

The role of dynamic subtraction MRI in detection of hepatocellular carcinoma

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PURPOSE

The aim of this study was to investigate the role of dynamic subtraction magnetic resonance imaging (MRI) in detection of hepatocellular carcinoma (HCC) in patients with cirrhosis.

MATERIALS AND METHODS

MR images of 32 patients with cirrhosis were retrospectively investigated. The standard sequence images of the patients were evaluated for detection of HCC, and then the subtracted images of dynamic contrast-enhanced series were evaluated. The sensitivity, specificity, and accuracy of standard technique and additional use of subtracted images were investigated.

RESULTS

In detection of at least one HCC, standard protocol was useful in 14 of 17 (82.3%) patients; by additional use of subtraction imaging all 17 (100%) patients with HCC were detected. For detection of the correct number of HCC tumors, standard protocol was found to have 61.5% sensitivity, 78.9% specificity, and 71.8% accuracy. The use of subtracted images increased the sensitivity to 85.7%, specificity to 83.3%, and accuracy to 84.3%.

CONCLUSION

Subtraction is a simple automatic procedure that is commonly available in most MRI systems. The use of subtraction of dynamic contrast-enhanced series facilitates the detection of HCC in disorganized architecture of cirrhotic livers.

Key words: • cirrhosis • carcinoma, hepatocellular • magnetic resonance imaging

Cirrhosis is a diffuse liver disease characterized by progressive parenchymal damage and nodular regeneration (1–3). Hepatocellular carcinoma (HCC) is a neoplasm that usually arises in a cirrhotic liver by a multistep carcinogenesis process (4). Recent studies have shown that in patients with cirrhosis and early stage HCC, liver transplantation offers the best chance for long-term survival (2, 5, 6). Therefore, early detection of HCC and accurate assessment of tumor burden are crucial to successful treatment planning and long-term survival. Magnetic resonance imaging (MRI) plays a prominent role in the evaluation of cirrhosis and screening for early HCC (5). Gadolinium-enhanced MRI with multiple phases of acquisition improves the detection of HCCs (1, 7). However, the determination of contrast enhancement is not always easy to accomplish for hyperintense lesions on arterial phase dynamic images (8). Subtraction of unenhanced images from gadolinium-enhanced images has been pursued in an attempt to maximize the qualitative recognition of lesion enhancement (8, 9).

The aim of this study was to investigate the role of subtraction MRI in detection of HCC in patients with cirrhosis.

Materials and methods

Patients

The study group of this retrospective investigation was composed of patients with cirrhosis who had liver MRI in picture archiving and communication system (PACS) archive. The MRI of the patients had been performed to evaluate the severity of cirrhosis or portal hypertension, screening for hepatic lesions suspected with other imaging modalities. Two investigators (C.A., O.G.) reviewed the clinical records and the images of the patients to determine the inclusion of the patients in the study. Inclusion criteria of the study were: histopathological diagnosis of cirrhosis, clinical and MRI follow-up >1 year, and presence of a complete series of standard liver MR images according to the protocol of our institute, including multiphasic dynamic contrast enhanced MRI series with high-quality breath holding.

MRI technique

MRI was performed with a 1.5-T unit (Intera, software version 8.1; Philips Medical Systems, Eindhoven, The Netherlands) by using a phased-array coil. The standard liver MR protocol of our institute included T2-weighted fat-saturated spin echo (SE) (TR/TE/FA, 1600/70/90°), heavy T2-weighted single shot (1312/325/90°), T1-weighted in-phase gradient echo (GRE) (196/4.6/80°), T1-weighted opposed-phase GRE (253/6.9/80°), T1-weighted water selective (WATS) fat-saturated multiphasic contrast-enhanced dynamic MRI (272/6.9/70°) in transverse plane, and delayed post-contrast T1-weighted WATS in coronal

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plane. Multiphase contrast enhanced dynamic series were obtained just before and during the rapid bolus intravenous injection of 0.1 mmol gadopentetate dimeglumine per kilogram of body weight while the patient was in the bore of the magnet. The imaging timing of the dynamic series included pre-contrast, arterial, portal, and equilibrium phases of the liver. Subtraction of multiphase contrast enhanced dynamic series was automatically acquired by the software of MR machine. The software provided a new series by image-by-image subtraction of pre-contrast series from each post-contrast series (arterial, portal, and equilibrium) of each patient.

Image analysis

Image analysis was performed independently by two other investigators (M.S., F.O.) who were experienced in liver MRI. The investigators were unaware of the clinical condition of the patients; all patient data were hidden during the image analysis. The investigators evaluated the standard protocol MR images first and noted their findings on the presence and number of HCC lesions. Later in the same session, subtracted images of patients were examined for the same purpose, and decisions were noted. In cases of conflict in the decisions of the investigators, the images were reevaluated jointly, and a final decision was reached by consensus.

Final diagnosis

The final HCC diagnoses of the patients were reached by histopathological examination of explanted liver (n = 4) or resected specimen (n = 1) in operable cases. In inoperable cases, percutaneous biopsy (n = 2) or chemoembolization and lipiodol CT (n = 5), plus ≥ 1 year MR follow-up of patients were used for final diagnoses. The absence of HCC was confirmed by histopathological examination of explanted liver (n = 1) and ≥ 1 year clinical follow-up. In patients with HCC, the absence of additional HCC lesions in other liver areas was confirmed by clinical evaluation and 1-year MRI follow-up.

Statistical analysis

A patient-based analysis of the results for standard protocol and for subsequent use of subtraction images

was performed, and basic statistical parameters of sensitivity, specificity, positive and negative predictive values, and the accuracy of each method were calculated.

Results

Thirty-two patients met the inclusion criteria of the study; 15 did not have HCC, and 17 had ≥ 1 HCC lesion. In detection of ≥ 1 HCC lesion, standard protocol was useful in 14 of 17 (82.3%) of the patients; by including subtraction imaging, all of 17 (100%) patients with HCC were detected. Among the patients with HCC, final diagnosis showed that 12 patients had a single tumor, 3 had two tumors, 1 had three tumors, and 1 had five tumors.

A comparison of methods for detection of HCC tumors is presented in Table 1. The patients who were underdiagnosed (false negative) by subtraction imaging were the patients who were also underdiagnosed by standard protocol. In one patient with 5 HCC lesions and another patient with 3 HCC lesions in whom the diagnoses were reached by histopathological evaluation of the explanted liver, each method underdiagnosed the number of tumors because the missed lesions were < 1 cm in diameter. The other underdiagnoses by standard protocol in 3 patients were found to originate from

equivalent intensity of lesions on T2 and high intensity on T1-weighted images when compared to the liver parenchyma (Fig. 1).

Overdiagnoses of tumors (false positive) by both methods occurred in 2 patients. One patient with HCC was found to have a hamartoma, which was misdiagnosed as a second HCC tumor. In the other patient, a faintly enhancing nodular area was assessed as an HCC by both methods, but histopathological diagnosis did not support this diagnosis. Standard protocol alone made an overdiagnosis in one patient, caused by a dysplastic nodule which caused difficulty in estimation of contrast enhancement on dynamic series of standard protocol because of hyperintensity on T1-weighted images (Fig. 2). Standard + subtraction imaging yielded overdiagnosis in one patient, in whom a dysplastic nodule was diagnosed as HCC subsequent to subtraction misregistration of the images (Fig. 3).

The true negative rate did not show any difference between the methods; however, true positive rates were found to increase and false negative and false positive rates were found to decrease by the use of subtraction imaging. The basic statistical results for detection of the number of HCC tumors in patient-based analysis are presented in Table 2.

Table 1. Patient-based analysis by both methods for detection of hepatocellular carcinoma

| | Patients (n) | |
|---------------------------------|-------------------|---------------------------------|
| | Standard protocol | Standard protocol + subtraction |
| True positive | 9 | 12 |
| False positive (overdiagnosis) | 5 | 3 |
| False negative (underdiagnosis) | 4 | 2 |
| True negative | 15 | 15 |

Table 2. Statistical results of methods for detection of hepatocellular carcinoma

| | Standard protocol | Standard protocol + subtraction |
|---------------------------|-------------------|---------------------------------|
| Sensitivity | 61.5% | 85.7% |
| Specificity | 78.9% | 83.3% |
| Positive predictive value | 66.6% | 80.0% |
| Negative predictive value | 75.0% | 88.2% |
| Accuracy | 71.8% | 84.3% |

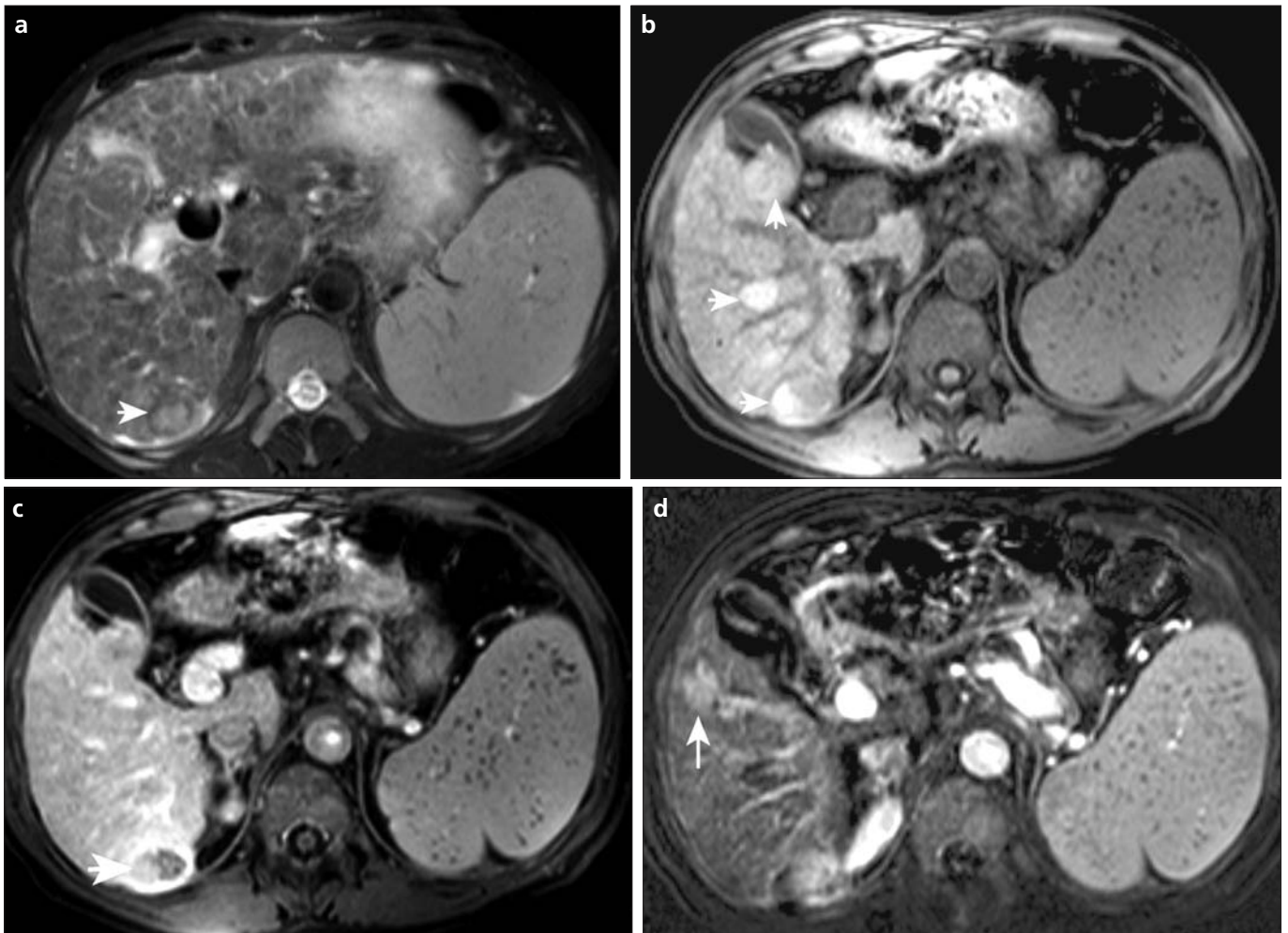


Figure 1. a–d. A 51-year-old man with cirrhosis. Axial T2-weighted MR image (a) shows heterogeneous parenchyma with multiple nodules and a hyperintense lesion in the posterior sector (*arrow*). Axial pre-contrast T1-weighted MR image (b) shows multiple hyperintense nodular lesions (*arrows*). On post-contrast axial T1-weighted MR image (c), the hyperintense lesions became isointense with the parenchyma except for the hepatocellular carcinoma (HCC) lesion in the posterior sector (*arrow*). Subtracted MR image (d) demonstrates a lesion in a different location (*arrow*) from the other nodular lesions, which was proven to be an HCC.

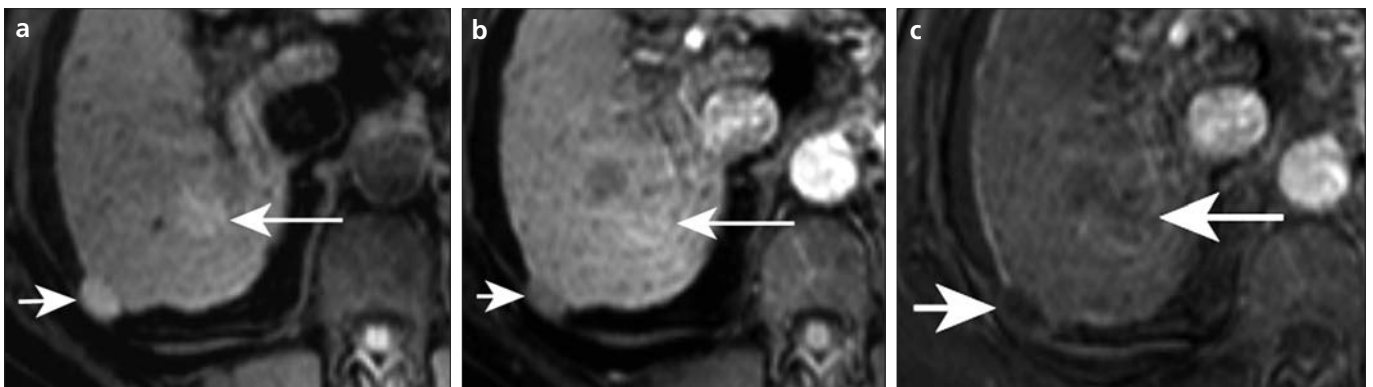


Figure 2. a–c. A 59-year-old man with cirrhosis. Axial pre-contrast T1-weighted MR image (a), shows two hyperintense nodules (*long and short arrows*). On axial post-contrast MR image (b), one of these lesions is isointense with the hepatic parenchyma (*long arrow*), and the other is hypointense (*short arrow*); in both, the estimation of contrast enhancement amount is difficult. By subtraction (c), both lesions appear non-enhancing lesions compatible with dysplastic nodules (*long and short arrows*). Both lesions were proven to be dysplastic nodules.

Discussion

The main purpose of imaging in cirrhosis is to identify HCC. The distorted architecture of liver parenchyma, nod-

ular regeneration, and signal intensity variability of the nodules cause difficulties in detection of HCC (8). Contrast-enhanced multiphasic dynamic

sequences have become a standard of liver MRI in cirrhosis. Arterial phase enhancement after gadolinium administration has been proposed as the

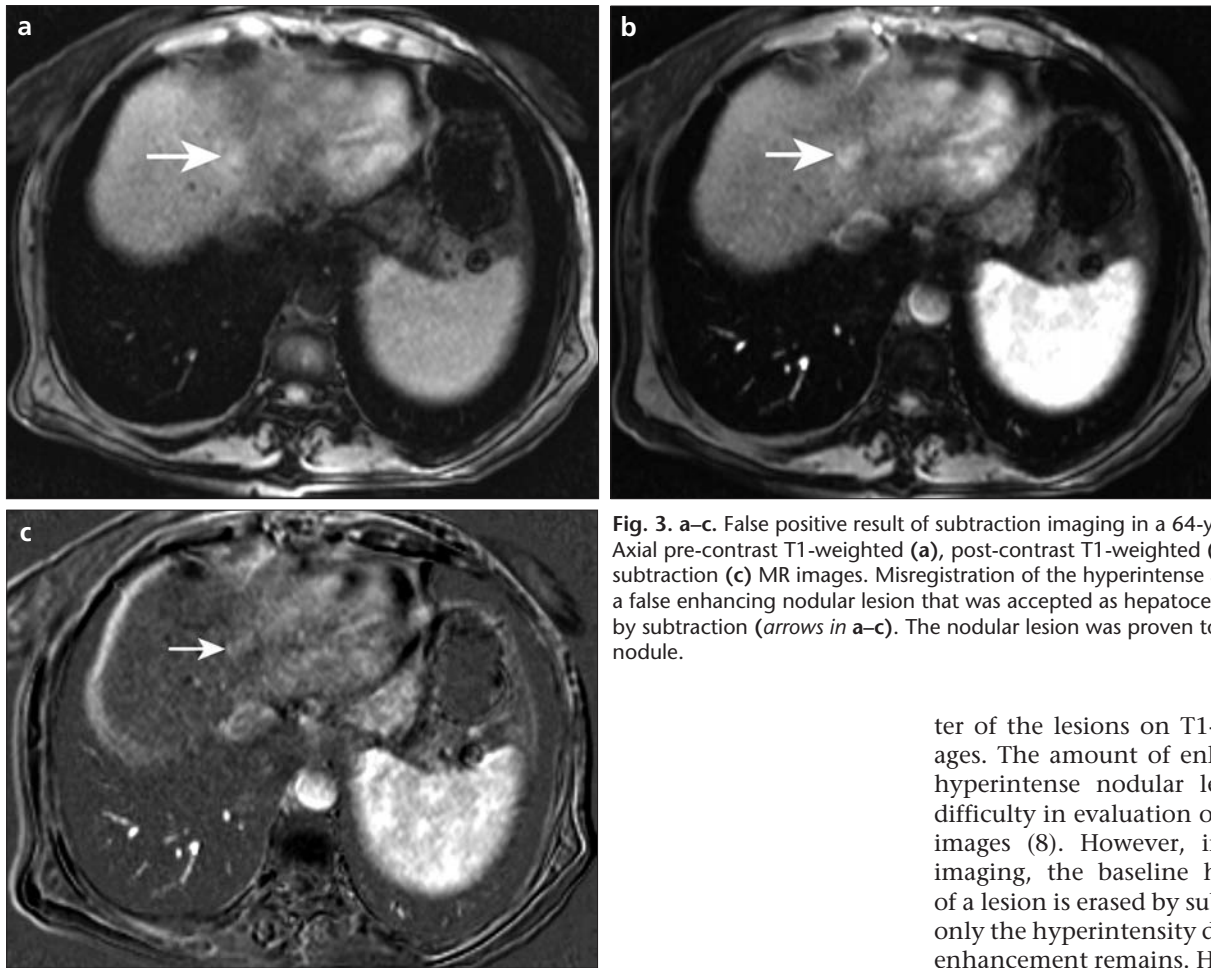


Fig. 3. a–c. False positive result of subtraction imaging in a 64-year-old woman. Axial pre-contrast T1-weighted (**a**), post-contrast T1-weighted (**b**), and subtraction (**c**) MR images. Misregistration of the hyperintense area has caused a false enhancing nodular lesion that was accepted as hepatocellular carcinoma by subtraction (*arrows in a–c*). The nodular lesion was proven to be a dysplastic nodule.

most sensitive sign for the detection of HCCs (10, 11). It is difficult, however, to visually detect enhancement generated by gadolinium-chelate administration for nodules with higher signal intensity than hepatic parenchyma. Although it has been used for years in MRI of breast and MR angiography, subtraction MRI in detection of HCC in cirrhosis is a fairly new concept, and only a few investigations exist in the literature (8, 9, 12, 13). One of these articles was a pictorial essay of the potential use of subtraction MRI for the liver (9); this was followed by an original research article on HCC detection performed by the same authors (8). Previous research on HCC detection used a two-step investigation that included first the technical feasibility of subtraction and then the characterization of hyperintense lesions by conventional versus subtraction images of post-contrast T1-weighted series. Our study has been designed as a retrospective investigation of the images of cirrhotic patients with archived images taken more

than a year after the original images. Technical feasibility of the subtraction method was not taken into consideration in our study by elimination of patients with low-quality breath-hold images that may cause subtraction artifact. The main concern of our study was to investigate the potential benefit of subtraction imaging in addition to the conventional sequences.

According to the results of our study, including use of subtraction imaging yielded increased sensitivity, specificity, and accuracy rates—positive and negative predictive values—compared to the use of standard protocol alone. In assessing absence of HCC, both methods obtained the same results and correctly determined tumor absence in all 15 patients. However, for detection of at least one HCC lesion, standard + subtraction imaging was superior to the standard protocol. In 3 patients, HCCs were overlooked by standard protocol images and detected by standard + subtraction imaging. The main reason for this was the hyperintense charac-

ter of the lesions on T1-weighted images. The amount of enhancement in hyperintense nodular lesions creates difficulty in evaluation of T1-weighted images (8). However, in subtraction imaging, the baseline hyperintensity of a lesion is erased by subtraction, and only the hyperintensity due to contrast enhancement remains. Hence, subtraction images facilitate the ability to see the contrast enhancement of a lesion.

The use of standard + subtraction imaging was also better than standard protocol alone for detection of the correct number of HCC lesions. All patients who were underdiagnosed by subtraction imaging were also underdiagnosed by standard protocol alone. The main reason for missing the existing tumors (false negatives) in these patients was the small size of the missed tumors. The limitation of MRI in detection of small size HCCs has been demonstrated (1). Moreover, these tumors may have low vascularity and may not show contrast enhancement (1, 2). Likely for these reasons, standard protocol and standard + subtraction imaging provided the same number of underdiagnosed tumors in these patients. Underdiagnosis of three other patients using standard protocol alone originated from equivalent intensity of lesions on T2- and high intensity on T1-weighted images when compared to the liver parenchyma. Previous studies have reported that the success of subtraction technique de-

depends on the degree of misregistration artifact between the non-enhanced and enhanced source images, as well as the size and location of the nodules (8). In our study, we tried to eliminate the risk of misdiagnosis caused by misregistration artifact by excluding patients with suboptimal breath-holding. However, a misregistered peripheral nodule at the dome of the liver caused a false positive result in one of our patients. Peripheral lesions at the liver dome have been reported to be at particular risk for misregistration artifact, despite efforts to optimize through use of coregistrations (8).

The reported sensitivity rates of MRI for detection of HCC vary widely, from 55% to 100% (2, 5–8, 12, 14–19). There have been various attempts to increase the detection rate of HCC with the use of new contrast agents or combined use of contrast materials (2, 15, 17, 20). Subtraction imaging is a no-cost method that is simply acquired by most of the MRI devices by automatic subtraction of pre-contrast images from post-contrast dynamic T1-weighted series. Our results suggest that further improvement of detection rate of HCC lesions by MRI may be achieved by inclusion of subtraction imaging in standard protocol.

This study has several limitations. First, there was no consistent gold standard for final diagnoses in our study. The ideal standard of histopathological evaluation of explanted liver could not be achieved in all patients. We tried to overcome this limitation by including patients who had available follow-up images taken more than one year after the initial images. This, however, led to the second limitation of the study, which was the relatively low number of patients. Third, the study was a retrospective investigation of archived images, which limited the use of newer pulse sequence designs such as thinner section three-dimensional imaging. Fi-

nally, the evaluation of both methods in the same session might seem to have introduced bias, but our aim was to determine the value of subsequent evaluation of subtraction imaging, which is commonly used in daily practice.

In conclusion, subtraction is a simple automatic procedure that is commonly available in most MRI machines and the use of subtraction of dynamic contrast enhanced series is a helpful, no-cost tool that improves detection of HCC.

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