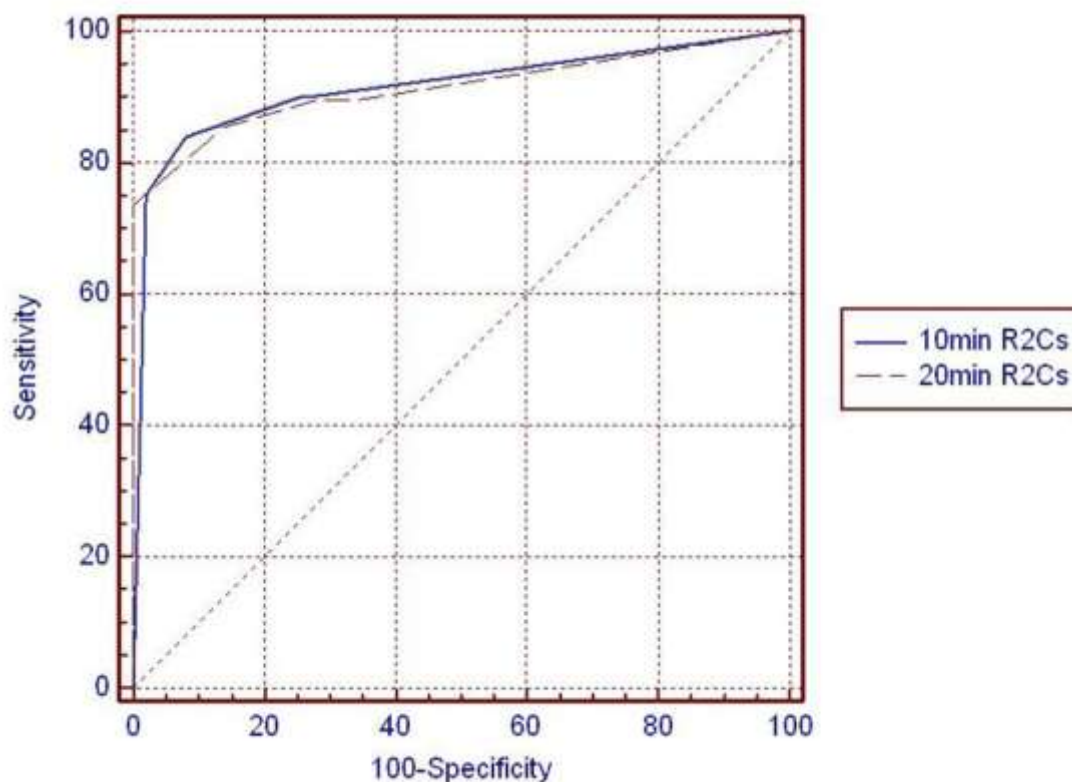
shown in Table 4.

Table 4. Sensitivity and Specificity of Readers 1 and 2

	10-minute R1	20-minute R1	10-minute R2	20-minute R2
Sensitivity (%)	84.03	83.33	90.98	85.42
Specificity (%)	84.00	76.00	92.00	86.00

Comparisons of ROC curves (Figures 2 and 3) showed no statistically significant differences in Az values between 10-minute and 20-minute delay images for either Reader 1 or Reader 2 (p= 0.117 and 0.936 respectively). There is no significant difference in sensitivity and specificity between 10-minute and 20-minute delay images (p= 0.117).
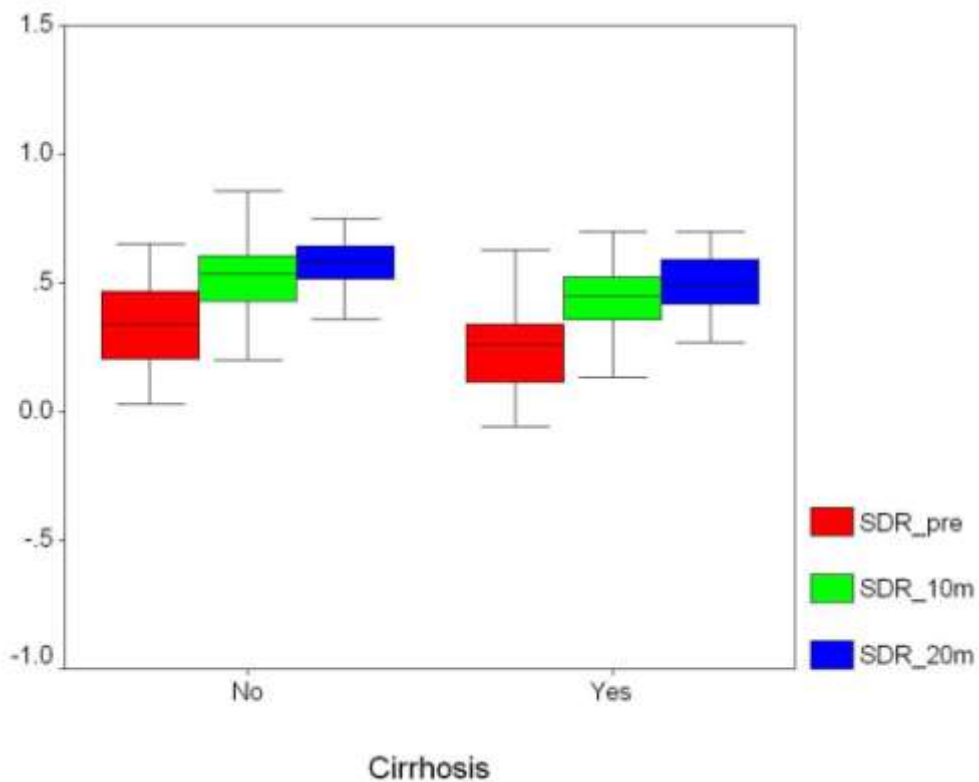

Figure 2. ROC curve of Reader 1

Figure 3. ROC curve of Reader 2

There is no significant difference in sensitivity and specificity between 10-minute and

20-minute delay images (p= 0.936).

The mean SDRs for 10-min delay images (0.49 ± 0.19 in non-cirrhotic and 0.42 ± 0.18 in

cirrhotic patients) were significantly higher compared to precontrast images in both non-

cirrhotic (0.34 ± 0.16, $p < 0.01$) and cirrhotic (0.20 ± 0.30, $p < 0.01$) patients. The SDR of 20-

min images in non-cirrhotic patients (0.54 ± 0.19) was significantly higher ($p < 0.01$) than that

of 10-min delay images. However, in cirrhotic patients, the SDR of 20-min images (0.46 ± 0.21)

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was comparable (p > 0.05) to the ratio calculated for 10-min delay images. There was no

significant difference between non-cirrhotic and cirrhotic patients for each value as shown in
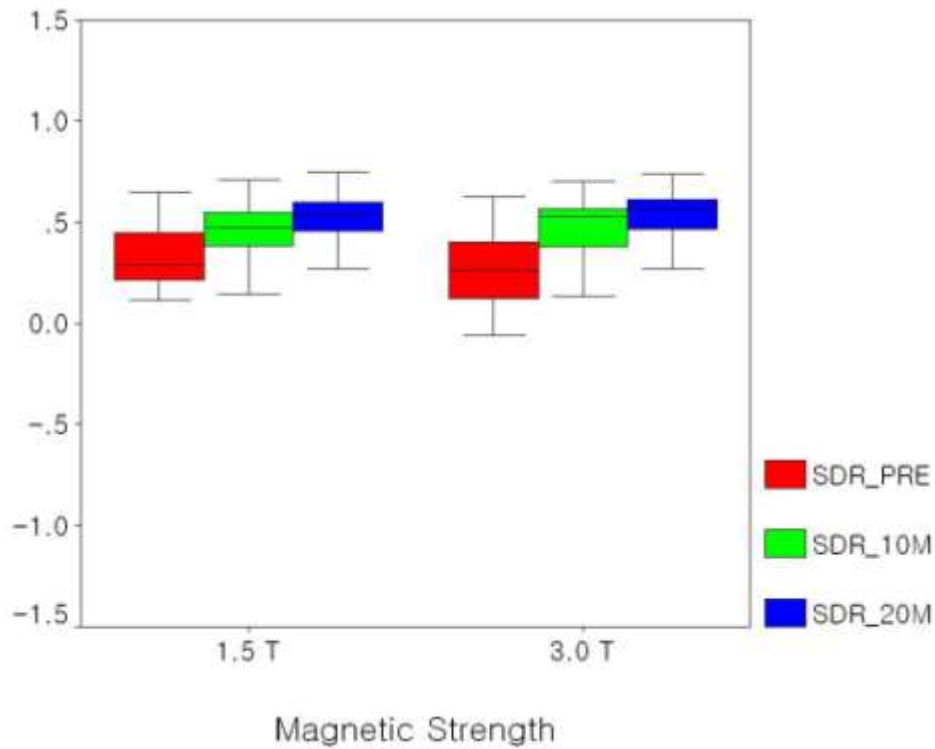
Figure 4.

Figure 4. Liver-to-Lesion Signal Difference Ratio (SDR): cirrhosis vs. non-cirrhosis

Shown is a summary plot based on the median, quartiles, and extreme values. The box

represents the interquartile range which contains 50% of all values. The whiskers extend

from the box to the highest and lowest values, excluding outliers. A line across the box

indicates the median.

The SDRs of 20-min images are significantly higher than those of 10-min images in

non-cirrhotic patients, but the difference is not significant in cirrhotic patients. There is

no significant difference between non-cirrhotic and cirrhotic patients for each value.

The mean SDRs for 10- and 20-min delay images are significantly higher compared to

those of precontrast images in both non-cirrhotic and cirrhotic patients.

In comparisons according to the magnetic strength of the imaging system, there were significant

($p < 0.05$) differences in all comparisons between SDRs of precontrast, 10-min, and 20-min

delay images on both 1.5-T (0.30 ± 0.21, 0.47 ± 0.16, and 0.50 ± 0.17, respectively) and 3-T

(0.24 ± 0.27, 0.46 ± 0.21, 0.50 ± 0.24, respectively) systems. There was no significant

difference between 1.5-T and 3T systems for each value as shown in Figure 5.

Figure 5. Liver-to-Lesion Signal Difference Ratio (SDR): 1.5-T vs. 3.0-T

There was a significant difference in all comparisons of SDRs of precontrast, 10-min,

and 20-min delay images from both systems. However, there was no significant

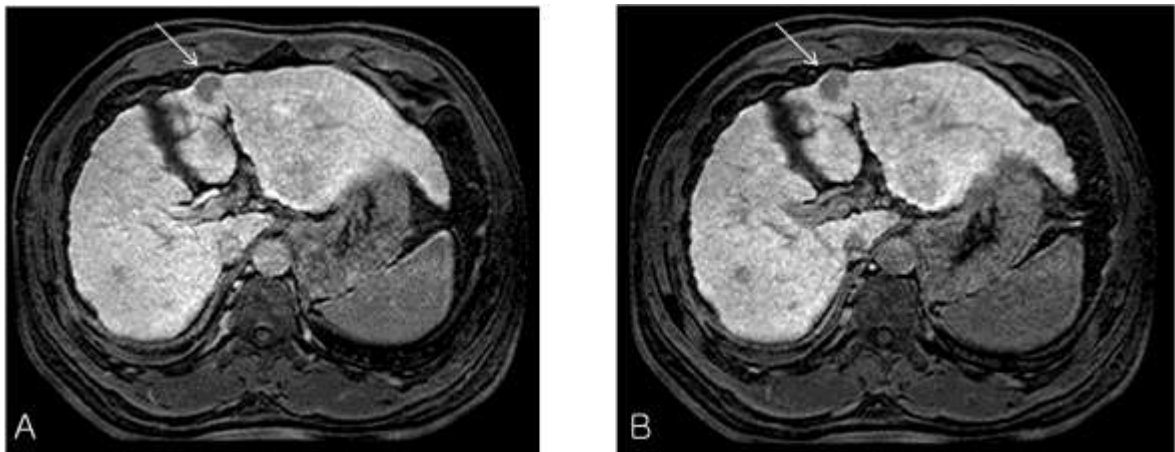difference between the 1.5-T and 3-T systems for each variable.

MELD scores were obtained for 64 patients. Twenty-eight patients did not have the laboratory

results necessary to calculate a MELD score including serum bilirubin level, creatinine level, or

coagulation test results from within three months of the time of the MRI examination. The

average MELD score value was 3.49 with a standard deviation of 3.08 (maximum 10 and

minimum -7). The SDRs from both 10-min and 20-min delay images showed statistically

significant inverse relationships to the MELD score. (P=0.07 and P<0.01 respectively). We also

calculated Child-Pugh scores in 83 patients; 81 patients with class A and 2 patients with class B.

We found no statistically significant correlation between SDR and Child-Pugh score.

IV. DISCUSSION

In this study, we used Gd-EOB-DTPA as an MRI contrast agent in 92 patients. We acquired the

images at 10 minutes and 20 minutes after injection and compared the SDRs from 10-minute

and 20-minute images between cirrhotic and non-cirrhotic patients. There was no significant

difference between the SDRs of 10-minute and 20-minute delay images in cirrhotic patients
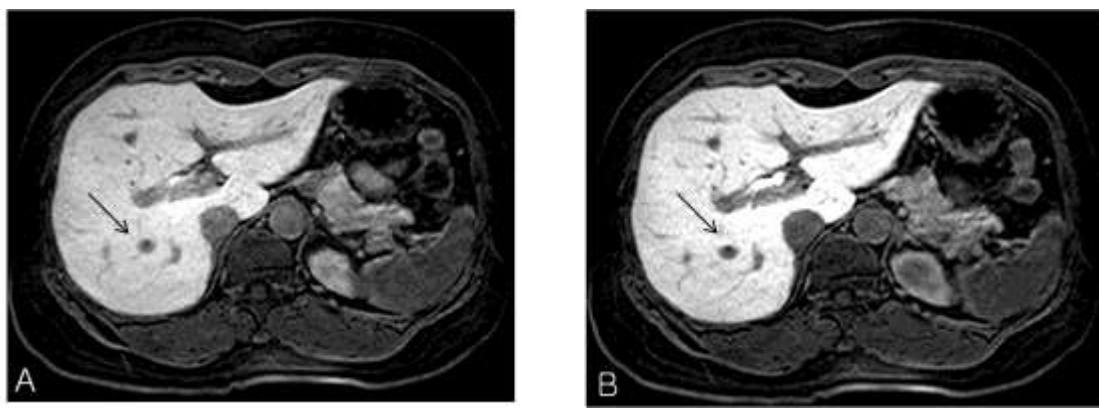
(Figure 6).

Figure 6. A 77-year-old male with hepatic dysfunction

The liver shows features of advanced cirrhosis including a nodular liver surface and

right lobe atrophy. The patient was diagnosed with hepatocellular carcinoma (white

arrows). There was no definite increase in the liver parenchymal enhancement and the

SDR measured was 0.43 on a 10-minute delay image (A) and 0.49 on the 20-minute

delay image (B).

On the other hand, there was a significant increase in the SDR of 20-minute delay images

compared to that of 10-minute delay images in non-cirrhotic patients (Figure 7).

Figure 7. A 59-year-old female without hepatic dysfunction

There is a cyst on liver segment 6 (black arrows). The 20-minute delay image (B) shows

increased hepatic parenchymal enhancement compared to the 10-minute delay image

(A). SDR was calculated to be 0.57 on the 10-minute delay image and 0.68 on the 20-

minute delay image.

The reason for this difference in enhancement is most likely related to hepatic function. In this

study, the SDRs on both 10-min delay and 20-min delay images showed a statistically

significant inverse relationship with the MELD score suggesting that the more impaired the

liver function, the less the signal difference between the liver and the focal lesion and a 20-minute delay image may not be sufficient for optimal enhancement of the liver in patients with impaired liver function. A recent study of Gd-EOB-DTPA-enhanced magnetic resonance cholangiography showed delayed excretion of Gd-EOB-DTPA in patients with impaired liver function as compared to individuals with normal liver function and suggested that this discrepancy may result in an inferior or even insufficient enhancement of the biliary tree in cirrhotic patients[8]. Since there are fewer functioning hepatocytes in livers with chronic liver disease, the capacity for the excretion of Gd-EOB-DTPA would be reduced and more Gd-EOB-DTPA would be excreted via the kidneys in competition with biliary excretion[10].

Our study found that there was no statistically significant relationship between SDR and Child-Pugh score. The Child-Pugh score includes subjective quantification of ascites and hepatic encephalopathy and is less precise as compared to the MELD score. In this study most of the patients were in class A and only two patients were in class B of the Child-Pugh classification, suggesting a lack of minute differentiation of liver function by the Child-Pugh system. Moreover, recent studies have indicated that the MELD score is superior to the Child-Pugh classification in predicting the 3-month mortality among patients with chronic liver disease[12, 13].

Comparisons of findings according to the magnetic strength of the imaging system revealed that

there were significant differences between SDRs on precontrast, 10-min, and 20-min delay

images on both 1.5-T and 3-T systems. However, there was no significant difference between

1.5-T and 3-T systems for each value suggesting that hepatic enhancement and tumor-to-liver

contrast on Gd-EOB-DTPA-enhanced MR images taken at 3.0 T are not different from those of

images taken at 1.5 T.

Quantitative analysis revealed no statistical significance between 10-minute delay images and

20-minute delay images in sensitivity or specificity. The increased tumor-to-liver contrast in 20-

minute delay images compared to 10-minute delay images in non-cirrhotic patients may not

provide diagnostic accuracy in practice while 10-minute delay image may provide adequate

parenchymal enhancement in non-cirrhotic patients. Longer delay images could improve liver

parenchymal enhancement in cirrhotic patients. However, a recent study on Gd-EOB-DTPA-

enhanced magnetic resonance cholangiography reported that 16 out of 40 cirrhosis patients

(40%) had an overall sufficient MRC image quality within 30 minutes while even after 180

minutes overall visualization of the biliary tree could be obtained in only 21 out of 40 patients

(53%)[8]. This finding suggests that a longer delay does not necessarily yield increased liver

parenchymal enhancement. Since Gd-EOB-DTPA is excreted through renal and biliary

pathways in competition, more contrast material may be excreted by glomerular filtration rather than being held for biliary excretion. Hence, a longer delay may be unnecessary even in cirrhotic patients.

Our study has several limitations. First, not all focal lesions were confirmed pathologically and most MR diagnosis was based on image findings and lab findings. Secondly, this study included various kinds of focal lesions including both malignancy and benign lesions and the result may differ according to the kind of lesions. Further research is necessary for each individual diagnosis. Thirdly, hepatobiliary phase MRI was obtained with 10 and 20 minutes delay in this study, however, further delay may result in different conclusion and this needs further future research.

V. CONCLUSION

The liver-to-lesion signal difference ratio was significantly higher on 20-min delay images compared to 10-min delay images in non-cirrhotic patients, but not in cirrhotic patients. An increase in the liver-to-lesion signal difference ratio on 10- and 20-min delay images was not dependent on the magnetic strength of the imaging system. Furthermore, there was no significant difference in sensitivity or specificity between the 10-minute and 20-minute delay images.

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ABSTRACT (IN KOREAN)

Gadoxetic acid 조영증강 자기공명영상에서 간 국소 병변의 진단: 지연시간,

간기능과 자기장의 영향

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김 화 선

목적 : Gadoxetic acid disodium 조영증강 자기공명영상의 간담도기

영상에서 지연시간, 간기능, 그리고 자기장의 영향을 평가하고 국소 병변의

진단에 끼치는 영향을 평가하였다.

결과 : 10 분 지연 영상에서의 평균 간-병변 신호차비는 간경화가 없는

환자와 있는 환자 모두에서 조영전 영상보다 유의하게 높았다. ($p < 0.01$)

그러나 20 분 지연영상에서 평균 간-병변 신호차비는 간경화가 없는

환자에서는 10 분지연영상보다 유의하게 높았으나($p < 0.01$) 간경변이 있는

환자에서는 그렇지 않았다. ($p > 0.05$) 자기장 세기에서는 1.5-T and 3.0-

T 에서 서로 차이가 없었다. 모두 195 개의 국소 병변의 진단되었는 데

10 분지연 영상과 20 분 지연영상 사이에서 민감도와 특이도에 통계학적으로

유의한 차이는 없었다.

결론 : Gadoxetic acid disodium 조영증강에서 간-병변 신호차비는

10 분지연영상과 20 분 지연 영상을 비교할 때 환자의 간기능의 영향은

받았으나 자기장의 세기는 영향이 없었다. 10 분 지연 영상과 20 분 지연

영상 상이에 진단에 있어서 민감도와 특이도의 차이는 없었다.

핵심되는 말 : 간세포암, 자기공명, gadoxetic acid, GD-EOB-DTPA