

## MR-arteriportography: A new technical approach for detection of liver lesions

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### Abstract

**AIM:** To evaluate the benefit and effectiveness of MR-arteriportography (MR-AP) to achieve the highest sensitivity for detection and evaluation of hepatocellular carcinoma (HCC).

**METHODS:** Twenty liver cirrhosis patients with suspected HCC were included before transarterial chemoembolization. In all patients double-enhanced Magnetic resonance imaging (MRI) was performed. A bolus of 10 mL Magnevist® was injected through a selectively placed catheter in the superior mesenteric artery and MRI of the liver was performed in arteriportographic phase. Two independent readers evaluated number, size and localization of detected lesions. Diagnostic quality was determined using a 4-point scale. Differences were analyzed for significance using a *t*-test. Interobserver variability was calculated.

**RESULTS:** In all 20 patients (100%), MR-AP was feasible. Diagnostic quality was, in all cases, between 1 and

2 for both modalities and readers. MR-AP detected significantly more lesions than double-enhanced MRI (102.5 vs 61, respectively,  $P < 0.0024$ ). The inter-observer variability was 0.881 for MRI and 0.903 for MR-AP.

**CONCLUSION:** Our study confirmed that the MR-AP as an additional modality for detection of HCC is beneficial, as significantly more lesions were detected compared to MRI with liver-specific contrast.

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**Key words:** MR-arteriportography; Magnetic resonance imaging; Hepatocellular carcinoma; Liver lesions

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### INTRODUCTION

Hepatocellular carcinoma (HCC) is the most common primary malignant tumor of the liver and often develops in patients with underlying liver cirrhosis due to excessive alcohol intake, chronic hepatitis or primary biliary cirrhosis.

In the treatment of hepatocellular carcinoma, surgical resection is considered the only potentially curative therapy. However, technical improvements in hepatic surgery have extended the indications for surgery remarkably, and also regional therapeutic procedures such as transcatheter

arterial chemoembolization (TACE)<sup>[1-3]</sup> and radiofrequency ablation (RFA)<sup>[1,4,5]</sup> have proved to be very successful. A prolonged time of survival following diagnosis is noted. Therefore, the pre-operative or pre-interventional workup of patients with suspected liver malignancy is even more important, especially concerning the evaluation and characterization of focal or diffuse lesions in the cirrhotic liver. Magnetic resonance imaging (MRI) has been used to improve identification of focal hepatic masses in a cirrhotic liver.

Dynamic MRI after a bolus injection of gadopentetate dimeglumine has been accepted as a valuable method for the detection and characterization of liver tumors<sup>[6-9]</sup>. Studies have shown that superparamagnetic iron oxide-enhanced magnetic resonance imaging (SPIO-MRI) increases sensitivity<sup>[4,10]</sup>.

In order to determine the treatment of choice for HCC, studies have shown that examinations by both computed tomography angiography (CTA) and computed tomography arteriography (CT-AP) are indispensable because of the high sensitivity of CT-AP in detecting hepatic lesions and the capability of CTA to characterize them<sup>[11,12]</sup>. However, in contrast to its high sensitivity in detecting lesions, the specificity of CT-AP for characterizing intrahepatic lesions is low. Tumor-mimicking benign perfusion abnormalities and benign lesions (e.g. hemangiomas, arterio-venous shunts) have led to a reported incidence of false-positive lesions between 9% and 63% in primary and secondary liver lesions<sup>[13,14]</sup>.

Despite advances in CT or MRI, ultrasound (US) with or without application of contrast agents also plays a key role in the diagnostic algorithm of HCC due to its low cost, availability and non-invasiveness.

Until now, there have hardly been any studies comparing the effectiveness of MR-arteriography (MR-AP) and contrast-enhanced MRI for diagnosis of malignant liver lesions. Thus, the purpose of this study was to combine the advantages of modern contrast-enhanced MRI with the technique of arteriography to achieve the highest sensitivity for diagnosis of malignant liver lesions in patients suffering from HCC.

## MATERIALS AND METHODS

### Patients

Approval for this study was obtained from the institutional review board in conformity with the Declaration of Helsinki. Before the procedures were conducted, written informed consent was obtained from each patient for MRI, MR-AP and angiography after the nature of the procedure was fully explained.

During the period from February 2005 to September 2007, 20 patients [18 men, 2 women, age range from 47 to 76 years (mean age, 62 years)] with symptoms suggestive of primary malignant hepatic tumors were referred to our department. As HCC is commonly associated with liver cirrhosis, all patients had deteriorated liver but a tolerable renal function, and the cardiovascular status was stable. Twelve of our 20 patients suffered from alcohol toxic

liver cirrhosis. In 4 out of 20 patients the underlying disease was chronic hepatitis (2 patients with chronic hepatitis B, 2 patients with chronic hepatitis C). In 4 out of 20 patients, the fundamental disease could not be elicited. Concerning the severity of cirrhosis, 8 out of 20 patients were classified as Child Pugh score A, 7 out of 20 patients as Child Pugh score B and 5 out of 20 patients as Child Pugh score C.

The existence of malignant hepatic tumors was confirmed using multislice MRI and CT. MR-AP was performed to evaluate the tumor extent in order to suggest interventional therapy, surgery or chemotherapy.

Diagnosis of HCC was histologically confirmed in 15 out of 19 patients. In one patient (patient No. 16), existence of a malignant hepatic lesion was excluded histologically following liver transplantation.

In 13 out of 20 patients the  $\alpha$ -fetoprotein (AFP) level was elevated, ranging from 16.4-2513 ng/mL (mean 488.1 ng/mL). In 7 patients (including patient No. 16) AFP levels were within a normal range.

### Imaging procedures

**Angiography:** Before TACE and for MR-arteriography, the femoral common artery was punctured under local anesthesia using the Seldinger technique and a 5-French angiographic catheter (Cobra, Cook Medical, USA) was positioned in the proximal superior mesenteric artery. A diagnostic angiography was performed to visualize the portal vein and to exclude shunts which could involve contrasting *via* the portal vein.

**MRI:** MRI was performed on a 1.5-T whole-body scanner (Magnetom Sonata, Siemens Medical Solutions, Germany) equipped with a high-performance gradient (Quantum) system (maximum gradient strength, 30 mT/m; slew rate, 125 T/ms). A combination of the standard body phased-array coil with spine array coils was used for signal reception.

**MR-AP standard protocol (Table 1):** For MR-AP, 10 mL gadopentetate dimeglumine was injected through the catheter placed in the superior mesenteric artery at a rate of 2 mL/s with a power injector (Medrad Spectris MR Injector, USA).

**MRI standard protocol (Table 2):** For MRI, 0.2 mmol/kg body weight gadopentetate dimeglumine was injected intravenously at a rate of 2 mL/s with a power injector (Medrad Spectris MR Injector). T1-weighted VIBE transversal Dynamic scans were acquired 20, 40, and 120 s after application of gadopentetate dimeglumine. T2-star-weighted Flash 2D scans and T2-weighted TSE FS scans were obtained after application of 1.4 mL Ferucarbotran (Resovist<sup>®</sup>, Bayer Schering Pharma AG, Germany).

### Image analysis

In the retrospective reviewing procedure, all images of each technique were interpreted and evaluated independently by two observers with great experience in abdominal MRI.

**Table 1 MR-arteriportography standard protocol**

Scans	Plane	TE	TR	Flip angle
Unenhanced				
T2-weighted TRUFI	Coronal	1.9	3.8	71°
T2-weighted TRUFI	Transversal	1.88	3.76	71°
T1-weighted VIBE	Transversal	2.02	4.78	10°
Enhanced				
T1-weighted FLASH FS CE	Transversal	4.76	123	70°
T1-weighted VIBE dynamic <sup>1</sup>	Transversal	2.02	4.78	10°

<sup>1</sup>Dynamic scans were started immediately following application of 10 mL Gd-DTPA. MRI: Magnetic resonance imaging.

**Table 2 Magnetic resonance imaging standard protocol**

Scans	Plane	TE	TR	Flip angle
Unenhanced				
T1-weighted VIBE	Transversal	1.59	4.37	10°
T2-star-weighted FLASH 2D	Transversal	10.00	169.00	90°
T2-weighted TSE FS	Transversal	105.00	2740.00	170°
T1-weighted FLASH opp	Transversal	2.71	100.00	70°
T1-weighted FLASH in	Transversal	4.76	87.00	60°
T2-weighted HASTE	Transversal	85.00	1000.00	150°
T2-weighted TRUFI	Coronal	1.83	3.65	71°
T1-weighted VIBE	Transversal	1.55	4.81	10°
Enhanced				
T1-weighted VIBE dynamic <sup>1</sup>	Transversal	1.55	4.81	10°
T1-weighted FLASH FS	Transversal	4.76	123.00	70°
T1-weighted FLASH FS	Coronal	4.76	94.00	70°
T2-star-weighted FLASH 2 <sup>2</sup>	Transversal	10.00	169.00	90°
T2-weighted TSH FS <sup>2</sup>	Transversal	105.00	2740.00	170°

<sup>1</sup>Dynamic scans were started immediately following application of Gd-DTPA (0.2 mmol/kg); <sup>2</sup>Following application of 1.4 mL Resovist.

No clinical information or patient diagnosis was given to the observers. The images from each technique were interpreted in separate sessions in a randomized sequence. In the first session, the two observers reviewed a set of images that included both unenhanced and gadopentetate dimeglumine-enhanced, as well as Resovist-enhanced, images.

In the second session, each observer reviewed a set of images (MR-AP set) that included gadopentetate dimeglumine-enhanced images after injection *via* the superior mesenteric artery.

For characterization of liver lesions, all images of each examination were reviewed together using all the sequences available. Each observer recorded the number of suspected lesions noted, their size, and the segmental location. Furthermore, the image quality of MR and MR-arteriportography was documented on a four point scale: 1-excellent, 2-minor diagnostic limitations, 3-major diagnostic limitations, 4-non-diagnostic.

**Statistical analysis**

Statistical software (SPSS, version 14, Chicago, USA) was used for statistical analysis. We evaluated the differences with regard to number of lesions found using MR-arteriportography and MRI. Furthermore, the inter-observer differences in evaluation of MR-arteriportography and double-enhanced MRI were analyzed. Paired-samples

**Table 3 Number of lesions detected in MR-arteriportography and magnetic resonance imaging**

Patient	Age (yr)	MR-AP number of lesions Σ 102/103		Double-enhanced MRI number of lesions Σ 60/56	
		Reader 1	Reader 2	Reader 1	Reader 2
		1	62	9	9
2	47	7	8	2	2
3	70	4	5	2	2
4	74	7	8	4	3
5	51	3	3	3	3
6	76	1	2	1	1
7	70	6	6	9	8
8 <sup>1</sup>	63	-	-	(7)	(7)
9	70	4	4	2	2
10	63	9	8	2	2
11	51	9	8	6	5
12	63	10	11	3	2
13	57	6	6	2	2
14	67	5	4	4	5
15	51	4	3	3	2
16	53	0	0	1	1
17	51	2	2	2	2
18	54	5	6	3	3
19	57	9	8	4	4
20	73	2	2	3	3

<sup>1</sup>Patient No. 8 was excluded from the evaluation for diffuse infiltration of virtually all liver segments. *P* = 0.0024 (relation of the number of lesions detected in MR-AP and MRI). MR-AP: MR-arteriportography; MRI: Magnetic resonance imaging.

*t* tests and  $\chi^2$  test were used to compare. In paired-samples *t* tests, *P* < 0.05 indicated a statistically significant difference.

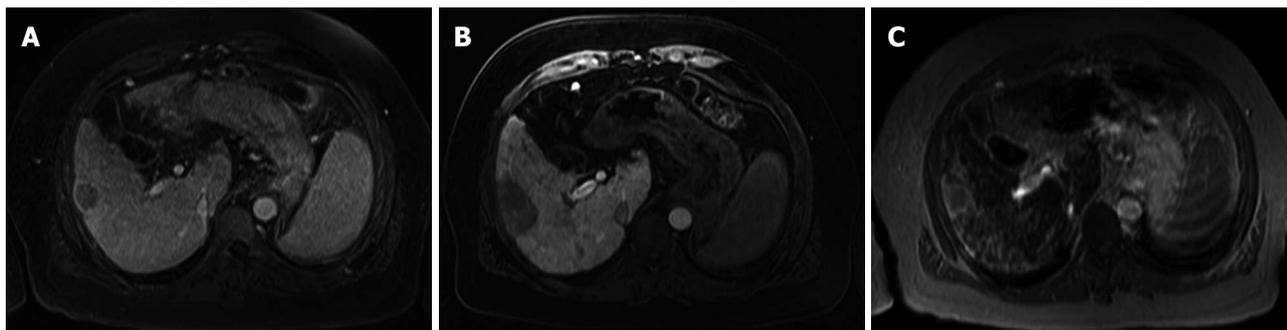
**RESULTS**

Twenty patients with liver cirrhosis underwent combined MR-arteriportography and SPIO-MRI examinations. No adverse reactions were experienced by any of the patients who received Gd-DTPA and SPIO.

In all 20 patients (100%), MR-arteriportography was feasible. The image quality in both modalities (MR-AP and MRI) was excellent (1-2 in MR-arteriportography, SD: 0.4865; 1-2 in MR, SD: 0.4292). In patient No. 8, a MR-AP evaluation was not suitable due to a diffuse infiltration of virtually all liver segments, thus the patient was excluded. Altogether, 102.5 hepatic lesions were detected using MR-AP, whereas only 61 lesions could be detected using MRI (Table 3). This difference is considered to be statistically significant (*P* < 0.0024).

The kappa analyses of two observers regarding the number of lesions detected by both modalities showed substantial to excellent agreement ( $\kappa$  = 0.903, 95% CI: 0.844 to 0.962 for MR-AP; and  $\kappa$  = 0.881, 95% CI: 0.795 to 0.966 for MRI). In particular,  $\kappa$  values with MR-AP imaging indicated excellent agreement.

The lesions found in all patients ranged in size from 7-120 mm (mean 28.24 mm) for MRI and from 4-120 mm (mean 24.62 mm) for MR-AP. This difference is not con-



**Figure 1** A 49-year-old man with hepatic cirrhosis due to chronic hepatitis B and C infection. Histology obtained following liver transplantation confirmed the diagnosis of a multifocal hepatocellular carcinoma. A: Magnetic resonance imaging (T1-weighted VIBE) during early venous phase shows a low signal intensity nodule with a diameter of approximately 3 cm in segment VIII/V; B: SPIO-enhanced T2-weighted fast image shows an area of increased signal intensity (segment VIII/V) within the otherwise lower but very inhomogenous signal of the liver parenchyma with profound cirrhosis; C: MR-AP (T1-weighted VIBE) during early venous phase displays an area of decreased enhancement (approx. 4.5 cm diameter) in segment VIII/V. Note the multiple smaller hypointense lesions in segments VII/VI. SPIO: Superparamagnetic iron oxide-enhanced.

sidered to be statistically significant. In MRI, 16 lesions (26.2%) were 10 mm or less in diameter. In MR-AP, 30 lesions (29.3%) were 10 mm or less in diameter.

In a total of 15 out of 19 patients, more lesions were detected by MR-AP compared to MRI with liver-specific contrast. According to the characteristic features displayed in MR-AP, all lesions were classified as malignant. Thus, as a consequence of the finding of these additional lesions, further treatment (TACE, RFA or surgery) was performed upon the patients.

In all but one patient (patient No. 16), the lesions found displayed a characteristic MRI signal, including arterial enhancement to a greater or lesser extent, with late wash out and an absent accumulation of Ferucarbotran (Resovist®). Thus, these lesions were classified as malignant. In addition, these lesions also showed characteristic features in MR-AP, such as absent enhancement of gadopentetate dimeglumine with profound demarcation compared to healthy liver tissue. Hence, the lesions were also classified as malignant.

Diagnosis of HCCs was histologically confirmed in 15 out of 19 patients. In patient No. 16, one lesion was found in segment 8 of the liver which showed a portal venous enhancement with accumulation of Ferucarbotran and no traceability in MR-AP. The lesion therefore was classified as benign, i.e. regenerated nodule that was confirmed histologically following liver transplantation (Figures 1 and 2).

## DISCUSSION

Before decisions are made as to hepatic resection of hepatocellular carcinoma or interventional treatment such as TACE, percutaneous ethanol injection therapy and radiofrequency ablation (RFA), accurate information regarding the number and localization of lesions is essential.

Because of its high sensitivity for detecting lesions, CT-AP is one of the most reliable tools for detection of liver lesions. The rationale of CT-AP is for contrast material to be delivered directly to the liver through the portal vein before it can return to the hepatic artery from the

systemic circulation, to optimize the detection of tumor lesions that do not have portal vein flow and appear as hypodense nodules. The aim of our study was to combine the advantages of arteriportal contrast and MRI to detect liver lesions in patients with HCC. MRI with liver-specific contrast agents is currently the imaging modality of choice. Most studies that have directly compared MRI with CT-AP in patients with HCC or metastases reported no significant differences in sensitivity<sup>[15-17]</sup>, but in some studies a higher specificity for MRI is reported<sup>[13]</sup>.

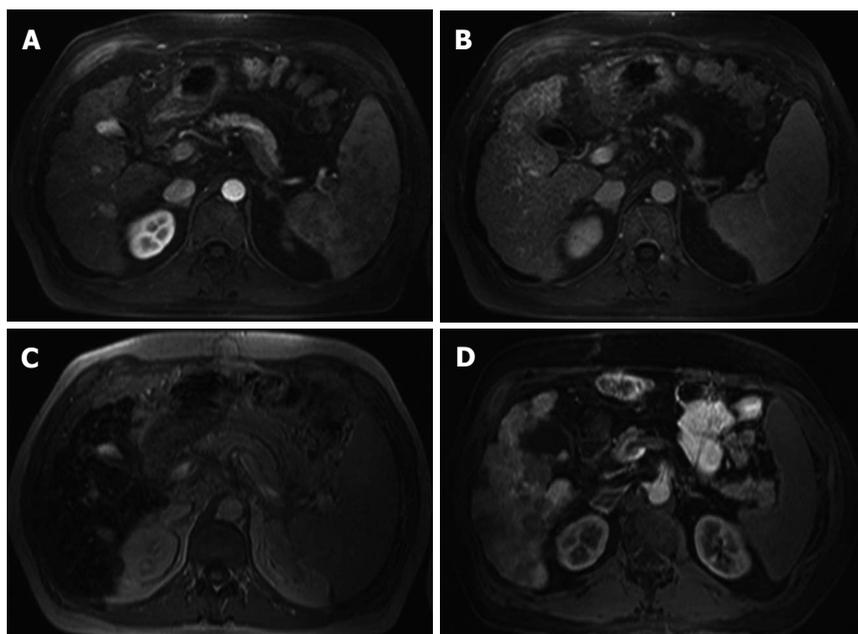
Preoperative or pre-interventional workup of patients with suspected liver malignancy is even more important, especially concerning the evaluation and characterization of a focal lesion or diffuse infiltration of the cirrhotic liver.

Previous studies have shown the usefulness of ferumoxide-enhanced MR imaging for the detection of hepatic tumors of different histological types<sup>[18,19]</sup>. After intravenous injection, the SPIO-particles are cleared by macrophages and can be identified histologically in Kupffer's cells of the liver. Poorly differentiated hepatic tumors lack Kupffer's cells; therefore, the T2 relaxation does not change after the administration of SPIO causing an increased lesion-to-liver contrast.

Studies of patients with hepatic metastases have shown that ferumoxide-enhanced MR imaging is more sensitive than unenhanced MR imaging<sup>[20,21]</sup> or contrast-enhanced CT<sup>[22,23]</sup>, and at least as accurate as CT during arteriportography<sup>[10]</sup>.

Regarding the detection of HCCs, it has been reported that the sensitivity of combined CT during arteriportography and CT hepatic arteriography is 89%-95%<sup>[24,25]</sup> in comparison to 80.4% on contrast-enhanced CT alone<sup>[26]</sup>. Furthermore, the sensitivity of MR sequences with ferumoxide enhancement was reported to be 78%-92%<sup>[18,19,24]</sup>, and that of MR-AP 94%-97%<sup>[27,28]</sup>.

Diffusion-weighted imaging (DWI) is a MRI technique that provides imaging of diffusion in biological tissues. Recent technical developments have reduced the image deformation associated with this technique and have increased the signal to-noise ratio, thus making DWI of the



**Figure 2** A 63-year-old man with hepatic cirrhosis due to a chronic hepatitis C infection. Histology obtained following liver transplantation confirmed the diagnosis of a well differentiated hepatocellular carcinoma. A: Magnetic resonance imaging (T1-weighted VIBE) during arterial phase shows a singular hyper-vascularized nodule with a diameter of approximately 2 cm in segment VII; B: T1-weighted VIBE during early venous phase shows an inhomogenous signal of the liver parenchyma with masking of the lesion in segment VII; C: SPIO-enhanced T2-weighted fast image shows an area of increased signal intensity (segment VII) within a low signal of the liver parenchyma; D: MR-AP (T1-weighted VIBE) during early venous phase displays an area of decreased enhancement (approx. 3 cm diameter) in segment VII and various low signal lesions in segments I, IVa, VIII and VII. SPIO: Superparamagnetic iron oxide-enhanced.

body feasible<sup>[29]</sup>, especially for detection of liver malignancies<sup>[30]</sup>. Studies have reported a higher sensitivity of DWI for detection of small hepatic metastases compared to SPIO-enhanced T2-weighted images and breath-hold T2-weighted images<sup>[31,32]</sup>, particularly due to a profound signal intensity of the HCC in the cirrhotic liver. In comparison, cysts and hemangiomas, the most frequently found benign lesions of the liver, typically show low or absent signal intensities<sup>[33]</sup>.

Our study demonstrated that MR-arteriportography as an alternative method for detection of HCC is not only feasible but showed a significantly larger number of lesions than ferumoxide-enhanced MR imaging, especially in patients with hepatic cirrhosis.

Also, the lesion's size seems to play a crucial role. Out of the 41 lesions that were exclusively found using MR-AP, 21 were 10 mm or less in diameter. This confirms the high sensitivity of MR-AP, especially regarding smaller lesions. However, a definite differentiation among HCC nodules, regenerative dysplastic nodules or, for example, small arterio-venous shunts that are very common in patients with hepatocellular carcinoma is not possible.

One limitation of the study is that a histological confirmation of HCC or benign lesions could only be obtained in 16 out of 20 patients. In the other 4 patients, further treatment was based upon the combination of typical image morphology and elevated alpha fetoprotein. Another limitation is the relatively small number of patients that were examined in this study. Prospective studies are necessary in order to ascertain the diagnostic reliability of MR-AP compared to established methods.

In summary, our study confirmed that the use of MR-arteriportography as an additional modality for detection of hepatocellular carcinoma is useful. Using this technique, significantly more lesions could be detected in comparison to MRI with liver-specific contrast agent.

## COMMENTS

### Background

Hepatocellular carcinoma (HCC) is the most common primary malignant tumor of the liver and often develops in patients with underlying liver cirrhosis. In the treatment of HCC, surgical resection is considered the only potentially curative therapy; however, other regional therapeutic procedures such as transcatheter arterial embolization or radiofrequency ablations have proved to be very successful. Thus, the pre-interventional evaluation of patients with suspected liver malignancy is even more important, especially concerning the evaluation and characterization of focal or diffuse lesions in the cirrhotic liver.

### Research frontiers

MR imaging with liver-specific contrast agents has been used to improve identification of focal hepatic masses in a cirrhotic liver. Also, studies have shown that examinations by computed tomography arteriportography (CT-AP) have a very high sensitivity for detection of hepatic lesions compared to a relatively low specificity. In this study, the benefit and effectiveness of MR-arteriportography (MR-AP) in achieving the highest sensitivity for detection and evaluation of HCC was evaluated.

### Innovations and breakthroughs

Until now, there have hardly been any studies comparing the effectiveness of MR-AP and contrast-enhanced MRI for diagnosis of malignant liver lesions. This study confirmed that MR-arteriportography as an additional modality for detection of HCC is truly beneficial and may lead to change in treatment in many patients.

### Applications

The results showed that using the MR-AP approach, significantly more lesions could be detected in comparison to MRI with liver-specific contrast agent. Thus, it might play an important role for future strategy of therapeutic interventions.

**Terminology**

MR-AP is an MRI procedure where the contrast agent is injected through a catheter placed in the superior mesenteric artery.

**Peer review**

It is well-written and is novel work.

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