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ORIGINAL ARTICLE

Retrospective Study

Comparison of unenhanced magnetic resonance imaging and ultrasound in detecting very small hepatocellular carcinoma

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Abstract

BACKGROUND

In hepatocellular carcinoma (HCC), detection and treatment prior to growth beyond 2 cm are important as a larger tumor size is more frequently associated with microvascular invasion and/or satellites. In the surveillance of very small HCC nodules (≤ 2 cm in maximum diameter, Barcelona clinical stage 0), we demonstrated that the tumor markers alpha-fetoprotein and PIVKA-II are not so useful. Therefore, we must survey with imaging modalities. The superiority of magnetic resonance imaging (MRI) over ultrasound (US) to detect HCC was confirmed in many studies. Although enhanced MRI is now performed to

accurately diagnose HCC, in conventional clinical practice for HCC surveillance in liver diseases, unenhanced MRI is widely performed throughout the world. While, MRI has made marked improvements in recent years.

AIM

To make a comparison of unenhanced MRI and US in detecting very small HCC that was examined in the last ten years in patients in whom MRI and US examinations were performed nearly simultaneously.

METHODS

In 394 patients with very small HCC nodules, those who underwent MRI and US at nearly the same time (on the same day whenever possible or at least within 14 days of one another) at the first diagnosis of HCC were selected. The detection rate of HCC with unenhanced MRI was investigated and compared with that of unenhanced US.

RESULTS

The sensitivity of unenhanced MRI for detecting very small HCC was 95.1% (97/102, 95% confidence interval: 90.9-99.3) and that of unenhanced US was 69.6% (71/102, 95% confidence interval: 60.7-78.5). The sensitivity of unenhanced MRI for detecting very small HCC was significantly higher than that of unenhanced US ($P < 0.001$). Regarding the location of HCC in the liver in patients in whom detection by US was unsuccessful, S_{7-8} was identified in 51.7%.

CONCLUSION

Currently, unenhanced MRI is a very useful tool for the surveillance of very small HCC in conventional clinical follow-up practice.

Key Words: Comparison of magnetic resonance imaging and ultrasound; Surveillance of very small hepatocellular carcinoma; Magnetic resonance imaging; Ultrasound; Unenhanced magnetic resonance imaging

Core Tip: Recent technological development of magnetic resonance imaging (MRI) scanners has been excellent. The 3.0-tesla (T) MR scanner with a higher field strength has been increasingly used because improved lesion detection can be expected as a result of the increased signal-to-noise ratio, which is theoretically twice with 3.0-T compared with 1.5-T. Another important improvement in MRI is the practical use of diffusion-weighted imaging. In this study, a comparison of unenhanced MRI and ultrasound in detecting very small hepatocellular carcinoma (2 cm in maximum diameter) was made. The sensitivity of unenhanced MRI for detecting very small hepatocellular carcinoma was as high as 95.1% as compared with 69.6% of unenhanced ultrasound ($P < 0.001$).

INTRODUCTION

If hepatocellular carcinoma (HCC) tumors are growing up to more than 2 cm in diameter, they are often associated with microvascular invasion and/or satellites, which are major predictors of recurrence after initial effective treatments[1]. The same tendency was observed by Stravitz *et al*[2], who reported that the early detection of HCC improves the prognosis. Therefore, we must identify very small HCC nodules (≤

2 cm in maximum diameter) in the surveillance of HCC.

Recently, we demonstrated that more than one third of patients with very small HCC nodules were dropped from surveillance using the tumor markers alpha-fetoprotein (AFP) and PIVKA-II[3]. Therefore, we must survey patients with liver diseases using imaging modalities.

Surveillance of HCC in liver diseases, especially in liver cirrhosis, has been conducted by ultrasound (US) or magnetic resonance imaging (MRI) throughout the world.

Although US was performed more popularly than MRI in the surveillance of HCC, the superiority of MRI over US has been demonstrated in many studies since 2001-2003[4,5]. Although enhanced MRI is now performed for the accurate diagnosis of HCC[5-9], in conventional clinical practice for HCC surveillance in liver diseases, unenhanced MRI is widely performed throughout the world. On the other hand, MRI has made much progress in recent years.

In this study, a comparison of unenhanced MRI and US in surveying very small HCC was made. In order to conduct precise evaluation, we selected patients in whom MRI and US were performed at about the same time.

MATERIALS AND METHODS

Study population
This was a retrospective observational study that included 403 patients with small single HCC nodules (≤ 2 cm in maximum diameter, Barcelona clinical stage 0) who visited the following three hospitals and one clinic in Yokohama City for the first time between January 2008 and September 2020: Gastroenterological Center, Medical Center, Yokohama City University; Department of Gastroenterology, Yokohama Municipal Citizen's Hospital; Department of Gastroenterology, National Hospital Organization, Yokohama Medical Center; and Tarao's Gastroenterological Clinic. Of the 403 patients with very small HCC, 102 were selected in whom MRI and US were conducted simultaneously (on the same day or at least within 14 days of one another) (Figure 1). In this series of the study, MRI and US were performed in unenhanced states because we wanted to study the usefulness to survey HCC in routine follow-up study. In the unenhanced MRI, a very small HCC usually appears as a dark spot in T_1 image and light white spot in T_2 image (see Figures 2-5). It is important that characteristics of both T_1 and T_2 images were present at the same time. In the US images, it usually appears as a dark round spot.

HCCs were diagnosed chiefly by dynamic computed tomography (CT) and abdominal angiography, which showed early enhancement and early washout. This work was performed in accordance with the Declaration of Helsinki.

Previously diagnosed HCC was excluded from the protocol. This study was performed after approval by the respective institutional review boards.

The patients were classified according to the etiologies of liver diseases (Table 1).

HCC detection
The diagnosis of HCC was confirmed by US, MRI, CT, enhanced dynamic CT, and abdominal angiography. All patients underwent abdominal angiography to confirm the single nodules. The maximum diameter of the HCC nodules was scaled by US or MRI.

Helical dynamic CT and abdominal angiography were performed in almost all patients except those with hypersensitivity to iodine and advanced kidney disease. In the helical dynamic CT, an intravenous bolus injection of contrast material and sequential scanning were performed, and an intense homogenous arterial phase (early enhancement) and early washout in the venous phase were considered to be characteristic of HCC[10-12]. Abdominal angiography was also performed to exclude the benign nodular lesions and exclude HCC patients with macrovascular invasion. Of course, the characteristic features of very small HCC in unenhanced MRI as mentioned above were taken into account.

Patients with macrovascular invasion or extrahepatic metastasis were excluded. In patients undergoing hepatectomy, the final decision on HCC was made by pathological diagnosis, and cases of benign nodules were excluded.

Statistical analysis
We calculated the detection rate and its 95% confidence interval (CI) for each method. We then compared the detection rates between MRI and US using McNemar's test.

Table 1 Background of hepatocellular carcinoma patients (≤ 2 cm in diameter) who underwent unenhanced magnetic resonance imaging and unenhanced ultrasound simultaneously

Background of patients	
Number of patients	102
Age (yr)	72.4 ± 9.6
Sex (%)	
Male	52 (51.0)
Female	50 (49.0)
Etiology (%)	
HBV	13 (12.9)
HCV	61 (60.3)
Alcohol	14 (13.9)
NBNC	7 (6.9)
Autoimmune	2 (2.0)
NASH	2 (2.0)
PBC	1 (1.0)
Others	2 (2.0)

HBV: Hepatitis B virus; HCV: Hepatitis C virus; NBNC: Non-B non-C; NASH: Nonalcoholic steatohepatitis; PBC: Primary biliary cirrhosis.

Total number of patients with HCC
n = 942

Patients with
HCC nodules ≤ 2 cm
n = 403

Patients with
HCC nodules > 2 cm
n = 539

Patients in whom
MRI and US were performed simultaneously
on the first diagnosis of HCC
n = 102
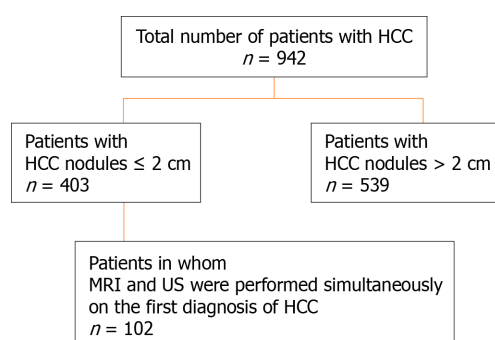
Figure 1 Patient selection. HCC: Hepatocellular carcinoma; MRI: Magnetic resonance imaging; US: Ultrasound.

RESULTS

The sensitivity of unenhanced MRI for detecting very small HCC (≤ 2 cm in diameter) was 95.1% [97/102, 95%CI: 90.9-99.3] and that of unenhanced US was 69.6% (71/102, 95%CI: 60.7-78.5) ($P < 0.001$).

Table 2 shows the location of the HCC in the liver of patients in whom detection by US was unsuccessful. S_{7-8} was the site in 51.7% of these patients. Thus, HCC lesions in S_{7-8} may be difficult to identify by US. Representative images of four cases of very small HCC (A, B, C, and D) by unenhanced MRI are shown in Figures 2-5. In all the four cases, HCC was confirmed using hepatectomized specimens.

Moreover, the treatment methods for 102 HCC patients are shown in Table 3.

DISCUSSION

For the surveillance of very small HCC, US was hitherto performed worldwide. However, in recent years, the superiority of MRI over US to detect very small HCC has been reported in many articles.

Table 2 Location of hepatocellular carcinoma in the liver in patients for whom detection by ultrasound was unsuccessful

Location in the liver	Number of patients (%)
S_{1-4}	6 (20.7)
S_{5-6}	8 (27.6)
S_{7-8}	15 (51.7)

Table 3 Treatment methods for hepatocellular carcinoma in 102 very small hepatocellular carcinoma patients

Therapy	Number of treated patients
Hepatectomy	19
RFA	58
TACE	14
TACE + RFA	2
TAI	1
Chemotherapy	2
BSC	3
Others	3

BSC: Best supportive care; RFA: Radiofrequency ablation; TACE: Transcatheter arterial chemoembolization; TAI: Transcatheter arterial infusion.
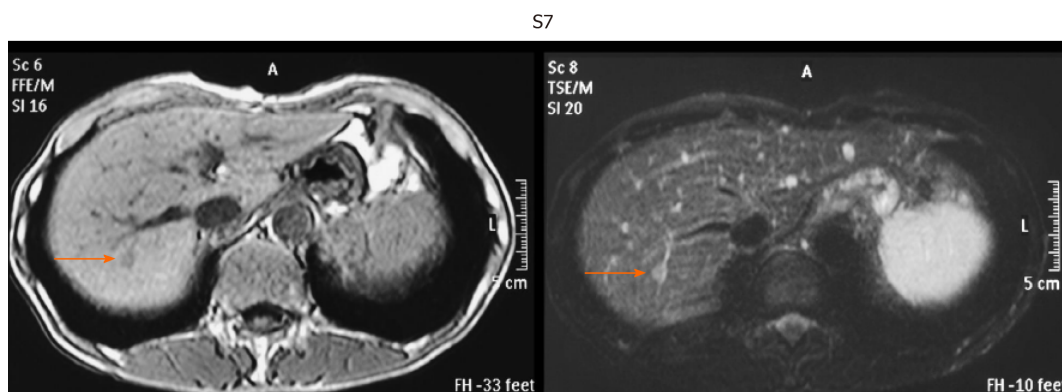
Figure 2 Representative image of very small hepatocellular carcinoma by unenhanced magnetic resonance imaging. Hepatocellular carcinoma in S7 segment. T1-weighted image (left, light dark spot). T2-weighted image (right, light white spot).

Colli *et al*[4] conducted a systemic review on this issue, and found that the pooled estimate of 14 US studies was 60.5% (95%CI: 44-76) for sensitivity[13-25], and that of 9 MRI studies was 80.6% (95%CI: 70-91) for sensitivity[9,23,24,26-31]. The difference in sensitivity between US and MRI may be due to the fact that MRI is less influenced by the operator's technique, patient's body type, and location of HCC lesions.

More recently, in 2017, Kim *et al*[5] compared MRI and US in a cohort of 407 patients with cirrhosis who underwent 1100 surveillance examinations, and found that MRI had a sensitivity of 83.7% (95%CI: 69.7-92.2) for early HCC detection, which was significantly higher than that of US (25.6%, 95%CI: 14.8-49.4).

We demonstrated in this study that 95% of cases with very small HCC can be detected by unenhanced MRI. This figure is very high compared with previous reports published between 2001 and 2003 concerning the sensitivity of unenhanced MRI for detecting very small HCC. Table 4 shows the reported sensitivity of unenhanced MRI for detecting very small HCC between 2001 and 2003 when MRI used 1.5-tesla (T) imaging. The average sensitivity in that period was 60.3% (95%CI: 52.2-68.4)[25,27,28, 30,31].

Table 4 Reported sensitivity of unenhanced magnetic resonance imaging to detect very small hepatocellular carcinomas (≤ 2 cm in diameter) between 2001 and 2003

| Ref.	Sensitivity (%)
Krinsky *et al*[27], 2001	7/15 (46.7)
de Lédinghen *et al*[28], 2002	33/54 (61.1)
Libbrecht *et al*[25], 2002	7/10 (70.0)
Bhartia *et al*[30], 2003	15/21 (71.4)
Burrel *et al*[31], 2003	23/41 (56.1)
Pooled estimates	85/141 (60.3)
	95%CI: 52.2-68.4

CI: Confidence interval.

Figure 3 Representative image of very small hepatocellular carcinoma by unenhanced magnetic resonance imaging. Hepatocellular carcinoma in S4 segment. T1-weighted image (left, light dark spot). T2-weighted image (right, light white spot).
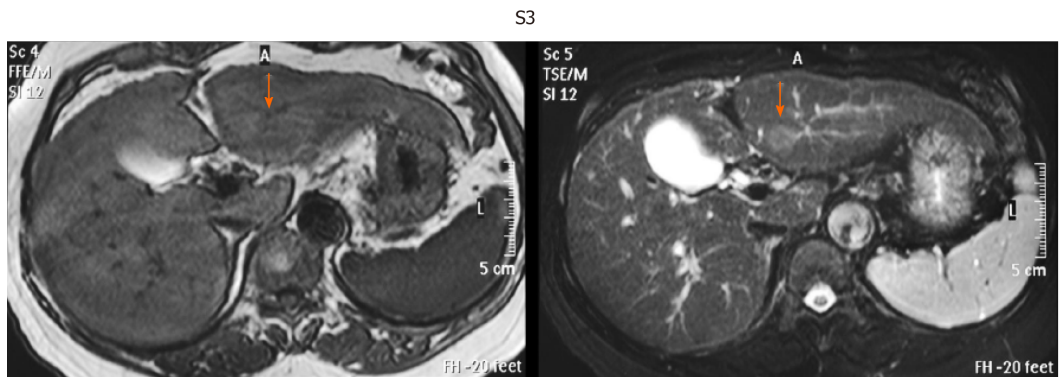
Figure 4 Representative image of very small hepatocellular carcinoma by unenhanced magnetic resonance imaging. Hepatocellular carcinoma in S3 segment. T1-weighted image (left, light dark spot). T2-weighted image (right, light white spot).

The reasons why this marked improvement appeared in the sensitivity of unenhanced MRI with regard to detecting very small HCC must be considered.

First of all, MRI has made marked progress in its ability in recent years. Recent technological development of MRI scanners has allowed high-quality multiphasic imaging of the entire liver. Since 2003-2005, the 3.0-T magnetic resonance (MR) scanner with a higher field strength has been increasingly used because improved lesion detection can be expected as a result of the increased signal-to-noise ratio (SNR), which is theoretically twice the SNR at 1.5-T[32,33]. Indeed, it was demonstrated that
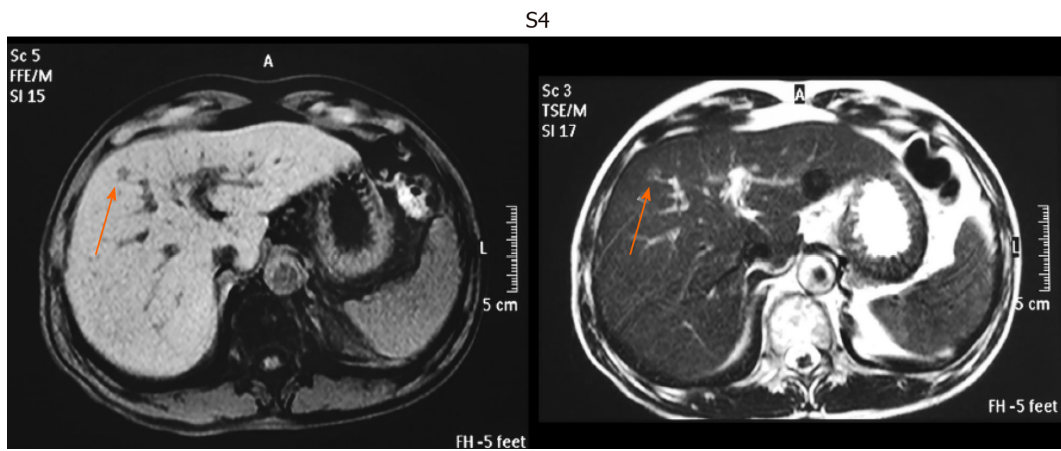
S8

Figure 5 Representative image of very small hepatocellular carcinoma by unenhanced magnetic resonance imaging. Hepatocellular carcinoma in S8 segment. T1-weighted image (left, light dark spot). T2-weighted image (right, light white spot).
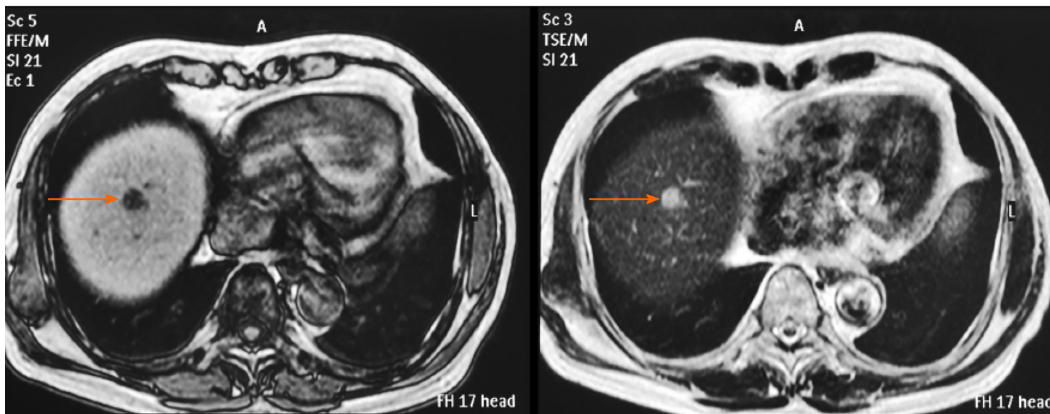
3.0-T images were superior to 1.5 T images for detecting hepatic metastases[34]. Previous misdiagnoses of HCC on MRI maybe have been due to poor patient compliance, especially the inability to suspend respiration. These problems can be resolved by the new advancements mentioned above to develop faster and motion-robust sequences.

Another important improvement of MRI is the practical use of diffusion-weighted imaging. Indeed, it was demonstrated that the sensitivity of detecting pancreatic cancer rose with the use of diffusion-weighted imaging[35].

On the other hand, the sensitivity of unenhanced US in our study for detecting very small HCC was 69.6%, which was nearly the same as those in previous reports[9,22,24, 26-29]. One of the reasons for the inferiority of US may be the location of HCC in the liver. A lesion located at S_{7-8} (the most frequent HCC lesion in the liver) may be difficult to identify by US.

Our present study indicates the importance of unenhanced MRI in detecting very small HCC, because more than one third of these patients were dropped from surveillance by tumor markers AFP and PVKA-II. However, there are two limitations of unenhanced MRI. First, it is more expensive than US. Second, in case of very tiny HCC (3-5 mm), it is difficult to find HCC by unenhanced MRI.

CONCLUSION

Considering the above-mentioned facts, unenhanced MRI is a very useful tool for detecting very small HCC in the conventional follow-up of patients with liver diseases, especially liver cirrhosis.

ARTICLE HIGHLIGHTS

Research background

Nowadays advancement of magnetic resonance imaging (MRI) has markedly improved the quality of liver imaging. We believe that a high-speed scan and diffusion-weighted imaging are two major factors that have contributed to the improved detection of hepatocellular carcinomas (HCCs). In early MRI, a respiration artifact was the most troublesome factor deteriorating the quality of images of the liver. A high-speed scan brought by the conversion from 1.5-tesla (T) to 3.0-T facilitates whole-liver MRI while patients hold their breath. Breath-holding scans reduce motion and misregistration artifacts, and create high-quality liver images. In addition, the practical use of diffusion-weighted imaging has contributed to the detection of cell-rich lesions. Tumors are proper objects of these sequences. There is a report (or several reports) that the sensitivity of detecting pancreatic cancer rose with the use of diffusion-weighted imaging. We believe that the same can be applied to detect HCC. Currently, dynamic MRI with contrast media is considered the standard procedure to diagnose HCC. However, with improved images, non-contrasted liver MRI is still a

useful modality to detect HCCs.

Research motivation

Previous reports in 2001-2003 stated that the sensitivity of unenhanced MRI to detect very small HCC (≤ 2 cm in diameter) was about 60%. Since then, there have been few reports on the sensitivity to detect very small HCC, especially in recent years.

Research objectives

Surveillance of HCC in liver diseases, especially in liver cirrhosis, has been conducted by ultrasound (US) or MRI throughout the world. Although US was performed more popularly than MRI in the surveillance of HCC, the superiority of MRI over US has been demonstrated in many studies since 2001-2003. Although enhanced MRI is now performed for the accurate diagnosis of HCC, in conventional clinical practice for HCC surveillance in liver diseases, unenhanced MRI is widely performed throughout the world. On the other hand, MRI has made marked improvements in recent years. In this study, a comparison of unenhanced MRI and US in detecting very small HCC was made. In order to conduct precise evaluation, we selected patients in whom MRI and US were performed at about the same time (on the same day whenever possible or at least within 14 d of one another).

Research methods

Out of the 403 patients with very small HCC nodules (≤ 2 cm in maximal diameter), 102 who underwent unenhanced MRI and US at nearly the same time (on the same day whenever possible or at least within 14 d of one another) at the first diagnosis of HCC were selected. The detection rate of HCC by unenhanced MRI was studied in comparison with unenhanced US.

Research results

We found that the sensitivity of unenhanced MRI for detecting very small HCC was as high as 95.1%, as compared with 69.6% by unenhanced US ($P < 0.001$).

Research conclusions

Currently, unenhanced MRI is a very important imaging modality for picking up very small HCC in usual clinical practice.

Research perspectives

As in this study, the marked superiority of unenhanced MRI to detect very small HCC as compared with unenhanced US was confirmed, and it may be desirable to perform routine surveillance of HCC in liver diseases by unenhanced MRI.

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