Benefit of Double Contrast MRI in Diagnosis of Hepatocellular Carcinoma in Patients with Chronic Liver Diseases

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Objective: *To assess the benefit on diagnosis of hepatocellular carcinoma (HCC) in patients with chronic liver disease or cirrhosis with double contrast MR imaging compared to the routine gadolinium-based MR imaging.*
Material and Method: *Seventy-one consecutive patients with cirrhosis or chronic hepatitis underwent multiphase, gadolinium-enhanced liver MRI examination and sequentially superparamagnetic iron oxide (SPIO)-enhanced images. The presence signal intensities of lesions on non-contrast sequences, dynamic gadolinium-enhanced images and delayed 10-min post-SPIO T2*-weighted images were recorded.*
Results: *Among 27 patients, 15 HCCs from 12 patients were diagnosed by surgical (n = 7) and non-surgical (n = 8) proofs. The overall sensitivity, specificity, positive predictive value, and negative predictive value of double contrast-enhanced images in 12 patients were 83.3% (95% CI: 58.5, 96.2), 33.3% (95% CI: 5.4, 88.4), 88.2% (95% CI: 63.5, 98.2), and 25% (95% CI: 4.1, 79.6) and these of gadolinium-enhanced images were 72.2% (95% CI: 46.5, 90.2), 33.3% (95% CI: 5.4, 88.4), 86.6% (95% CI: 59.5, 97.9), and 16.6% (95% CI: 2.7, 63.9), respectively. There were two benign hepatic nodules (1 adenoma, 1 dysplastic nodule) suspected as HCCs on MR images and two surgically proven-HCCs, invisible on gadolinium-enhanced images, detected as defect on only delayed 10-min post-SPIO T2*-weighted images.*
Conclusion: *SPIO-enhanced images in double contrast-enhanced MR imaging had an additional value on HCC detection, compared to gadolinium-enhanced MR imaging, in patients with chronic liver disease or cirrhosis.*

Keywords: *Hepatocellular carcinoma, Chronic liver disease, Cirrhosis, Magnetic resonance imaging, SPIO, Double contrast*

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Currently, pre-operative staging of hepatocellular carcinomas are necessary to obtain optimal treatment of choices, especially in candidates for liver transplantation. Conventional single-chelated contrast-enhanced magnetic resonance imaging (MRI) is limited diagnosis of small hepatocellular carcinoma (HCC) with low sensitivity and specificity, especially in cirrhotic patients[1]. Continuous improvement of MRI protocols, as well as the alternative liver-specific MR contrast agents, have been developed and led to improve the diagnostic performance of MRI. A number of studies reported the better results with superparamagnetic iron oxide (SPIO)-enhanced MR imaging compared to those using paramagnetic gadolinium-diethylenetriaminepentaacetic acid (Gd-DTPA: gadolinium)-enhanced images[2,3]. However, there is a critical weakness in assessing the tumor perfusion on early phase SPIO-enhanced of T1W-GRE images. The complementary gadolinium-enhanced (Gd-enhanced) images plus SPIO-enhanced images as double contrast agents, sequentially administered in the same MR examination, are more accurate on HCC detection and hepatic characterization than dynamic SPIO images alone[4,5]. SPIO is a reticulo-endothelial (RE) tissue specific MR contrast agent, administered intravenously. It has been applied specifically with decreased signal intensity on RE-uptaked hepatic and splenic parenchyma because HCC is a hepatocyte-based tumor that rarely contains RE cells. Using RE tissue specific contrast agent combines with gadolinium-based contrast agent, as double contrast MRI, might be increased an opportunity in HCC detection, even in small tumors (≤20 mm in size)[4].

To our knowledge, the present study aimed to assess the benefit on diagnosis of HCC in patients with chronic liver disease/cirrhosis with double contrast MRI compared to the routine gadolinium-based MRI.

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Material and Method

The present retrospective study was critically reviewed and approved by the Institutional Review Board of the Siriraj Hospital, Faculty of Medicine, Mahidol University. The study was conducted under the declaring of Helsinki.

Over a 2-year periods (2006-2008), seventy-one consecutive patients with cirrhosis or chronic hepatitis underwent multiphase, Gd-enhanced liver MRI examination and sequentially SPIO-enhanced images with a 3D interpolated, gradient-echo technique. From this group, 27 patients were identified as having, a) pathologic proof for mass confirmation on benignity or malignancy, b) a minimum of 24-months follow-up with computed tomography (CT) or MRI for cases without histological proof, or c) no any prior hepatic treatments, including wedge resection, hepatectomy, transarterial chemoembolization (TACE) or radiofrequency ablation (RFA).

These 27 patients (21 men, 6 women; age range = 40-80 years; mean age = 52.3 years) underwent double contrast MR examinations with underlying history of hepatitis B (n = 16), hepatitis C (n = 7), alcoholic hepatitis (n = 3), and hemochromatosis (n = 1). Eighteen lesions from 12 patients were seen on double contrast MRI. Fourteen patients had rising alpha-fetoprotein (AFP) levels (range: 6.32-1136 IU/ml)) and thirteen patients had normal range of AFP levels. On 18 lesions, eight patients had one lesion, two patients had two lesions, and two patients had three lesions. The size of lesions was more than 2 cm in fifteen lesions, 1 to 2 cm in two lesions and less than 1 cm in one lesion. The rest of the 15 patients had no lesions on double contrast MR examinations. From 18 lesions, fifteen lesions were diagnosed as HCC by surgical resection (n = 7), significant rising AFP and presence of hepatic mass (n = 6), or increasing size or change in imaging appearance in 3-month follow-up images (n = 2). From these, two lesions were diagnosed as dysplastic nodule and hepatic adenoma by surgical resection. The last lesion was diagnosed as benign lesion from evidence of stable lesion size on 24-month follow-up images.

MR imaging technique

MR imaging was performed on a 1.5 T system (Gyroscan Intera; Philips, Erlangen, Germany), using a SENSE four-element phased-array multicoil. All patients underwent unenhanced axial T1-weighted gradient-recalled echo in-/opposed-phase (TR/TE 120/4.6-; 2.3-, 4.8, flip angle 80°, section thickness 8 mm; interslice gap 2 mm, matrix 256x375) and inversion-recovery T2-weighted (STIR, TR/TE 800/70, flip angle 150°, section thickness 8 mm, interslice gap 2.5 mm, matrix 165x256, inversion time 165 sec) imaging. The multiphase SPIO-enhanced MR imaging was performed with a fat-suppressed volumetric interpolated-breath-hold sequence (THRIVE, TR/TE 4.7/2.3, flip angle10°, matrix 256x127, 330-395-mm rectangular field of view, slab thickness 204-230 mm, effective slice thickness 3 mm). For SPIO-enhanced MRI, 1.4 (equivalent to 0.7 mmol iron) and 0.9 ml (equivalent to 0.45 mmol iron) furocarbotran (Resovist^{R}; Schering, Berlin, Germany) was bolusly administered in patients with body weights of more than 60 kg and less than 60 kg, respectively, via an anticubital vein. Scans were acquired at 25, 70, and 120 seconds following contrast administration.

After multiphase SPIO-enhanced MR images, the multiphase gadolinium-enhanced (Gd-enhanced) MR imaging was performed with a fat-suppressed volumetric interpolated-breath-hold sequence (THRIVE, TR/TE 4.7/2.3, flip angle10°, matrix 256x127, 330 to 395-mm rectangular field of view, slab thickness 204 to 230 mm, effective slice thickness 3 mm). For Gd-enhanced MRI, 0.1 mmol/kg body weight gadopentetate dimeglumine (Magnevist; Schering, Berlin, Germany) or gadodiamine (Omniscan; Nycomed Amersham, Amersham, United Kingdom) was administered at a rate of 2 ml/sec followed by a 20-ml flush of normal saline solution via an antecubital vein. Scans were acquired at 25, 70, and 120 seconds following contrast administration. The scan was acquired again at 10-min delayed SPIO-enhanced images.

Image interpretation

The non-contrast, dynamic Gd-enhanced, delayed 10-min post-SPIO MR studies were separately reviewed on a PACS workstation by one abdominal radiologist with 10-year MR experience. The MR criteria in diagnosis of HCC on lesions with 1) Presence of enhancement on arterial Gd-enhanced images, 2) Presence of wash-out pattern on subsequent contrast-enhanced images, or 3) Presence of hyperintense on delayed 10-min post-SPIO images.

The arterial-phase images were characterized by hepatic-artery enhancement with heterogeneous splenic enhancement without significant liver parenchymal or hepatic-vein enhancement. The reader was blinded to pathology results, and imaging studies were viewed in temporal order. When a

suspected HCC lesion was detected, the lesion size was measured in two dimensions with electronic calipers.

The signal intensities of arterially-enhancing lesions on T1-weighted gradient echo and T2-weighted images were recorded as hyperintense, isointense, or hypointense to the liver. Lesions that were isointense or hypointense on portovenous images were considered to demonstrate rapid wash-out. The enhancing lesions were considered to demonstrate delayed wash-out when they remained hyperintense relative to the liver on the portovenous and became isointense or hypointense on equilibrium phase images.

The signal intensities of lesions on delayed 10-min post-SPIO T2*-weighted images were recorded as homogenous or heterogenous hyperintense (presence of internal small hypointense areas), isointense, or hypointense to the liver.

Statistical analysis

For purposes of analysis, lesions that remained stable on imaging exams for at least 24 months were considered presumed benign (including lesions that initially showed minimal growth but which were subsequently stable in size for at least 24 months). The lesions considered as HCCs were confirmed by histopathologic results or were clinically suspicious of HCC as high-level AFP. The sensitivity, specificity, positive predictive value, and negative predictive value of presumed benign and HCC were statistically analyzed by two-by-two table test.

Results

From 27 patients with chronic liver diseases/cirrhosis, the mean age of 12 patients with suspected HCC and 15 patients with no suspected HCC were 58.9 (range = 40-80 years) and 59.3 (range = 40-80 years), respectively. In 12 patients with suspected HCCs by MR images, nine lesions in seven patients who proven by surgery (Sx) (7 HCCs, 1 dysplastic nodule and, 1 hepatic adenoma). Another nine lesions who proven by diagnosis from AFP level and subsequent MR images in which eight are increased size (presumed diagnosis as HCCs), and one is stable size over 24 months on subsequent MR images (presumed diagnosis as benign).

The mean lesion sizes of HCCs were 3.1 cm, respectively. The lesion size on nine surgical masses were one less than 1 cm and eight more than 2 cm.

The distribution of initial signal intensities for benign lesions, presumed benign lesion and hepatocellular carcinomas were presented in Table 1. Most of HCC were hypointense T1 and hyperintense T2 images. Table 2 showed the distribution of lesions based on gadolinium-enhanced images and delayed

Table 1. Noncontrast MR features of 18 detectable lesions

Diagnosis	T1WI			T2WI	
	Hypointense	Isointense	Hyperintense	Isointense	Hyperintense
HCC (n = 15)	4/5	1/0	3/0	1/0	7/5
Dysplastic nodule (n = 1)		1			1
Adenoma (n = 1)			1		1
Benign nodule (n = 1)	1			1	

T1WI = T1-weighted images; T2WI = T2-weighted images; HCC = hepatocellular carcinoma

Table 2. Dynamic double-contrast MR features of 18 detectable lesions

Diagnosis	Dynamic Gd-enhanced images				Hepatobiliary post-SPIO images	
	Arterial		Venous-equlibrium			
	Homogenous	Heterogenous	Early wash-out	Delayed wash-out	Homogenous	Heterogenous
HCC (n = 15)	13	0	11	2	13	2
Dysplastic nodule (n = 1)	1		1*			1
Adenoma (n = 1)	-	1	-	-		1
Benign (n = 1)	1		1		1	

HCC = hepatocellular carcinoma; Gd = gadolinium, SPIO = furocarbotran
* Presence of delayed pseudocapsule enhancement

SPIO T2* images. There were two patients diagnosed as HCCs based on MR images, but surgical-proven results were benign (Fig. 2, 3). Most of the washout characteristics on the HCC lesions were rapid wash-out pattern. Two HCCs showed heterogenous hyperintense on delayed SPIO T2* images with presence of central/small hypointense areas.

There were two surgical-proven HCC lesions, detected on pathologic specimens measured 2 mm and 3 mm, invisible on non-contrast and gadolinium-enhanced images, but detected on SPIO T2* images alone with final diagnosed as satellite nodules (Fig. 1).

From 15 patients with chronic liver disease/cirrhosis and no abnormal hepatic mass, three patients were considered as false negative results that were later diagnosed as HCCs in short subsequent images. One was detected from higher AFP level with presence of a 1.5-cm new abnormal hepatic mass in interval subsequent MR images at less than three months. Another two patients were presented as 1.8-cm and 2-cm lesions with MRI-findings of HCCs in interval subsequent MR images of less than 6 months.

The overall sensitivity, specificity, positive predictive value, and negative predictive value of double contrast-enhanced images in 12 patients were 83.3% (95% CI: 58.5, 96.2), 33.3% (95% CI: 5.4, 88.4), 88.2% (95% CI: 63.5, 98.2), and 25% (95% CI: 4.1, 79.6) and those of gadolinium-enhanced images were 72.2% (95% CI: 46.5, 90.2), 33.3% (95% CI: 5.4, 88.4), 86.6% (95% CI: 59.5, 97.9), and 16.6% (95% CI: 2.7, 63.9), respectively.

Discussion

The present study's results confirmed that conventional MR findings of HCCs are variable and still problematic in diagnostic settings of patients with chronic liver disease/cirrhosis, especially in small HCCs (less than 2 cm)[6]. European Association Society of Liver (EASL) recommend that non-invasive imaging diagnosis of HCC can be made without biopsy in patients with liver cirrhosis who had some typical imaging findings showing of arterial phase enhancement and venous or delayed phase washout on CT or MRI[7]. However, the small lesions (less than 2 cm) or lesions with atypical MR findings are recommended to perform liver biopsy, according to EASL.

The advantages of SPIO-enhanced MR images have also been reported in tissue characterization[2], especially on some types of focal hepatic lesions such as focal nodular hyperplasia (FNH), hepatic adenoma (HA), dysplastic nodule (DN), and well-differentiated HCC. FNHs can sustain its phagocytic activity and may demonstrate most of its iron oxide uptake. The phagocytic activity presents as signal loss of less than 10% on SPIO-enhanced MR images is helpful evidence in diagnosis of FNH. However, well-differentiated HCC and DN can be uptaken SPIO within the lesions and also decreasing SPIO uptake followed a declining degree of HCC differentiation[8]. We found that our HA and DN could be uptaken of SPIO and decreased internal signal in some areas of lesions which could be mimicking the findings of some HCCs. Because of a variety of

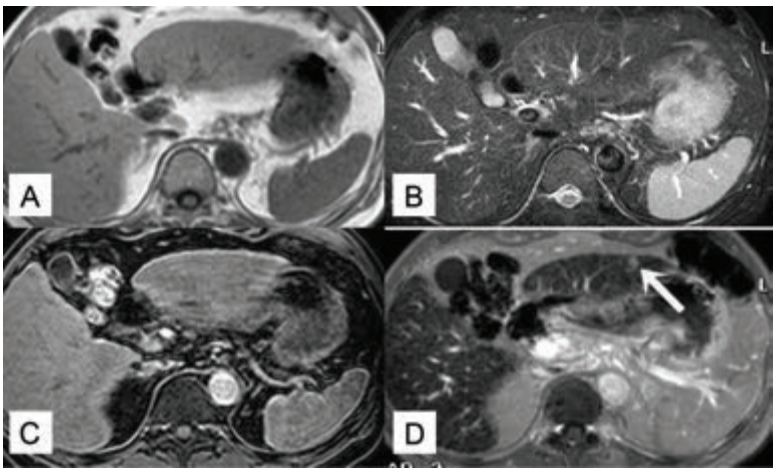

Fig. 1 A 2 mm, small hepatocellular carcinoma in a 56-year-old man. In precontrast (A, B) and multiphase of dynamic (C) MR imaging showed no detectable abnormality. On SPIO-enhanced T2W image, the tumor at hepatic segment 3 is not uptake SPIO and its signal intensity is increased (D, arrow).

phacocytic activity, evaluation of hepatic tumors by only delayed SPIO-uptake images is limited. Causes of mimics could be overlapping phacocytic activity among hepatic tumors and some technical problems such as little or large signal loss on T2*W-GRE images from the small intracellular cluster of SPIO produced, depending on the degree of the magnetic susceptibility artifact.

Double-contrast enhanced (DCE)-MRI had been reported on increased sensitivity, compared to

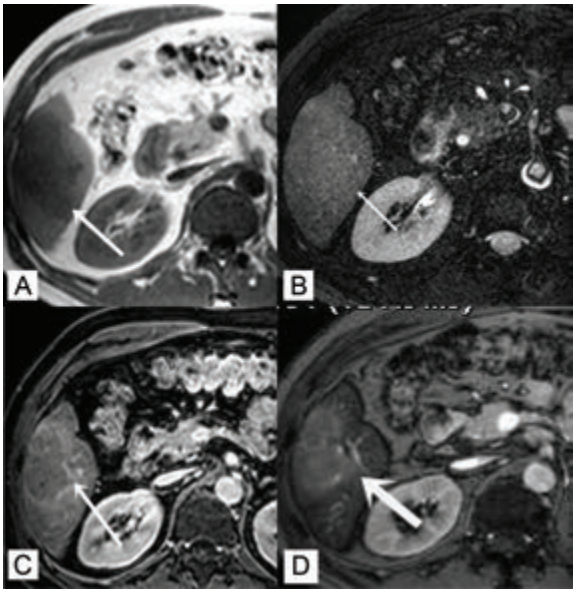

Fig. 2 A 2.5cm, hepatic adenoma in a 57-year-old man. Precontrast T2W image reveals a hyperintense mass at inferior right hepatic lobe (B, arrow).In arterial phase of dynamic MR images, a well-enhanced tumor is noted at inferior right hepatic lobe (C, arrow). On SPIO-enhanced T2W image, the tumor is not uptake SPIO and its signal intensity is increased (D, arrow).

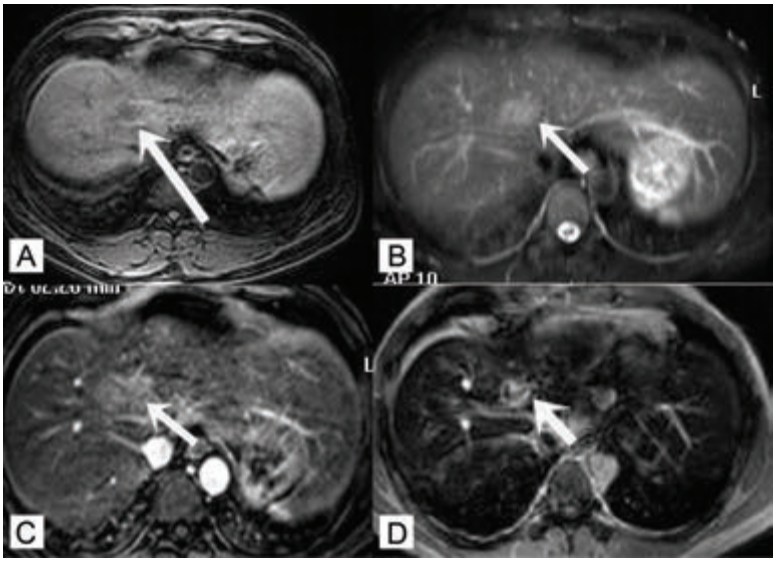

Fig. 3 A 2.1-cm, dysplastic nodule in 40-year-old man. Precontrast T2W image reveals a hyperintense mass (B, arrow). In arterial phase of dynamic MR images, a well-enhanced tumor is noted in segment 8 (C, arrow). On SPIO-enhanced T2W image, the tumor is not uptake SPIO and its signal intensity is increased (D, arrow).

conventional MRI[9], with extensive evaluation on its function and vascularity. The present study's results confirmed that DCE-MRI had higher sensitivity on two subcentrimeter HCC detections from 18 lesions that were identified on only delayed SPIO T2W* images (classified as hypovascular),with a 25% negative predictive value. However, there were no statistical differences of diagnostic performance between SPIO-enhanced MR and Gd-enhanced MR. Gd-enhanced MR was slightly better than SPIO-enhanced MR in lesion conspicuity because of SPIO-enhanced MR being inability to assess lesion vascularity especially in dynamic images[10]. However, SPIO-enhanced MR was more accurate than non-contrast MR[11,12] with additional tissue-specific information. On management of hepatocellular carcinoma, the Japan Society of Hepatology (JSH)[13] and a recent publication[14] recommended the value of SPIO-enhanced MR be added to diagnostic algorithm for diagnosis of hypovascular HCCs. Based on the present study's results, DCE-MRI could provide combined benefits on vascular findings from Gd-enhanced MRI and tissue-specific findings from SPIO-enhanced MR, and was considered as one of imaging choices to evaluate HCCs in patients with chronic liver diseases/cirrhosis.

The present study had some limitations. First, this was retrospective study and there was no proven surgical pathology in half of the lesions. Despite the efforts made to match with the explanted and resected livers, precise lesion-by-lesion correlation was extremely difficult owing to variation in size and orientation of liver after explantation. Second, the decreased signal intensity of liver cirrhosis with SPIO was limited compared to that in normal liver[3,12]. Our study was not focused on Child-Pugh classification of liver cirrhosis, which directly affects hepatic SPIO uptake. Third, there was some selection bias as the reviewer was knowledgeable regarding the design study in reviewing Gd-enhanced MR and SPIO-enhanced MR. Fourth, we used DCE-MRI as standard technique. The T2 effect of SPIO could have effect on vascular findings on Gd-enhanced dynamic MR and might reduce enhancement of wash-out pattern on portal/delayed dynamic phases. Finally, the present study had small sample size. A further large-study group is required for the larger group compared to lesion by lesion with histological proof.

Conclusion

SPIO-enhanced images in double contrast-enhanced MRI have an additional value on HCC detection, compared to conventional gadolinium-enhanced MRI, in patients with chronic liver diseases/cirrhosis.

What is already known on this topic?

Accurate pre-operative imaging for diagnosis of HCC is very important for selection of most appropriate treatment, especially in candidates for liver transplantation. Excellent diagnostic performance of conventional gadolinium-based contrast-enhanced MRI for diagnosis of HCC is well recognized. However, it is still problematic in cases of small HCC (less than 2 cm), especially in cirrhotic liver.

Development of alternative liver-specific MR contrast agents, superparamagnetic iron oxide (SPIO), helps to improve the diagnostic performance of MRI for diagnosis of HCC. However, there is a critical weakness in assessing the tumor perfusion on early phase SPIO-enhanced of T1W-GRE images. The complementary gadolinium-enhanced images plus SPIO-enhanced images as double contrast agents, sequentially administered in the same MR examination, are more accurate on HCC detection and hepatic characterization than dynamic SPIO-enhanced or conventional gadolinium-enhanced images alone. However, in case of small HCCs, especially in cirrhotic liver, the benefit of double contrast MRI for diagnosis of HCC is still controversial.

What this study adds?

There are no statistical differences of diagnostic performance between double contrast MRI and conventional gadolinium-enhanced MRI for diagnosis of HCC. However, double contrast MRI had higher sensitivity for HCC detection in two cases of subcentrimeter hypovascular HCCs.

Accordingly, SPIO-enhanced images in double contrast-enhanced MRI have an additional value on HCC detection, compared to conventional gadolinium-enhanced MRI, in patients with chronic liver diseases/cirrhosis, especially in subcentrimeter hypovascular HCCs.

Potential conflicts of interest

None.

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การศึกษาประสิทธิภาพของการตรวจ double contrast MRI ในการวินิจฉัยมะเร็งตับชนิด hepatocellular carcinoma ในกลุ่มผู้ป่วยที่มีโรคตับอักเสบเรื้อรังหรือตับแข็ง

วรรณวรางค์ ตีรสมิทธ์, ไพรัช สายวิรุณพร, อนัญญา พงษ์ไพบูลย์, พรพิมพ์ กอแพร่พงศ์

วัตถุประสงค์: เพื่อศึกษาประสิทธิภาพของการตรวจ double contrast MRI ในการวินิจฉัยมะเร็งตับชนิด hepatocellular carcinoma ในกลุ่มผู้ป่วยที่มีโรคตับอักเสบเรื้อรังหรือตับแข็ง โดยเปรียบเทียบกับการตรวจ gadolinium-enhanced MRI

วัสดุและวิธีการ: ผู้ป่วยจำนวน 71 ราย ที่มีโรคตับอักเสบเรื้อรังหรือตับแข็ง และได้รับการตรวจ double contrast MRI เพื่อวินิจฉัยมะเร็งตับชนิด hepatocellular carcinoma โดยรังสีแพทย์จะทำการแปลผลภาพการตรวจและบันทึกลักษณะ signal intensities ของก้อนเนื้องอกที่ตรวจพบในภาพ non contrast, dynamic gadolinium-enhanced และ delayed 10-min post-SPIO T2*-weighted

ผลการศึกษา: ผู้ป่วยที่สามารถเข้าเกณฑ์การศึกษามีจำนวน 27 ราย พบว่ามีมะเร็งตับชนิด hepatocellular carcinoma จำนวน 15 ก้อน จากผู้ป่วย 12 ราย ซึ่งได้รับการวินิจฉัยจากการผ่าตัดจำนวน 7 ก้อน และด้วยวิธีอื่นอีก 8 ก้อน ความไว ความจำเพาะ ค่าพยากรณ์บวก และค่าพยากรณ์ลบของ double contrast MRI ในจำนวนผู้ป่วย 12 ราย เท่ากับ 83.3% (95% CI: 58.5, 96.2), 33.3% (95% CI: 5.4, 88.4), 88.2% (95% CI: 63.5, 98.2), และ 25% (95% CI: 4.1, 79.6) และของ gadolinium-enhanced MRI เท่ากับ 72.2% (95% CI: 46.5, 90.2), 33.3% (95% CI: 5.4, 88.4), 86.6% (95% CI: 59.5, 97.9), และ 16.6% (95% CI: 2.7, 63.9) ตามลำดับ ในการศึกษานี้พบว่ามีก้อนเนื้องอกชนิดไม่ร้ายจำนวน 2 ก้อน คือ hepatic adenoma 1 ก้อน และ dysplastic nodule 1 ก้อน ที่ให้ลักษณะภาพการตรวจคล้ายกับมะเร็งตับชนิด hepatocellular carcinoma และนอกจากนี้ยังพบว่ามีก้อนมะเร็งตับชนิด hepatocellular carcinoma จำนวน 2 ก้อน ที่ไม่พบจากการตรวจ gadolinium-enhanced MRI แต่สามารถพบได้จากภาพ delayed 10-min post-SPIO T2*-weighted

สรุป: ภาพ SPIO-enhanced จากการตรวจ double contrast MRI ช่วยเพิ่มความสามารถในการตรวจพบมะเร็งตับชนิด hepatocellular carcinoma ในกลุ่มผู้ป่วยที่มีโรคตับอักเสบเรื้อรังหรือตับแข็ง เมื่อเทียบกับการตรวจ gadolinium-enhanced MRI