

---

---

## ORIGINAL ARTICLE

---

---

# Comparison of Superparamagnetic Iron Oxide-enhanced Magnetic Resonance Imaging and 5-Phase Computed Tomography in the Detection and Characterisation of Focal Liver Lesions

GC Gan,<sup>1</sup> BJJ Abdullah,<sup>1</sup> G Kumar,<sup>1</sup> SI Bux,<sup>1</sup> KL Goh,<sup>2</sup> R Vijeyasingam<sup>3</sup>

Departments of <sup>1</sup>Biomedical Imaging, <sup>2</sup>Internal Medicine and <sup>3</sup>Surgery, Faculty of Medicine, University of Malaya, Petaling Jaya, Malaysia

### ABSTRACT

**Objective:** To compare superparamagnetic iron oxide-enhanced magnetic resonance imaging with 5-phase computed tomography in the detection and characterisation of focal liver lesions.

**Patients and Methods:** We prospectively performed 5-phase computed tomography scans followed by magnetic resonance imaging of the liver with superparamagnetic iron oxide magnetic resonance contrast medium in patients with focal liver lesions. A total of 18 patients were included, 11 male and seven female. Both dynamic and equilibrium phases magnetic resonance imaging were done. Lesion enhancement and number of lesions seen in each phase was then analysed.

**Results:** Thirty four lesions were detected and characterised. These comprised metastases (one), hepatocellular carcinomas (seven), cysts (two), haemangiomas (ten), lesions secondary to arterioportal shunting (eleven), and ablated lesions (three). There was no statistically significant difference in lesion detection and characterisation of focal lesions on superparamagnetic iron oxide magnetic resonance imaging.

**Conclusion:** Superparamagnetic iron oxide-enhanced magnetic resonance imaging is comparable to 5-phase computed tomography of the liver in the detection and characterisation of focal liver lesions.

**Key Words:** Contrast media, Differential diagnosis, Liver, Magnetic resonance imaging, Iron, Oxides, Tomography, X-ray computed

### INTRODUCTION

Early and accurate diagnosis is essential for the management and the successful treatment of patients with liver tumours. Pre- and post-therapeutic imaging is used to detect liver tumours and to differentiate malignant from benign liver lesions. Imaging modalities currently in use are contrast-enhanced magnetic resonance imaging (MRI) and computed tomography (CT). After a lesion is detected, the extent of involvement of the liver and distant involvement of other organs has to be assessed. Superparamagnetic iron oxide (SPIO) is a liver-specific particulate MR contrast agent that is taken up by the

reticuloendothelial system (RES) of the liver. It improves the focal hepatic lesion-to-liver contrast-to-noise ratio and the detection of hepatic tumour.<sup>1</sup> SPIO particles, as liver-specific contrast media, have increased the potential of MRI for the detection and characterisation of focal liver lesions.

In this study, we evaluated the diagnostic accuracy of SPIO-enhanced MRI compared to 5-phase CT in the detection and characterisation of liver lesions. In addition, we sought to determine in which cases 5-phase CT had higher diagnostic accuracy and to identify the patient population that would benefit from SPIO-enhanced MRI.

### PATIENTS AND METHODS

#### Selection and Description of Participants

The study subjects were patients with focal liver lesions diagnosed on a 5-phase CT of the liver. Patients who met the diagnostic criteria for hepatocellular carcinoma

---

---

*Correspondence:* Dr. GC Gan, Department of Biomedical Imaging, University of Malaya Medical Centre, Jalan University, 59100 Petaling Jaya, Malaysia.

Tel: (60 3) 7949 2091; Fax: (60 3) 7958 1973;

Email: melina\_gan@hotmail.com

Submitted: 20 February 2006; Accepted: 16 October 2006.

(HCC) [based on hepatitis B-/C-positive status, raised alpha-fetoprotein (AFP)], or patients who had a known primary malignancy with no previous known liver lesions were included in this study. The SPIO-enhanced MR study was performed within 2 weeks of the 5-phase CT. Ethical clearance was obtained from our local hospital review board with informed consent for the MR study.

Patients aged less than 18 years, those with acute hepatic failure or serious liver dysfunction, and those who were pregnant or lactating were excluded. A history of severe adverse events related to drugs or contrast and claustrophobia were other criteria for exclusion.

A total of 40 patients were recruited. Of them, 22 were subsequently excluded as they did not fulfill the criteria of this study. Of the 18 patients studied, 11 (61%) were male and 7 (39%) female. Their ages ranged from 44 to 74 years (mean, 58.72 years). Thirteen of these patients were hepatitis B- or C-positive, two were non-hepatitis B carriers and three had known primary malignant tumours elsewhere (one had cervical carcinoma, one had previously resected gastric carcinoma, and one had a primary adrenal tumour). A raised AFP level was present in seven patients (at our centre, the laboratory normal reference range is 0 to 6.7 IU/L). Histopathology results of patients who underwent resection and imaging findings on follow-up scans were also collected.

### Technical Information

All patients were imaged with a 16-slice multidetector CT scan (GE Lightspeed, Milwaukee, WI, USA). A pre-contrast study of the liver was performed, after which scans were obtained in the early arterial, late arterial, portal venous and delayed phases [following administration of 120 mL of Iopromide (Schering, Berlin, Germany) containing 300 mg iodine/mL, at 4 mL/s]

For the SPIO-enhanced MRI, all patients were scanned on a 1.5 Tesla machine (Siemens Magnetom Vision, Erlangen, Germany) with software version b31b. The pre-contrast scanning sequences used were T2-weighted half-Fourier-acquired single-shot turbo spin echo (T2 HASTE), T2\*-weighted gradient echo (T2\* GRE), T1 GRE and volumetric interpolated breath-hold examination (Vibe) measurement. A bolus of 1.4 mL of SPIO MRI contrast medium (0.5 mmol/mL iron) [Resovist; Schering, Berlin, Germany] was injected intravenously via a 20G cannula, after which 20 mL of saline was used for flushing. Four Vibe measurements were done for the dynamic phase imaging (DPI) [at a delay of 20

seconds, 50 seconds, and three minutes post-injection]. T2 HASTE, T2\* GRE and T1 GRE and Vibe measurement sequences were done at 10 minutes post-injection. The patients were then followed up by the investigator to determine if resection had been done. The investigator also noted whether the histological diagnosis or follow-up scans had been done, and if any changes were seen in the subsequent scans.

### Image Analysis

The images printed on films were interpreted prospectively and independently by 2 radiologists experienced in the interpretation of gastrointestinal CT and MRI, who were blinded to the patient's history or presenting symptoms, histological and biochemical information. The CT and MRI images were evaluated at different sittings. The number of lesions detected was noted, and their location in the liver was assigned to segments as defined by the Couinaud segmental classification. The presence or absence of enhancement in the post-contrast phases was also noted. Enhancement was defined as increase in attenuation of the entire lesion, part of the lesion, or periphery of the lesion. For MRI, uptake or absence of uptake was recorded as evidenced by presence or absence of signal loss in the lesion(s) on the T2 HASTE sequence.

The observers indicated confidence in their findings in each phase and in their final diagnosis. Any difference in interpretation was settled by a third radiologist through consensus reading.

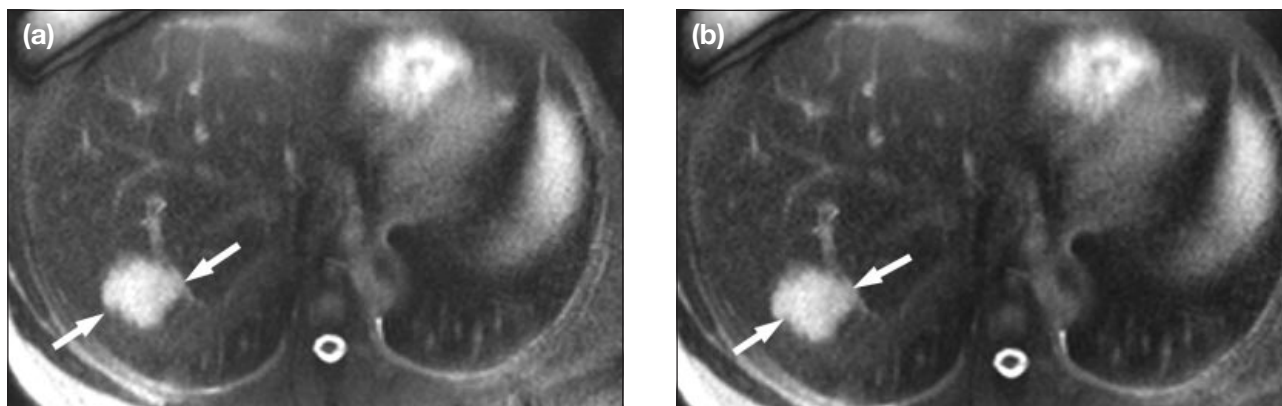
### Statistical Analysis

Lesions were diagnosed based on characteristic enhancement patterns on MRI compared to the combined characteristic enhancement pattern on 5-phase CT and the clinical and biochemical picture. We compared lesion detection in all the DPI sequences and the delayed-phase imaging sequences. Data were analysed using the Wilcoxon rank sum test and Friedman's test.

## RESULTS

In total, 34 lesions were detected in the 18 patients. These included three (8%) previously ablated lesions, one (3%) metastases, two (6%) cysts, seven (21%) HCCs, 10 (30%) haemangiomas and eleven (32%) arterioportal shunting.

We did not detect any significant signal loss after administration of SPIO MRI contrast medium in the T2 HASTE sequence for haemangiomas (Figure 1). For the



**Figure 1.** Haemangioma in segment VII of the liver. (a) Pre-contrast axial T2-weighted half-Fourier-acquired single-shot turbo spin echo (T2 HASTE) showing a high signal intensity lesion in segment VII. (b) Superparamagnetic iron oxide-enhanced at 10 minutes delay axial T2 HASTE with no significant signal loss detected.

ablated lesions, the appearances were variable, with one patient showing no enhancement on both CT and MR (with no change seen on a follow-up CT), one showing enhancement only in the late arterial phase on CT, but not on SPIO-enhanced MRI, and one showing enhancement in all phases on CT and in the dynamic phases on MRI with a low signal rim on delayed SPIO T2 HASTE sequence. In this third patient, a follow-up scan did not show any change, while AFP level remained unchanged; it was inferred that this was an ablated lesion with rim-enhancing granulation tissue. The metastatic lesion showed enhancement in the late arterial, portal, and delayed phases on CT. On MRI, this lesion showed enhancement in the DPI and did not show uptake of SPIO on the T2 HASTE sequence, and therefore showed no evidence of signal loss.

Out of the seven HCCs detected, four showed enhancement in both the early and the late arterial phases with contrast washout in the portal and the delayed phases on CT. In two patients, enhancement was seen in all of the post-contrast phases, and in one patient enhancement was seen only in the late arterial phase. Contrast washout was seen in the other phases. On SPIO-enhanced MR, five lesions showed enhancement in both the early and the late arterial phases of the Vibe sequence and six lesions showed enhancement in the 3-minute and 10-minute delay Vibe sequences (see Figure 2). The two lesions that did not show enhancement in the arterial phases were in the patient who had two foci of HCC; she showed enhancement only in the 3-minute and 10-minute Vibe delay sequences.

In the T2 HASTE sequence, there was consistent lack of uptake in all seven HCCs, with increase in conspicuousness of the lesions against the low signal

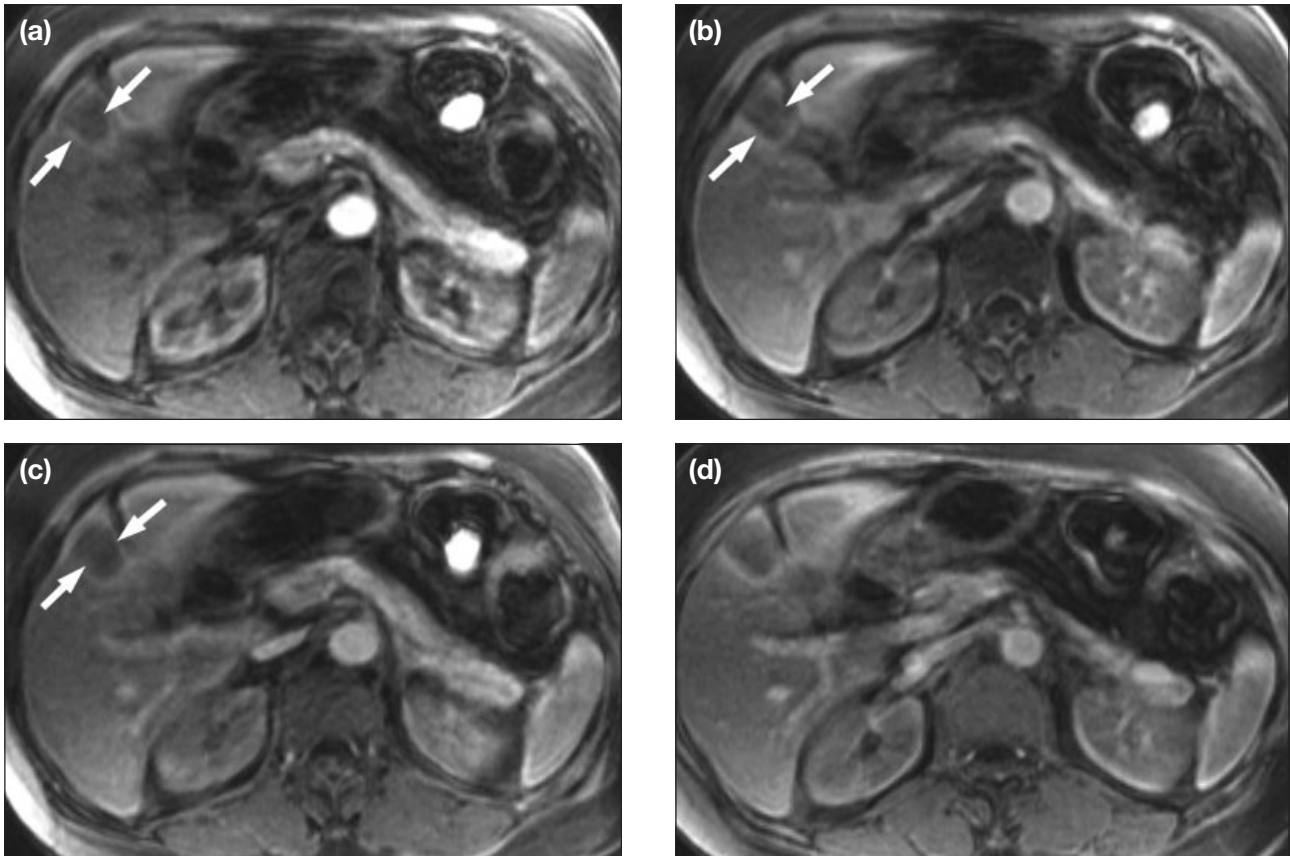
intensity liver background (Figure 3). Enhancement was seen in all lesions in both the T2\* GRE and T1 GRE 10-minute delay sequences.

When comparing the early arterial phase on CT with the 20-second delay Vibe sequence using the Wilcoxon signed ranks test, there was no statistically significant difference ( $p = 0.007$ ). Similarly, no statistically significant difference was seen when comparing the portal venous phase on CT versus the 50-second delay Vibe sequence ( $p = 0.166$ ) and also when comparing the delayed-phase CT against the delayed phases of SPIO-enhanced MRI phases.

The Friedman test did not show any statistically significant difference in lesion detection when the delayed-phase imaging sequences [that is, the T2 HASTE, T2\*FL 2d, T1 FL 2d, and Vibe sequences] were compared with one another ( $p = 0.572$ ). The observers, however, found that they were more comfortable with the T2 HASTE sequences in all instances. No statistically significant difference was found when the DPI sequences were compared ( $p = 0.801$ ). The observers also preferred the delayed-phase imaging sequences to the DPI, as artifacts occurred on most of the DPI images.

## DISCUSSION

In imaging of the liver, it is not only important to accurately detect and localise a lesion, but also to characterise it, as the latter has an important bearing on the prognosis and the planning of patient management. Both benign and malignant focal liver lesions may coexist in the same patient, at the same time. Advances in the available treatment options for patients with either primary or secondary malignant liver lesions has made this even more crucial for the best treatment choice to be made for the patient.

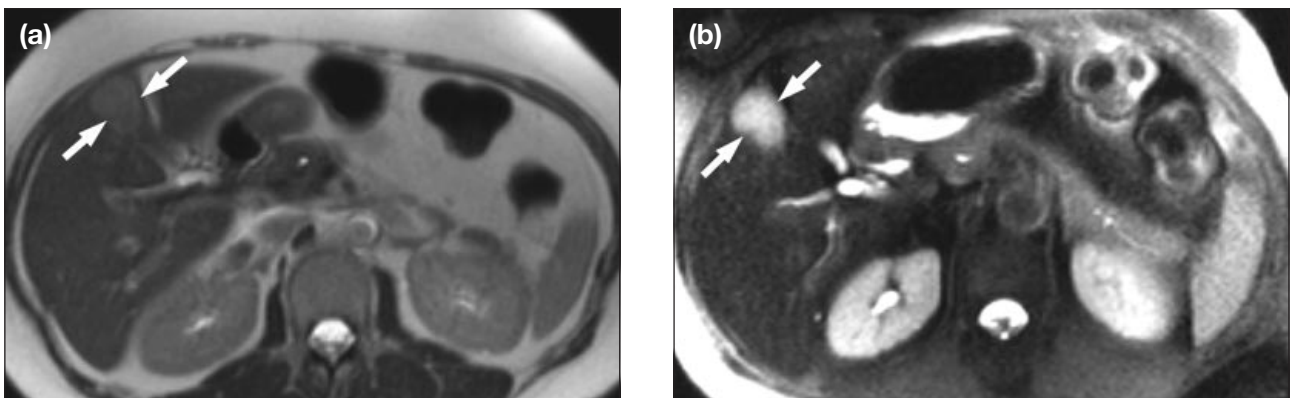


**Figure 2.** Hepatocellular carcinoma in segment V of the liver showing peripheral rim enhancement. (a) Superparamagnetic iron oxide (SPIO)-enhanced at 20 seconds delay volumetric interpolated breath-hold examination (Vibe). (b) SPIO-enhanced at 50 seconds delay Vibe. (c) SPIO-enhanced at 3 minutes delay Vibe. (d) SPIO-enhanced at 10 minutes delay Vibe.

With the advent of reticuloendothelial cell-specific and hepatocyte-specific contrast media for MRI, the potential for MRI in detection and characterisation of focal liver lesions is promising. The strong susceptibility effect of SPIO on both T1- and T2-weighted images results in signal loss.<sup>2</sup> As SPIO imaging shows tumours by using RES cell function, it is a completely different imaging technique compared with dynamic CT or MRI. This enables detection of tumours usually missed on

dynamic CT.<sup>3</sup> As malignant tumours typically do not contain RES cells, they appear as hyperintense lesions against a hypointense liver on T2-weighted images.<sup>1</sup>

Analysis of a combination of unenhanced and SPIO-enhanced images resulted in more accurate differentiation of benign and malignant lesions as well as better lesion characterisation.<sup>4</sup> Dynamic imaging with SPIO could overcome the problem of distinguishing small



**Figure 3.** Hepatocellular carcinoma in segment V of the liver. (a) Pre-contrast axial T2-weighted half-Fourier-acquired single-shot turbo spin echo (T2 HASTE). (b) Superparamagnetic iron oxide-enhanced at 10 minutes delay axial T2 HASTE.

lesions from vessels and improve characterisation of lesions. In addition, in patients with cirrhosis, it is important to distinguish between a dysplastic nodule and HCC. Dysplastic nodules are believed to be precursors of HCC. Since there is an overlap in the characteristics of dysplastic nodules and well-differentiated HCCs, performing a combined SPIO and gadolinium-enhanced MR would be helpful.<sup>5</sup>

Several papers have studied the use of double contrast MRI. Simultaneous use of both gadolinium and iron oxide particles significantly improved the diagnosis of HCC, compared with SPIO-enhanced imaging.<sup>5,6</sup> Double contrast imaging was more sensitive to dynamic gadolinium-enhanced imaging because the signal intensity of the background liver on T1WI, after SPIO-enhanced images, was lower than that on the non-enhanced images. Therefore, there was a synergistic increase in the intensity of the enhancing lesions and the more hypointense background liver. These studies suggest that dual contrast imaging may be helpful in patients with cirrhotic livers because iron oxide uptake in cirrhotic livers is patchy secondary to areas of fibrosis and there is also a reduction in K upffer cell activity and greater contrast uptake in the spleen. Therefore, in these patients, gadolinium imaging is used for lesion detection and characterisation of HCCs. This method of imaging is, however, severely limited by cost, and further work needs to be done to determine if its benefits would outweigh the cost.

So far, to our knowledge, there have been no previous studies comparing 5-phase CT of the liver with SPIO-enhanced MR. In our series, we found that SPIO-enhanced MR was able to characterise the detected lesions accurately when compared to a standard of 5-phase enhanced CT combined with the clinical and the biochemical picture. Our study did not show any statistically significant difference between SPIO-enhanced MRI and 5-phase CT. In the T2 HASTE sequence there was consistent lack of uptake in all seven HCCs, with increase in conspicuousness of the lesions against the low signal intensity liver background similar to other studies.<sup>7</sup> Unlike that study, we did not encounter lack of signal intensity loss in any HCCs that was attributed to the HCC being well-differentiated or small, with enough K upffer cell activity to have signal intensity loss on iron oxide imaging.

All seven HCCs showed early arterial phase enhancement on CT. On SPIO-enhanced MR, however,

contrast washout appeared to occur later, with five lesions still showing enhancement in the portal phase (50 seconds delay) and six lesions still enhancing in the early delayed-phase (3 minutes delay) and delayed-phase imaging (10 minutes delay) in Vibe sequence. In two lesions that occurred in the same patient, enhancement was only seen in the 3-minute and 10-minute delay Vibe sequences and not in the arterial phase. We are uncertain as to the cause of this enhancement pattern. The patient was diabetic, hypertensive and had chronic renal failure on haemodialysis.

It has been stated that there is difficulty in distinguishing between small haemangiomas and metastases, as both lesions may have similar signal intensities.<sup>8</sup> This may be due to the lack of dynamic imaging capability of ferumoxides that was used. With dynamic scanning with SPIO, haemangiomas are hyperintense on T1WI due to uptake by macrophages and blood pool accumulation.<sup>9</sup> In our patients with arterioportal shunting, although the area of contrast enhancement was well-appreciated on 5-phase CT, a similar enhancement pattern was not appreciated on the DPI. In T2 HASTE, the areas of enhancement seen on CT were isointense to the rest of the liver. Follow-up CT did not show any change or progression of these lesions. We postulate that perhaps the T1 effect was fairly homogeneous for the whole liver because the K upffer cell function was not in anyway deranged in any part of the liver. Liver cysts were of fluid intensity and did not show any enhancement on DPI nor uptake of SPIO. They also appeared of higher signal than HCCs in the T2 HASTE sequence, post-SPIO.

This study was limited by both the number and the variation in the types of lesions analysed. This reflects the groups of patients seen in our daily practice. In addition, there was a lack of histological proof for the lesions, since benign lesions are never biopsied and our current practice is not to biopsy malignant lesions unless there is uncertainty of diagnosis. The use of follow-up, characteristic enhancement features, and signal intensities were deemed sufficient for diagnosis, without the need to resort to biopsy and its attendant risks. Histologic confirmation of HCC was available for only two patients (after resection for HCC), while the remaining 8 had interventional procedures (radiofrequency ablation or transarterial chemoembolisation). A presumptive diagnosis of HCC was made based on raised AFP levels and chronic hepatitis B/C carrier status. Follow-up imaging after intervention of these patients' lesions were

done and they also showed decreasing AFP levels. The patient with the metastatic lesion had histologically proven cervical carcinoma that was resected and then presented with rising Ca-125 levels. CT of the pelvis did not reveal recurrent local disease or lymphadenopathy, and the liver lesion was not present in previous scans. We also found that respiratory artifacts, especially on the Vibe sequences, were often problematic as our patient population was elderly and could not breath hold for long.

We concluded that both imaging modalities are comparable. SPIO-enhanced MRI can be used as an alternative to 5-phase CT in the detection and characterisation of liver lesions without the risks of radiation, especially in those patients who require repeated imaging. However, with longer examination time plus significantly higher cost, SPIO-enhanced MRI should be used selectively, and appears especially suited to those with lesions of indeterminate origin, e.g., those with areas of arteriportal shunting with no definite focal liver lesion on 5-phase CT.

### ACKNOWLEDGEMENTS

The authors express their gratitude to Professor KH Ng and Mr LK Tan and Mr JW Tan for assistance with this research.

### REFERENCES

1. Reimer P, Balzer T. Ferucarbotran (Resovist): a new clinically approved RES-specific contrast agent for contrast-enhanced MRI of the liver: properties, clinical development and applications. *Eur Radiol* 2003;3:1266-1276.
2. Vogl TJ, Schwarz W, Blume S, et al. Preoperative evaluation of malignant liver tumors: comparison of unenhanced and SPIO (Resovist)-enhanced MR imaging with biphasic CTAP and intraoperative US. *Eur Radiol* 2002;13:262-272.
3. Abella H. SPIO-enhanced MRI edges out MRI for detecting liver lesions. *Diagnostic Imaging Online*; 2003. Available from: <http://www.diagnosticimaging.com/dinews/2003012301.shtml>
4. Reimer P, Jahnke N, Fiebich M, et al. Hepatic lesion detection and characterization: value of nonenhanced MR imaging, superparamagnetic iron oxide-enhanced MR imaging, and spiral CT-ROC analysis. *Radiology* 2000;217:152-158.
5. Ward J, Guthrie JA, Scott DJ, et al. Hepatocellular carcinoma in the cirrhotic liver: Double-contrast MR imaging for diagnosis. *Radiology* 2000;216:154-162.
6. Kubaska S, Sahani DV, Saini S, Hahn PF, Halpern E. Dual contrast enhanced magnetic resonance imaging of the liver with superparamagnetic iron oxide followed by gadolinium for lesion detection and characterization. *Clin Radiol* 2001;56:410-415.
7. Paley MR, Mergo PJ, Torres GM, Ros PR. Characterization of focal hepatic lesions with ferumoxides-enhanced T2-weighted MR imaging. *AJR Am J Roentgenol* 2000;175:159-163.
8. Kim MJ, Kim JH, Chung JJ, Park MS, Lim JS, Oh YT. Focal hepatic lesions: detection and characterization with combination gadolinium- and superparamagnetic iron oxide-enhanced MR imaging. *Radiology* 2003;228:719-726.
9. Kumano S, Murakami T, Kim T, et al. Using superparamagnetic iron oxide-enhanced MRI to differentiate metastatic hepatic tumors and nonsolid benign lesions. *AJR Am J Roentgenol* 2003; 181:1335-1339.