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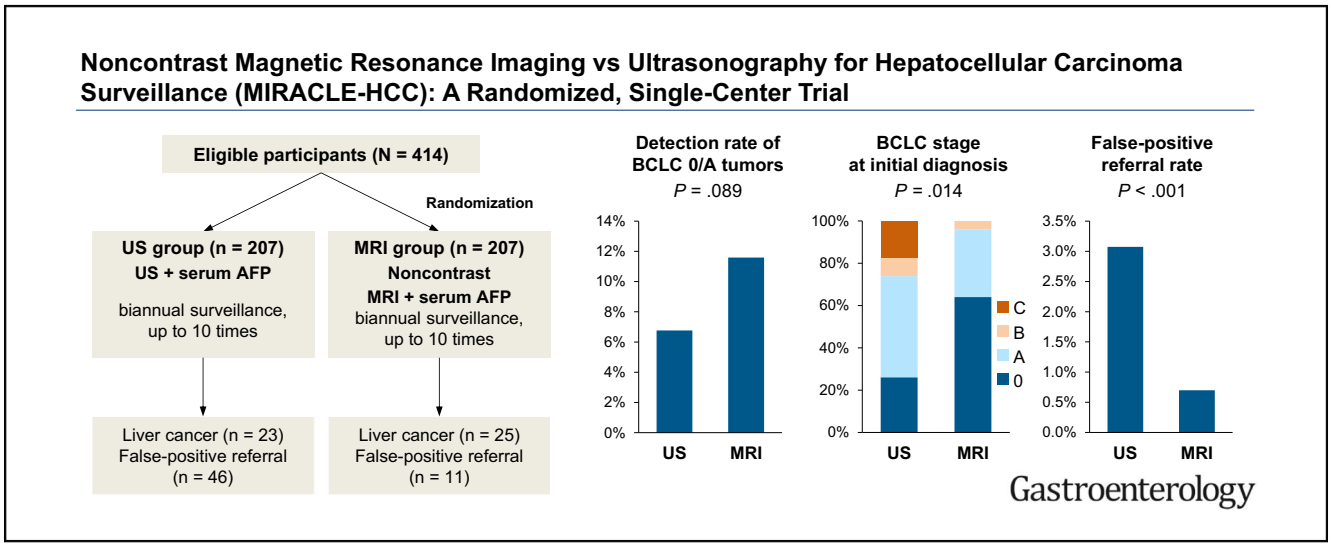
Noncontrast Magnetic Resonance Imaging vs Ultrasonography for Hepatocellular Carcinoma Surveillance: A Randomized, Single-Center Trial

Hyungjin Rhee,[1] Myeong-Jin Kim,[1] Do Young Kim,[2] Chansik An,[1] Wonseok Kang,[2] Kyunghwa Han,[1] Yun Ho Roh,[3] Kwang-Hyub Han,[2] Sang Hoon Ahn,[2] Jin-Young Choi,[1] Jun Yong Park,[2] Yong Eun Chung,[1] Seung Up Kim,[2] Beom Kyung Kim,[2] Sunyoung Lee,[1] Hye Won Lee,[2] and Jae Seung Lee[2]

[1]Department of Radiology, Research Institute of Radiological Science, Severance Hospital, Yonsei University College of Medicine, Seoul, South Korea; [2]Department of Internal Medicine, Severance Hospital, Yonsei University College of Medicine, Seoul, South Korea; and [3]Biostatistics Collaboration Unit, Medical Research Center, Yonsei University College of Medicine, Seoul, South Korea



BACKGROUND & AIMS: This study aimed to compare ultrasonography (US) and noncontrast magnetic resonance imaging (MRI) in the surveillance of hepatic malignancy. **METHODS:** We conducted a randomized, nonblinded trial at a single center in South Korea. Eligible individuals were aged 20 to 70 years with liver cirrhosis, Child-Pugh class A, and no history of liver cancer or other recent malignancy. Participants were randomized 1:1 to receive up to 10 semiannual surveillance using US or noncontrast MRI with serum alpha-fetoprotein testing. The primary endpoints were the detection rates of Barcelona Clinic Liver Cancer (BCLC) stage 0 or A tumors, stage distribution at initial diagnosis, and false-positive referral rates. **RESULTS:** From June 2015 to November 2017, 416 patients were screened, and 414 were enrolled and assigned to the US (n = 207) or MRI (n = 207) group. In total, 23 participants in the US group and 25 in the MRI group were diagnosed with liver cancer by November 2022. The detection rates of BCLC stage 0 or A tumors were not different between the US and MRI groups (7% [95% confidence interval (CI), 4%–11%] vs 12% [8%–17%]). BCLC stage 0 tumors were more frequently detected in the MRI group than in the US group (8% vs 2%). The MRI group had earlier BCLC stage ($P = .014$) and lower false-positive referral rate (0.7% [95% CI, 0.4%–1.2%] vs 3.1% [2.3%–4.1%], $P < .001$) compared with the US group. **CONCLUSIONS:** Noncontrast MRI is a better alternative to US for the surveillance of cirrhotic patients offering earlier stage at initial diagnosis and lower false-positive referral rate. (ClincalTrials.gov, Number: NCT02514434.)

Keywords: Cirrhosis; Hepatocellular Carcinoma; Surveillance; Magnetic Resonance Imaging; Ultrasonography.

Biannual surveillance of hepatocellular carcinoma (HCC) in at-risk populations improves early tumor detection and overall survival.[1,2] Most contemporary guidelines suggest ultrasonography (US) with or without

Abbreviations used in this paper: **AFP, alpha-fetoprotein; BCLC, Barcelona Clinic Liver Cancer; CI, confidence interval; CT, computed tomography; HCC, hepatocellular carcinoma; IQR, interquartile range; LI-RADS, Liver Imaging Reporting and Data System; MRI, magnetic resonance imaging; US, ultrasound.**

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WHAT YOU NEED TO KNOW

BACKGROUND AND CONTEXT

Noncontrast magnetic resonance imaging has been proposed as a promising tool for hepatocellular carcinoma surveillance; however, there has not been a randomized trial comparing noncontrast magnetic resonance imaging to ultrasonography for hepatocellular carcinoma surveillance.

NEW FINDINGS

In this randomized, single-center trial for hepatocellular carcinoma surveillance in patients with liver cirrhosis, hepatocellular carcinoma was detected at a significantly earlier stage in the magnetic resonance imaging group compared with the ultrasonography group, along with a lower surveillance failure rate and lower false-positive referral rate.

LIMITATIONS

The enrollment was conducted without risk stratification at a single center in South Korea, where hepatitis B is the dominant etiology. Therefore, validation is required in patient groups with various etiologies and/or severe cirrhosis. In addition, due to the extended period of surveillance, a significant number of patients were lost to follow-up.

CLINICAL RESEARCH RELEVANCE

Our study suggests that noncontrast magnetic resonance imaging is a better alternative to ultrasonography for the surveillance of patients with liver cirrhosis.

BASIC RESEARCH RELEVANCE

Considering the higher cost and limited availability of noncontrast magnetic resonance imaging compared with ultrasonography, it may be more cost-effective to selectively apply noncontrast magnetic resonance imaging surveillance in patients at very high risk for hepatocellular carcinoma. Further research is needed to determine how best to stratify hepatocellular carcinoma risk using clinical, serological, imaging, or genetic factors, in order to decide on the most appropriate surveillance modality.

serum alpha-fetoprotein (AFP) testing as a surveillance method.[3–6] However, the sensitivity of US for early-stage HCC (Barcelona Clinic Liver Cancer [BCLC] stage 0 or A) is suboptimal at only approximately 47%, and surveillance failure occurs in approximately 31% of patients undergoing US surveillance.[7,8] The limited sensitivity of US may be attributed to the low detectability of infiltrative tumors and patient characteristics, such as a poor echogenic window and liver macronodularity.[9]

To supplement the limited sensitivity of US, diagnostic imaging modalities, such as contrast-enhanced US, contrast-enhanced computed tomography (CT), and contrast-enhanced magnetic resonance imaging (MRI), are commonly used in real clinical practice; for example, US and contrast-enhanced CT can be performed alternately in a patient with a poor echogenic window.[10] Recently, attempts have been made to replace biannual US entirely with these diagnostic imaging modalities, which have shown improved sensitivity to early-stage HCCs.[11–13] Nevertheless, contrast-enhanced US continues to be considerably affected by patient characteristics and the operator's experience. Moreover, contrast-enhanced CT may not be desirable as a surveillance modality owing to the potential hazard of radiation exposure.[14] Contrast-enhanced MRI is restricted by high cost, concerns about renal function, and accumulation of gadolinium-based contrast agents in human organs.[15] In addition, these diagnostic modalities require intravenous catheterization for the administration of contrast media for each test, which can reduce patient adherence to surveillance.

To overcome the disadvantages of contrast-enhanced MRI, noncontrast MRI has been proposed as a surveillance tool.[16] Even without contrast enhancement, MRI is expected to exhibit good sensitivity in the detection of hepatic malignancies.[17,18] Compared with contrast-enhanced MRI, noncontrast MRI has the advantage of not only being potentially less expensive owing to shorter scan times, but also eliminating concerns related to the use of contrast agents. We postulated that these benefits could render noncontrast MRI a viable alternative to US in HCC surveillance.

This study aimed to compare US and noncontrast MRI as tools for the surveillance of liver cancer in patients with liver cirrhosis in terms of the detection rate at an early stage, stage distribution at initial diagnosis, and false-positive referral rate.

Methods

Ethics Statements

This study was approved by the Institutional Review Board of Severance Hospital (number: 4-2015-0029) and performed in accordance with the ethical principles of the Declaration of Helsinki and Good Clinical Practice guidelines. All patients provided signed informed consent before participating in the study. All authors had access to the study data and have reviewed and approved the final manuscript. The study was registered with ClinicalTrials.gov (NCT02514434).

Study Design

The MIRACLE-HCC study was a randomized, nonblinded, single-center trial comparing US and noncontrast MRI in HCC surveillance in patients with liver cirrhosis. It was conducted in an academic tertiary referral hospital in South Korea.[19] The full study protocol is provided as Supplementary Material.

Participants

The eligibility criteria were as follows: (1) adults aged 20–70 years without a history of liver cancer, (2) those at risk of developing HCC with clinically or radiologically diagnosed cirrhosis of any cause, (3) those with preserved liver function (Child-Pugh class A), and (4) the absence of a liver tumor confirmed clinically and radiologically at the time of screening. Patients with the following conditions were excluded: (1) a diagnosis of malignancy in the past 5 years; (2) possible

pregnancy; and (3) severe cardiovascular, respiratory, renal, or infectious disease.

Randomization and Masking

The participants were assigned in a 1:1 ratio by a research nurse using a computer-generated randomization list with a random block size of 4 (SAS 9.2; SAS Institute, Inc., Cary, NC). Only the research nurse had knowledge of the randomization sequence. Blinding was not possible due to the different surveillance methods used in each group.

Surveillance Protocol

For HCC surveillance, the participants in the US group underwent abdominal US and serum AFP testing, whereas the participants in the MRI group underwent noncontrast MRI and serum AFP testing. Each participant was scheduled to undergo 10 surveillance examinations. The intended interval for surveillance tests was every 6 months,[4,5] with a preference for a range of 5 to 7 months. If the participants' circumstances were unavoidable, they were permitted to have an interval of 3 to 9 months.

If a new lesion detected during US or MRI surveillance was suspected to be malignant according to the predefined criteria (see the Imaging Evaluation and Interpretation section) or if the serum AFP level was elevated with an increasing trend for 2 consecutive tests or significantly increased according to the investigator's discretion, dynamic contrast-enhanced CT and/or MRI was performed for further characterization. If the surveillance test result was determined to be a false-positive by subsequent tests, the patient returned for the next scheduled surveillance test. If patients were confirmed to have a hepatic malignancy, they received standard treatment according to the guidelines.[3–5]

A participant was considered a dropout if the participant (1) withdrew consent, (2) received liver transplantation without a diagnosis of liver cancer, (3) was diagnosed with malignancies other than liver cancer, (4) died, or (5) did not undergo 2 or more consecutive surveillance tests during the study period.

The study was planned to end when the prevalence of liver cancer in the study population reached or exceeded 18% or when the last enrolled participant completed 5 years of study participation, whichever occurred first.

Imaging Evaluation and Interpretation

Abdominal noncontrast US was performed and interpreted by clinical fellows of hepatology, same as the current clinical practice at our institution. During US, a newly appearing nodule measuring >1 cm or a diffuse infiltrative lesion with or without a suspected tumor-in-vein was considered suspicious.

Abdominal noncontrast MRI was performed using a 3.0-T system, including dual-echo T1-weighted gradient-echo images, 3-dimensional interpolated T1-weighted images, T2-weighted images with fat suppression, T2-weighted images with long echo times, diffusion-weighted images, and calculated apparent diffusion coefficient images (Supplementary Table 1). The total scanning time was approximately 7–10 minutes. MRI was evaluated by 1 of 6 board-certified abdominal radiologists (M.-J.K., J.-Y.C., Y.E.C., C.A., H.R., and S.L.). A suspicious nodule was defined as a newly appearing nodule measuring >1 cm that showed at least 1 of the following imaging features: T1 hypointensity, T2 hyperintensity, diffusion restriction, nodule-in-nodule pattern (mosaic appearance), iron sparing, heterogeneous fatty changes, blood products, or a definite increase in tumor diameter. Diffuse infiltrative lesions with or without a suspected tumor-in-vein were also considered suspicious.

AFP levels were not blinded to the investigators interpreting the US and MRI. For suspicious lesion(s) and/or elevation of the AFP level, dynamic contrast-enhanced CT and/or MRI findings were evaluated and reported using the latest Liver Imaging Reporting and Data System (LI-RADS).[20] If participants did not undergo an AFP examination, it was assumed that their serum AFP levels were normal.

Reference Standard

The final diagnosis was preferably determined based on the histopathological findings obtained through surgery or biopsy. The radiological diagnosis was made when the histopathological diagnosis was not possible or when an invasive biopsy was deemed to do more harm than good. The dynamic CT or MRI was evaluated by 1 of 6 board-certified abdominal radiologists. For the radiological diagnosis, lesions categorized as LR-5, LR-5V (LR-TIV in LI-RADS version 2017 or later), or LR-M according to the LI-RADS diagnostic algorithm were diagnosed as hepatic malignancies.

Outcomes

The primary endpoints were the detection rates of BCLC stage 0 or A liver cancers, stage distribution at initial diagnosis, and false-positive referral rates. The detection rate was defined as the number of patients whose liver cancer was detected using a given surveillance modality divided by the total number of patients under surveillance, and it is expressed as a percentage. Very-early-stage (0) cancer was defined as a single tumor measuring <2 cm, early-stage (A) cancer was defined as a single tumor measuring <5 cm or up to 3 tumors measuring <3 cm, intermediate stage (B) cancer was defined as a single tumor measuring ≥ 5 cm or multinodular (>3 nodules) tumors, and advanced stage (C) cancer was defined as a tumor with macrovascular invasion or extrahepatic metastasis, based on the contrast-enhanced CT and/or MRI findings at diagnosis.[4,5] Surveillance was considered a failure when patients were diagnosed with stage B or C disease. The false-positive referral rate was defined as the number of positive test results that were eventually confirmed as negative on subsequent dynamic imaging and/or pathological examination, divided by the total number of tests in a specific surveillance modality and expressed as a percentage. The secondary endpoints were the surveillance failure rate and overall survival. Overall survival was defined as the time from enrollment to death. Patients who were still alive at their last visit were censored at the date of their last follow-up before the study period ended. Time to tumor detection was defined as the time from enrollment to tumor detection. Patients who did not have tumor detection by their last visit were censored at their last visit. Both overall survival and time to tumor detection analyses included patients who had at least 1 surveillance visit.

Statistical Analysis

Based on the expected sensitivities of US and noncontrast MRI at 60% and 90%, respectively, and a dropout rate of 15%

over 5 years, we calculated that a sample size of 416 (208 for each group) would be required to achieve 80% power. The detection rate and stage distribution were compared between the US and noncontrast MRI groups using the Fisher's exact or χ^2 test. The false-positive referral rates were compared between the 2 groups using Poisson regression analysis, with the number of surveillance exams per patient as an offset. To compare the variables between the 2 groups, χ^2 or Fisher's exact test for categorical variables was used. Kaplan-Meier methods with the log-rank test was used to compare the time to tumor detection and overall survival between the 2 groups. A per-protocol analysis was executed as the final analysis for this study. Statistical analyses were performed using R software (version 4.2.1; https://www.R-project.org/). Because this study had 3 primary outcomes, statistical significance was defined as a 2-sided P value $< .017$.

Results

Participants

The patient characteristics at enrollment are summarized in Table 1. The median age at randomization was 58 (interquartile range [IQR]: 53–63) years and 57 (IQR: 51–63) years in the US and MRI groups, respectively. Approximately 53% (109 of 207) and 66% (136 of 207) of the patients were male in the US and MRI groups, respectively. Most participants had hepatitis B virus–related liver cirrhosis (84%, 348 of 414), whereas others had hepatitis C virus (5%, 22 of 414) or other etiologies (11%, 44 of 414). All participants had Child-Pugh class A liver cirrhosis, and most of them had Child-Pugh score of 5 (98%, 407 of 414). The baseline characteristics of the 2 groups were well balanced.

Table 1. Baseline Participant Characteristics at Enrollment

	US group (n = 207)	MRI group (n = 207)
Age, *y*, median (IQR)	58 (53–63)	57 (51–63)
Sex, male/female, n (%)	109 (53) / 98 (47)	136 (66) / 71 (34)
Etiology of cirrhosis, n (%)		
HBV	176 (85)	172 (83)
HCV	10 (5)	12 (6)
Others	21 (10)	23 (11)
Height, *cm*, median (IQR)	164 (157–170)	167 (160–173)
Weight, *kg*, median (IQR)	65 (58–72)	68 (59–77)
BMI, *kg/m²*, median (IQR)	23.8 (22.4–26.1)	24.4 (22.5–26.6)
Total bilirubin, *mg/dL*, median (IQR)	0.9 (0.7–1.2)	0.9 (0.7–1.3)
Albumin, *g/dL*, median (IQR)	4.2 (4.0–4.4)	4.3 (4.0–4.5)
Creatinine, *mg/dL*, median (IQR)	0.7 (0.6–0.8)	0.8 (0.7–0.9)
PT/INR, median (IQR)	1.0 (1.0–1.1)	1.0 (1.0–1.1)
Platelets, *1000/μL*, median (IQR)	127 (88–160)	127 (100–169)
AFP, *ng/mL*, median (IQR)	3.3 (2.2–4.9)	3.0 (2.1–4.6)
Child-Pugh score, n (%)		
5	203 (98)	204 (99)
6	4 (2)	3 (1)

BMI, body mass index; HBV, hepatitis B virus; HCV, hepatitis C virus; PT/INR, prothrombin time/international normalized ratio.

The study flow is summarized in Figure 1, with additional details provided in Supplementary Figure 1. From June 25, 2015, to November 29, 2017, 416 individuals were screened for eligibility, 2 of whom did not meet the eligibility criteria, and 414 were enrolled and randomly assigned to either the US (n = 207) or MRI (n = 207) group. Five years after the last patient was enrolled, the study was concluded on November 29, 2022. In the US and MRI groups, 68 and 49 participants dropped out during the study period, 23 and 25 participants were diagnosed with liver cancer, 105 and 122 participants completed 10 surveillance examinations without a diagnosis of liver cancer, and 11 and 11 participants did not complete the 10 surveillance examinations during the study period, respectively. The cause and time of dropout are summarized in Supplementary Table 2. The baseline characteristics were similar between nondropouts and dropouts in both groups, except for the notably high dropout rate among participants with nonviral hepatitis (Supplementary Table 3). Among the participants in the MRI group, 2 experienced claustrophobia and were subsequently dropped due to a violation of the exam schedule. Of the two, one participant did not undergo any MRI examinations and the other completed 5 MRIs before dropping out.

Participants in the US and MRI groups underwent 1496 and 1575 surveillance examinations, respectively. The median intervals between surveillance examinations were 182 (IQR: 176–189) days and 182 (IQR: 178–189) days in the US and MRI groups, respectively. Serum AFP testing was not performed in 1.8% (27 of 1496) of surveillance examinations in the US group and 1.4% (22 of 1575) in the MRI group.

False-Positive Referral Rate

During surveillance, false-positive referrals were observed 46 and 11 times in the US and MRI groups, respectively (Table 2). The false-positive referral rate was significantly higher in the US group than that in the MRI group (3.1% [95% confidence interval (CI), 2.3%–4.1%] vs 0.7% [95% CI, 0.4%–1.2%]) ($P < .001$).

In the US group, participants with parenchymal nodularity had a false-positive referral rate of 5.1%, whereas those without it had a rate of 1.2%. Participants with a poor echo window had a false-positive referral rate of 1.6%, whereas those without it had a rate of 3.8% (Supplementary Table 4). The rates and reasons for unscheduled dynamic examinations are summarized in Supplementary Table 5; unscheduled dynamic examinations occurred at rates of 1.5% in the US group and 0.4% in the MRI group.

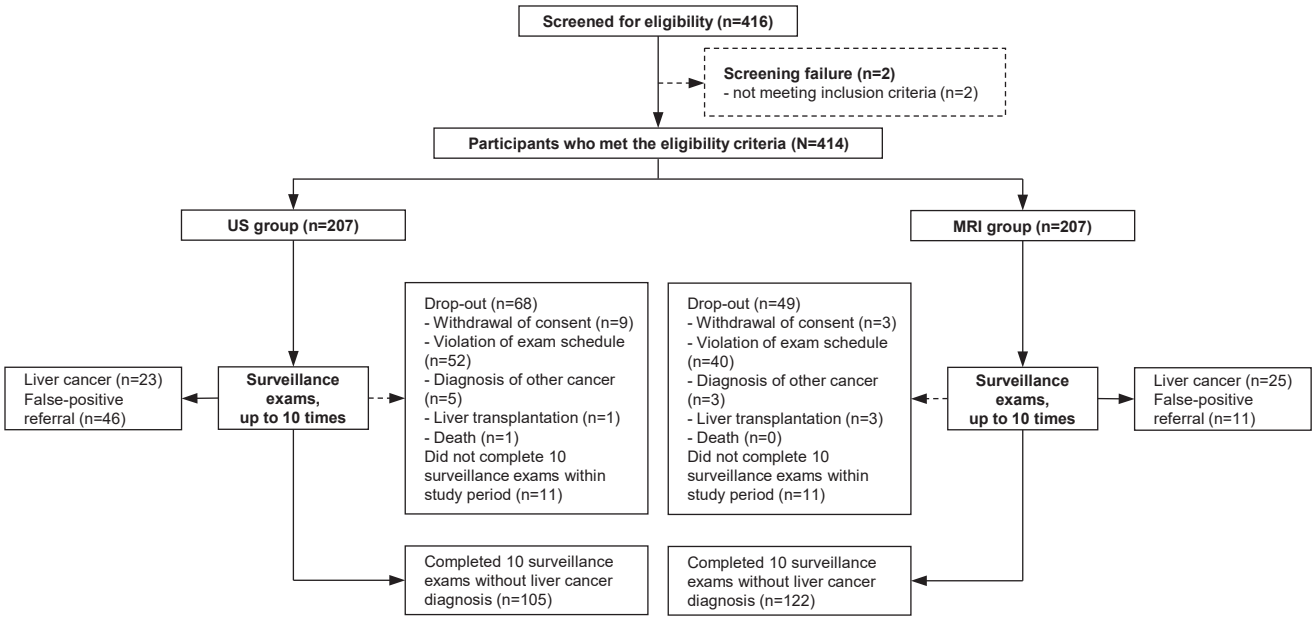

Figure 1. Study flow.

HEPATOBILIARY

Detection and Stage of Liver Cancers

Liver cancers were diagnosed in 11% (23 of 207) and 12% (25 of 207) of the participants in the US and MRI groups, respectively (Table 2, Supplementary Figures 2–5). The detection rates of BCLC stage 0 or A were not significantly different between the US and MRI groups (7%; 95% CI, 4%–11% and 12%; 95% CI, 8%–17%, respectively; $P = .089$). The detection rate of BCLC stage 0 was higher in the MRI group than that in the US group (8% vs 2%). The distribution of BCLC stages 0, A, B, and C was significantly different between the 2 groups: 26% [95% CI, 10%–48%], 48% [95% CI, 27%–69%], 9% [95% CI, 1%–28%], and 17% [95% CI, 5%–39%] in the US group and 64% [95% CI, 43%–82%], 32% [95% CI, 15%–54%], 4% [95% CI, 0.1%–20%], and 0% in the MRI group, respectively ($P = .014$) (Table 3).

Surveillance failure rate in the US group was 26% and that in the MRI group was 4%. The results of the last surveillance examination before the liver cancer diagnosis are summarized in Supplementary Table 6. In the US group, 22% were positive in both US and AFP, 22% were positive in US only, 30% were positive in serum AFP only, and 26% were false-negative. In the MRI group, 28% were positive in both MRI and AFP, 64% were positive in MRI only, 8% were positive in AFP only, and none were false-negative. The median interval between the last surveillance and diagnosis was 87 (IQR: 24–102) days in the US group and 44 (IQR: 15–100) days in the MRI group. The diagnosis of liver cancer was made with both dynamic imaging and pathology in 26% and 48%, dynamic imaging in 74% and 44%, and pathology in 0% and 8% of cases in the US and MRI groups, respectively. The time to tumor detection was not different between the US and MRI groups (Supplementary Figure 6).

In the US group, all 6 participants pathologically diagnosed with liver cancer had HCC(s), whereas in the MRI group, of the 14 participants pathologically diagnosed, 11 had HCC(s), 1 had a combined hepatocellular-cholangiocarcinoma (cHCC-CCA), 1 had 2 cHCC-CCAs and an HCC, and 1 had an intrahepatic cholangiocarcinoma (Supplementary Table 7).

Treatment and Outcome

Initial treatments for liver cancer are listed in Table 4. Among the patients diagnosed with liver cancer, 91% (21 of 23) in the US group and 92% (23 of 25) in the MRI group received initial treatment at our institution. The rate of curative initial treatment was 38% (8 of 21) in the US group

Table 2. Comparison of the False-Positive Referral and Detection Rates Between the US and MRI Groups

	US group (n = 207)	MRI group (n = 207)	*P* value
Rate of false-positive referral rate,[a] % (n/total N)	3.1% [2.3%–4.1%] (46/1496)	0.7% [0.4%–1.2%] (11/1575)	<.001
Detection rate of liver cancer, % (n/total N)			
All	8% (17/207)	12% (25/207)	
BCLC 0 or A[a]	7% [4%–11%] (14/207)	12% [8%–17%] (24/207)	.089
BCLC 0	2% (5/207)	8% (16/207)	

[a]Primary outcomes. The *P* value and 95% CI [in brackets] were assessed only for the primary outcomes.

Table 3. Comparison of the BCLC Stage at Initial Diagnosis

	Liver cancers in US group (n = 23)	Liver cancers in MRI group (n = 25)	*P* value
BCLC stage,[a] n (%)			.014
0	6 (26) [10%–48%]	16 (64) [43%–82%]	
A	11 (48) [27%–69%]	8 (32) [15%–54%]	
B	2 (9) [1%–28%]	1 (4) [0.1%–20%]	
C	4 (17) [5%–39%]	0 (0)	
Surveillance failure, n (%)	6 (26)	1 (4)	
Number of liver cancer lesions on dynamic imaging, n (%)			
1	17 (74)	21 (84)	
2	5 (22)	2 (8)	
3	1 (4)	1 (4)	
>4	0 (0)	1 (4)	
Size of the largest liver cancer on dynamic imaging, median (IQR), *mm*	25 (20–33)	17 (13–20)	
Macrovascular invasion, n (%)	3 (13)	0 (0)	
Extrahepatic metastasis, n (%)	1 (4)	0 (0)	

[a]Primary outcomes. The *P* value and 95% CI [in brackets] were assessed only for the primary outcomes.

and 83% (19 of 23) in the MRI group. The reasons for selecting noncurative treatment as the initial treatment are summarized in Supplementary Table 8.

The overall survival was not different between the US and MRI groups (Supplementary Figure 7). Incidental findings identified during the surveillance exams are summarized in Supplementary Table 9.

Discussion

In this study, we prospectively compared US and noncontrast MRI surveillance in patients with liver cirrhosis. The results demonstrated that HCC could be detected at a significantly earlier stage, with a higher detection rate of BCLC stage 0 HCC and a lower surveillance failure rate in the MRI group than that in the US group. In addition, the false-positive referral rate was significantly lower in the MRI group than that in the US group. Our results suggest that noncontrast MRI is a better alternative to US for surveillance of patients with liver cirrhosis.

MRI has emerged as a promising method for liver cancer surveillance; however, the use of dynamic MRI for routine surveillance is challenging owing to the cost and usage of contrast media.[21] Abbreviated or noncontrast MRI may be used to overcome these issues; abbreviated or noncontrast MRI also has excellent diagnostic performance, with a pooled sensitivity of 86% to 87% and specificity of 90% to 96% in recent meta analyses.[21,22] Although there is still some debate regarding whether abbreviated or noncontrast MRI is ideal for liver cancer surveillance, the sensitivity and specificity are comparable between the two modalities.[22] However, most studies to date have been retrospective, with simulated abbreviated or noncontrast MRI extracted from contrast-enhanced MRI, and few studies have directly compared MRI with US.[22,23] In a recent study comparing US and noncontrast MRI surveillance in a secondary analysis of data from a prospective study, noncontrast MRI demonstrated a significantly higher sensitivity (79% vs 28%) and specificity (98% vs 95%).[12,17] As this was a single-arm study in which US and noncontrast MRI surveillance were performed simultaneously in the same patient, it was not possible to compare the surveillance failure rate between the 2 modalities, which is one of the primary objectives of the surveillance. In the present study, we directly compared 1:1 randomized US and MRI groups and found that MRI had a lower surveillance failure rate and higher detection rate of

Table 4. Initial Treatment of Liver Cancers in US and MRI Groups

	Liver cancers in US group (n = 21)	Liver cancers in MRI group (n = 23)
Initial treatment, n (%)		
Resection	6 (29)	13 (57)
Ablation	1 (5)	5 (22)
Ablation + transarterial chemoembolization	1 (5)	0 (0)
Transplantation	0 (0)	1 (4)
External beam radiation therapy and/or intraarterial chemotherapy	2 (10)	1 (4)
Transarterial chemoembolization	11 (52)	3 (13)
Curative initial treatment, % (n/N)	38 (8/21)	83 (19/23)

BCLC stage 0 HCC compared with US. Moreover, noncontrast MRI demonstrated a significantly lower false-positive referral rate compared with US. These findings were consistent with the results of previous studies, and the presence of signal alterations, in addition to lesion size on MRI, may have contributed to the reduction of false positives.[22,23]

On the other hand, noncontrast MRI is still more expensive, less available, and has longer procedure times compared with US. Therefore, it may be necessary to apply noncontrast MRI surveillance specifically to patients at very high risk for HCC to ensure cost-effectiveness.[24] In addition, recently developed blood-based biomarkers, such as GALAD score, could further enhance the effectiveness of HCC surveillance.[25]

The expected dropout rate before the start of the study was 15%; however, the actual dropout rate was 28%. The dropout rate was not significantly different between the MRI and US groups. Our results suggest that adherence to noncontrast MRI surveillance was not significantly different from that to US surveillance, even over a long period. However, it is worth noting that the dropout rate among participants without viral hepatitis was considerably higher. In regions where etiologies other than viral hepatitis are more prevalent, adherence to surveillance may differ.

Another interesting finding of this study was that liver cancers in the MRI group were more frequently detected via imaging without AFP level elevation than those in the US group (64% vs 22%). This may be due to the ability of MRI to detect lesions at an earlier stage before AFP level elevation, whereas US usually detects lesions after AFP level elevation. In contrast, liver cancers in the MRI group were less frequently detected as AFP level elevation without visualization on imaging than those in the US group (8% vs 30%). There has been a debate about whether AFP has additional value over US in surveillance, and some current guidelines have regarded AFP testing as optional.[4,5] In our study, it seemed difficult to ignore the role of AFP in the US group, but the MRI group seemed to benefit less from AFP testing. If the role of MRI in liver cancer surveillance expands in the future, the value of AFP testing may need to be reevaluated.

This study had some limitations. First, it was conducted at a single center in South Korea; in addition, 84% of the participating patients had hepatitis B virus infection, whereas only 11% had nonviral hepatitis. We enrolled patients with suspected liver cirrhosis without risk stratification, and the incidence of HCC was not as high as that reported in previous studies.[12,13] Therefore, it is possible that the study included relatively fewer patients with severe fatty liver disease or advanced cirrhosis, conditions that are challenging to visualize with US. Validation is required in Western countries where etiologies other than viral hepatitis are prevalent.[26] Third, this study had a long surveillance period, and a considerable number of participants dropped out. This likely reduced the effective sample size, potentially lowering the statistical power of the study. As we were unable to follow up with the participants lost to follow-up, we conducted a per-protocol analysis as the final analysis, which might be a potential source of selection bias. Finally, the study included a small number of patients with liver cancer. To determine the differences in overall survival according to surveillance methods, a study involving a larger number of patients is needed.

In conclusion, noncontrast MRI is a better alternative to US for surveillance in patients with liver cirrhosis, offering earlier stage detection at initial diagnosis and lower false-positive referral rate.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Gastroenterology* at www.gastrojournal.org, and at https://doi.org/10.1053/j.gastro.2024.12.035.

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Correspondence
Address correspondence to: Myeong-Jin Kim, MD, PhD, Department of Radiology, Yonsei University College of Medicine, 50–1 Yonsei-Ro, Seodaemun-gu, Seoul 03722, South Korea. e-mail: kimnex@yuhs.ac; or Do Young Kim, MD, PhD, Department of Internal Medicine, Yonsei University College of Medicine, 50–1 Yonsei-Ro, Seodaemun-gu, Seoul 03722, South Korea. e-mail: dyk1025@yuhs.ac.

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CRediT Authorship Contributions
Hyungjin Rhee, MD, PhD (Data curation: Lead; Formal analysis: Lead; Funding acquisition: Lead; Investigation: Lead; Methodology: Lead; Writing – original draft: Lead; Writing – review & editing: Lead)
Myeong-Jin Kim, MD, PhD (Conceptualization: Lead; Data curation: Lead; Formal analysis: Lead; Funding acquisition: Lead; Investigation: Lead; Methodology: Lead; Supervision: Lead; Writing – original draft: Lead; Writing – review & editing: Lead)
Do Young Kim, MD, PhD (Conceptualization: Lead; Data curation: Lead; Formal analysis: Lead; Funding acquisition: Supporting; Investigation: Lead; Methodology: Lead; Supervision: Lead; Writing – original draft: Lead; Writing – review & editing: Lead)
Chansik An, MD, PhD (Investigation: Supporting; Methodology: Supporting; Writing – review & editing: Supporting)
Wonseok Kang, MD, PhD (Investigation: Supporting; Methodology: Supporting; Writing – review & editing: Supporting)
Kyunghwa Han, PhD (Investigation: Supporting; Methodology: Supporting; Writing – review & editing: Supporting)
Yun Ho Roh, PhD (Investigation: Supporting; Methodology: Supporting; Writing – review & editing: Supporting)
Kwang-Hyub Han, MD, PhD (Investigation: Supporting; Writing – review & editing: Supporting)
Sang Hoon Ahn, MD, PhD (Investigation: Supporting; Writing – review & editing: Supporting)
Jin-Young Choi, MD, PhD (Investigation: Supporting; Writing – review & editing: Supporting)
Jun Yong Park, MD, PhD (Investigation: Supporting; Writing – review & editing: Supporting)
Yong Eun Chung, MD, PhD (Investigation: Supporting; Writing – review & editing: Supporting)
Seung Up Kim, MD, PhD (Investigation: Supporting; Writing – review & editing: Supporting)
Beom Kyung Kim, MD, PhD (Investigation: Supporting; Writing – review & editing: Supporting)
Sunyoung Lee, MD, PhD (Investigation: Supporting; Writing – review & editing: Supporting)
Hye Won Lee, MD, PhD (Investigation: Supporting; Writing – review & editing: Supporting)
Jae Seung Lee, MD, PhD (Investigation: Supporting; Writing – review & editing: Supporting)

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The authors disclose no conflicts.

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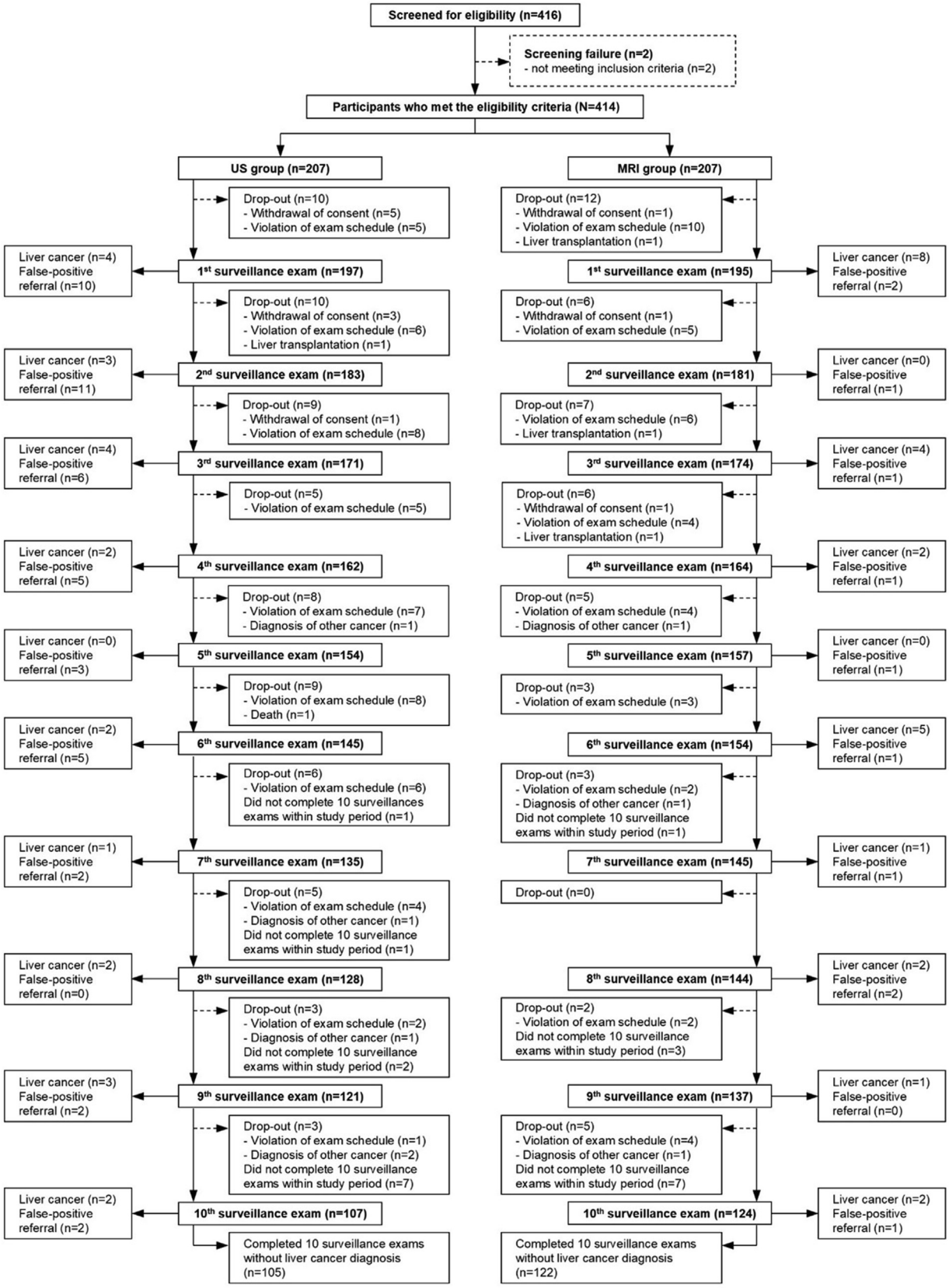
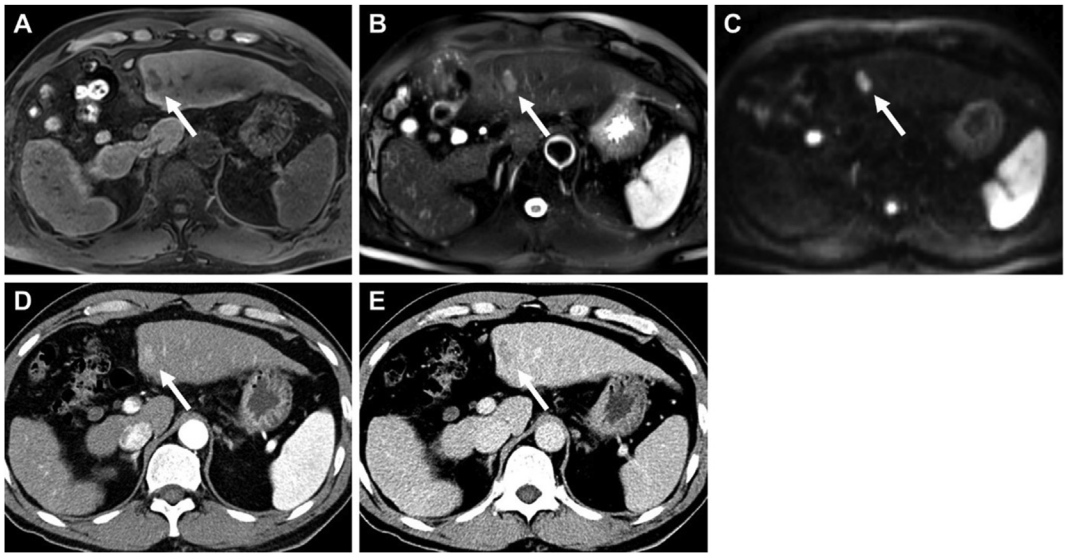
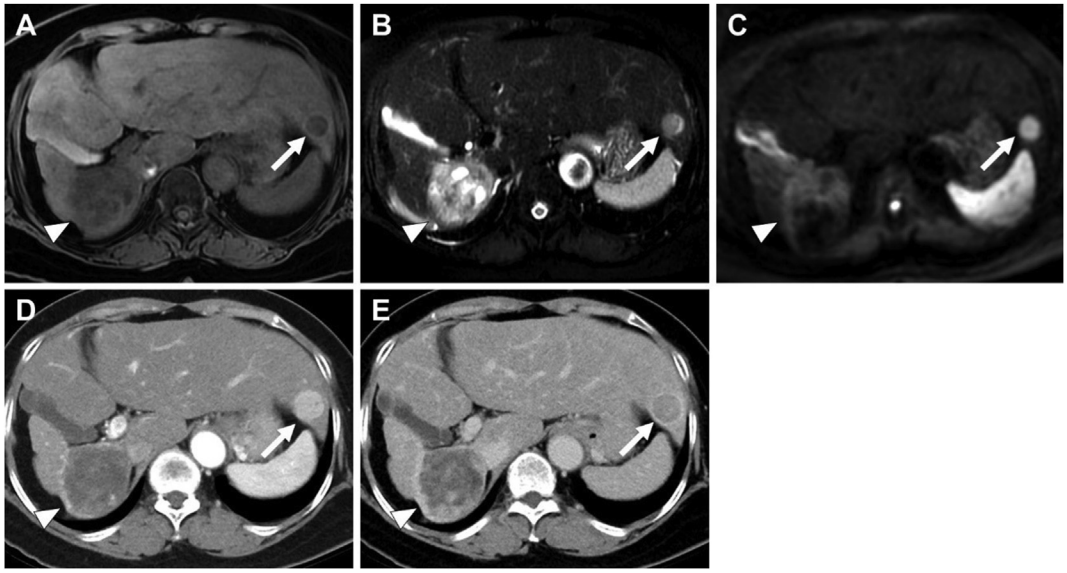
Data Availability
Data collected for the study, including de-identified participant data and a data dictionary, may be requested by qualified researchers who submit a methodologically sound proposal, which will be reviewed by our research team and institutional review board.



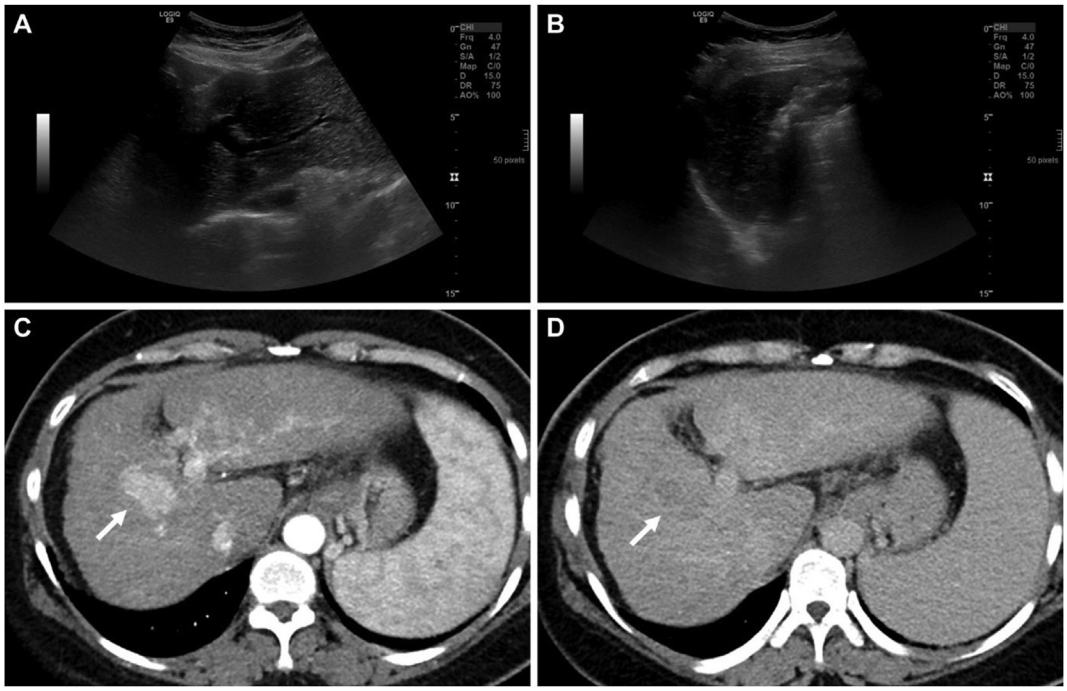
Supplementary Figure 1. Detailed study flow chart.



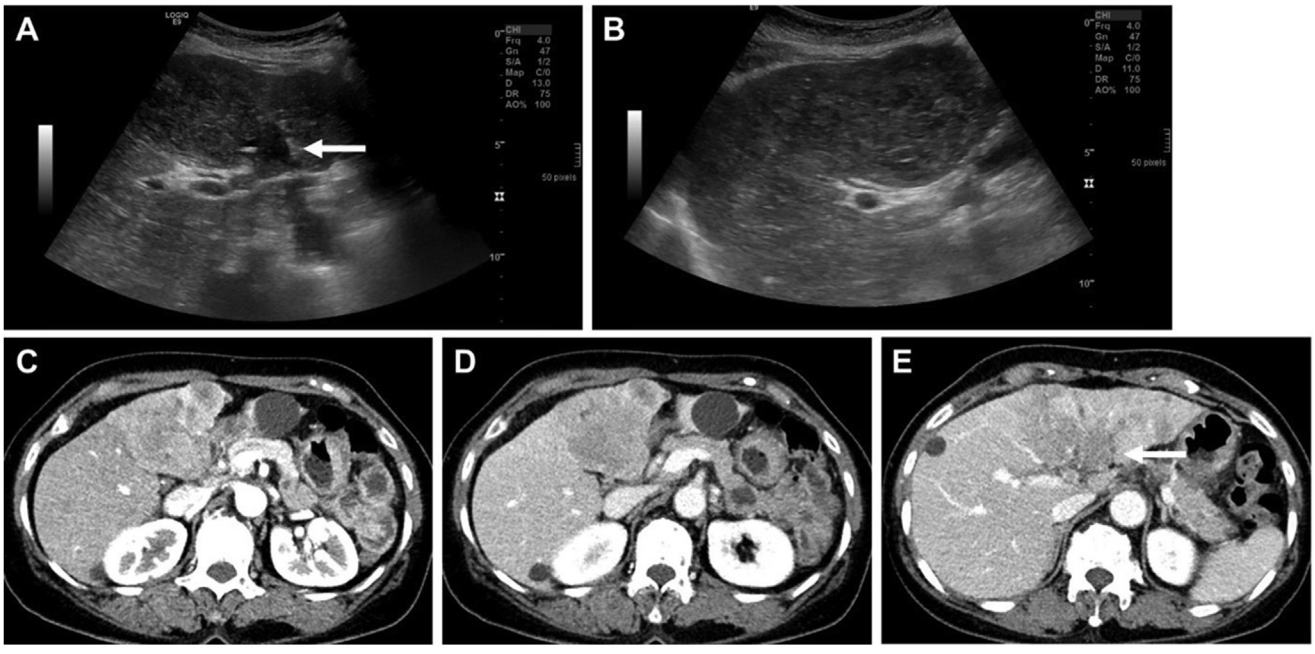
Supplementary Figure 2. A 58-year-old man in the MRI group who was diagnosed with BCLC stage 0 HCC. On the third surveillance noncontrast MRI scan, a hepatic nodule (*arrows*) is newly noted in segment 3, showing hypointensity on the T1-weighted image (*A*), hyperintensity on the T2-weighted image (*B*), and hyperintensity on the diffusion-weighted image (*C*, b = 800). The AFP level is elevated (2.1 ng/mL). On dynamic CT, the lesion is approximately 1.6 cm in size, with non-rim hyperenhancement in the arterial phase (*D*) and washout in the delayed phase (*E*), suggesting HCC (LR-5). The lesion was resected and pathologically confirmed to be HCC.



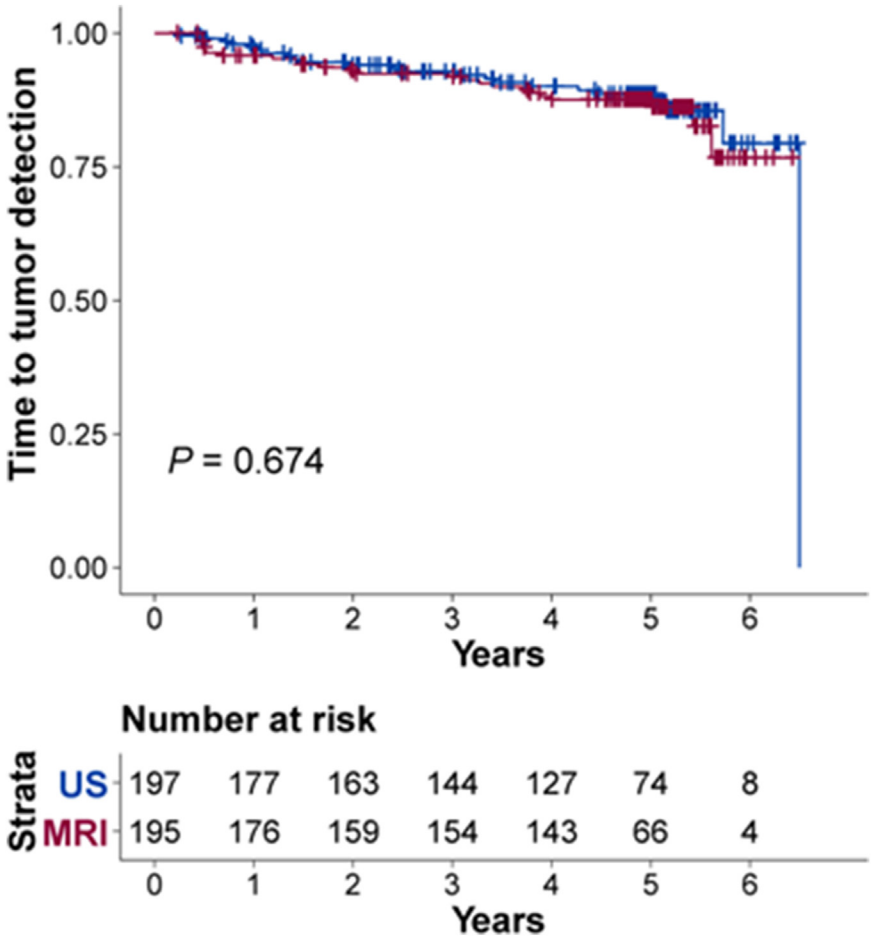
Supplementary Figure 3. A 71-year-old woman in the MRI group who was diagnosed with BCLC stage A HCC. On the sixth surveillance noncontrast MRI scan, a hepatic nodule (*arrows*) is identified at the tip of the left lateral section. The hepatic nodule shows hypointensity on a T1-weighted image (*A*), hyperintensity on a T2-weighted image (*B*), and hyperintensity on a diffusion-weighted image (*C*, b = 800). The AFP level is not elevated (3.8 ng/mL). There is no significant change in the known hepatic hemangioma in the right posterior section (*arrowheads*) compared with previous surveillance examinations. On dynamic CT, the lesion in the left lateral section is approximately 2·2 cm in size, with non-rim hyperenhancement in the arterial phase (*D*) and washout and enhancing capsule in the delayed phase (*E*), suggesting HCC (LR-5). The lesion was resected and pathologically confirmed as HCC.



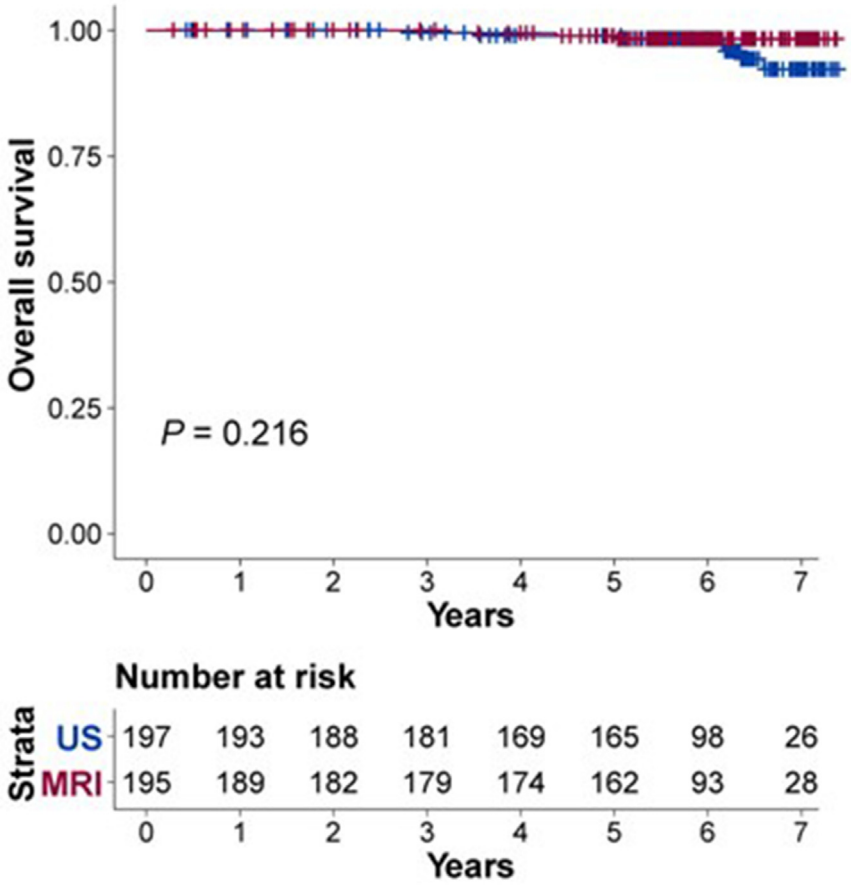
Supplementary Figure 4. A 53-year-old woman in the US group who was diagnosed with BCLC stage A HCC. In this patient, the echo window for the right liver is poor and no definite focal lesions are observed until the eighth surveillance US (*A* and *B*). However, the AFP level shows 2 consecutive increasing trends (3.9 ng/mL, 6.4 ng/mL, 186.2 ng/mL at the sixth, seventh, and eighth surveillance examinations, respectively), so dynamic CT was performed. On CT, an approximately 3.3-cm mass lesion is noted in liver segment 4/5, showing non-rim hyperenhancement in the arterial phase (*C*) and washout in the delayed phase (*D*), suggesting HCC (LR-5). The lesion was treated with drug-eluting bead transarterial chemoembolization.



Supplementary Figure 5. A 69-year-old woman in the US group who was diagnosed with BCLC stage A HCC. On third surveillance US, a hypoechoic mass lesion with portal vein thrombosis (*arrow*) is newly identified in the left liver (*A* and *B*). The AFP level also shows 2 consecutive increasing trends (2.4 ng/mL, 3.3 ng/mL, 19.8 ng/mL at the first, second, and third surveillance examinations, respectively). On dynamic CT, an approximately 12.6-cm mass lesion is noted in the left liver, demonstrating non-rim hyperenhancement in the arterial phase (*C*), and washout and portal vein thrombosis (*arrow*) in the portal phase (*D* and *E*), suggesting HCC (LR-TIV).



Supplementary Figure 6. Comparison of time to tumor detection of patients with liver cancer in the US and MRI groups. *P* values were calculated using the log-rank test.



Supplementary Figure 7. Comparison of overall survival of patients with liver cancer in the US and MRI groups. *P* values were calculated using the log-rank test.

Supplementary Table 1. Parameters of Surveillance Noncontrast MRI

Sequence	Scanner	Matrix size	ST (*mm*)	Gap (*mm*)	TR (*ms*)	TE (*ms*)	FA (°)
Dual-echo T1-WI GRE	Magnetom Trio Tim (2D)	256 × 192	6	1.2	150	1.23/2.46	65
	Ingenia CX (3D)	278 × 256	2	0	3.2	1.15/2.30	10
	Discovery MR750 (3D)	320 × 256	2	0	3.9	1.12/2.35	12
	Prisma Fit (3D)	320 × 256	2	0	9	1.34/2.73	9
T1-WI 3D GRE	Magnetom Trio Tim	256 × 192	2	0	2.54	0.95	13
	Ingenia CX	256 × 282	2	0	3.1	1.42	10
	Discovery MR750	320 × 288	2	0	4.2	1.9	12
	Prisma Fit	320 × 256	2	0	2.68	1.08	9
T2-WI with fat saturation	Magnetom Trio Tim	256 × 192	4	1	466	96	150
	Ingenia CX	320 × 212	4	1	758	80	90
	Discovery	320 × 256	4	1	2800	80	90
	Prisma Fit	320 × 182	4	1	620	105	107
T2-WI with long TE	Magnetom Trio Tim	320 × 168	4	1	450	148	150
	Ingenia CX	320 × 186	4	1	522	150	90
	Discovery MR750	320 × 224	4	1	840	150	90
	Prisma Fit	320 × 208	4	1	600	153	98
DWI	Magnetom Trio Tim	128 × 96	6	1	5200	67	90
	Ingenia CX	128 × 128	5	1	4848	55	90
	Discovery MR750	128 × 80	5	1	4800	51	90
	Prisma Fit	140 × 112	5	1	5500	63	90

2D, 2-dimensional; 3D, 3-dimensional; DWI, diffusion-weighted imaging; FA, flip angle; GRE, gradient-recalled echo; ST, slice thickness; TE, echo time; TR, repetition time.

Supplementary Table 2. The Cause and Time of Dropout

	Cause of dropout	Between enrollment and 1st exam	Between 1st and 2nd exam	Between 2nd and 3rd exam	Between 3rd and 4th exam	Between 4th and 5th exam	Between 5th and 6th exam	Between 6th and 7th exam	Between 7th and 8th exam	Between 8th and 9th exam	Between 9th and 10th exam	All, n (%)
US	Withdrawal of consent	5	3	1								9 (13)
	Violation of exam schedule	5	6	8	5	7	8	6	4	2	1	52 (76)
	Diagnosis of other cancers					1			1	1	2	5 (7)
	Liver transplantation		1									1 (1)
	Death						1					1 (1)
MRI	Withdrawal of consent	1	1		1							3 (6)
	Violation of exam schedule	10	5	6	4	4	3	2		2	4	40 (82)
	Diagnosis of other cancers					1		1			1	3 (6)
	Liver transplantation	1		1	1							3 (6)
	Death											0 (0)

Supplementary Table 3. Baseline Characteristics of Participants by Dropout Status

	US group		MRI group	
	(1) Non-dropout participants (n = 139)	(2) Dropout participants (n = 68)	(3) Non-dropout participants (n = 158)	(4) Dropout participants (n = 49)
Age, *y*, median (IQR)	58 (53–62)	57 (53–64)	57 (50–62)	59 (52–65)
Sex (male/female), n (%)	77 (55%) / 62 (45%)	32 (47%) / 36 (53%)	108 (68%) / 50 (32%)	28 (57%) / 21 (43%)
Etiology of cirrhosis, n (%)				
HBV	125 (90%)	51 (75%)	136 (86%)	36 (74%)
HCV	6 (4%)	4 (6%)	9 (6%)	3 (6%)
Others	8 (6%)	13 (19%)	13 (8%)	10 (20%)
Height, median (IQR), *cm*	165 (158–171)	162 (157–168)	168 (160–174)	165 (158–171)
Weight, median (IQR), *kg*	65 (59–73)	64 (58–70)	69 (59–77)	65 (60–73)
BMI, median (IQR)	24.1 (22.4–26.4)	23.5 (22.4–25.6)	24.3 (22.5–26.6)	24.6 (22.5–27.1)
Total bilirubin, median (IQR), *mg/dL*	1.0 (0.7–1.2)	0.9 (0.7–1.2)	0.9 (0.7–1.2)	0.9 (0.7–1.3)
Albumin, median (IQR), *g/dL*	4.3 (4.1–4.5)	4.2 (3.9–4.4)	4.3 (4.1–4.5)	4.3 (4.0–4.5)
Creatinine, median (IQR), *mg/dL*	0.8 (0.6–0.8)	0.7 (0.6–0.8)	0.8 (0.7–0.9)	0.8 (0.7–0.9)
PT/INR, median (IQR)	1.0 (1.0–1.1)	1.0 (1.0–1.1)	1.0 (1.0–1.1)	1.0 (0.9–1.1)
Platelets, median (IQR), *1000/μL*	128 (99–162)	125 (82–157)	126 (101–169)	136 (99–168)
Alpha-fetoprotein, median (IQR), *ng/mL*	3.2 (2.0–4.8)	3.7 (2.5–5.8)	2.9 (2.1–4.5)	3.1 (2.1–4.8)
Child-Pugh score, n (%)				
5	135 (97%)	68 (100%)	156 (99%)	48 (98%)
6	4 (3%)	0 (0%)	2 (1%)	1 (2%)

BMI, body mass index; HBV, hepatitis B virus; HCV, hepatitis C virus; PT/INR, prothrombin time/international normalized ratio.

Supplementary Table 4. False-Positive Referral Rate According to the Parenchymal Nodularity and Poor Echo Window of Ultrasonography and Body Mass Index

	US group		MRI group	
	Absent	Present	Absent	Present
Parenchymal nodularity on US	1.2% (9/775)	5.1% (37/721)	NA	NA
Poor echo window on US	3.8% (38/995)	1.6% (8/501)	NA	NA
Body mass index $\geq$ 25 kg/m^2	2.7% (26/958)	3.7% (20/538)	0.7% (6/917)	0.8% (5/658)

NA, not applicable.

Supplementary Table 5. The Rate and Reason for Unscheduled Dynamic Examinations

	US group	MRI group
Rate of unscheduled dynamic exams, n/total N (%)	23/1496 (1.5)	7/1575 (0.4)
Reason for unscheduled dynamic exams, n (%)		
Unspecified	6 (26)	2 (29)
Gastrointestinal tract bleeding	5 (22)	1 (14)
Poor echo window	3 (13)	0 (0)
Elevated PIVKA-II	2 (9)	0 (0)
Liver failure	1 (4)	0 (0)
Suspected liver lesion in images taken at outside hospital	1 (4)	1 (14)
Suspected liver lesion in images taken at emergency room	1 (4)	1 (14)
Subcentimeter hepatic nodule evaluation	1 (4)	1 (14)
Evaluation for liver transplantation	1 (4)	0 (0)
Evaluation for BRTO	1 (4)	0 (0)
Hemangioma follow-up	1 (4)	0 (0)
Elevated AFP at outside hospital	0 (0)	1 (14)

PIVKA-II, protein induced by vitamin K antagonist-II; BRTO, balloon-occluded retrograde transvenous obliteration.

Supplementary Table 6. Diagnosis of Liver Cancers in US and MRI Groups

	Liver cancers in US group (n = 23)	Liver cancers in MRI group (n = 25)
Result of last surveillance exam, n (%)		
Positive in both image and AFP	5 (22)	7 (28)
Positive only in image	5 (22)	16 (64)
Positive only in AFP	7 (30)	2 (8)
False-negative	6 (26)	0 (0)
Interval between last surveillance and diagnosis (*d*)	87 (24–102)	44 (15–100)
Method of diagnosis, n (%)		
With both dynamic imaging and pathology	6 (26)	12 (48)
With dynamic imaging	17 (74)	11 (44)
With pathology	0 (0)	2 (8)

Supplementary Table 7. Radiologic and Pathologic Diagnosis of Pathologically Proven Lesions

Group	No.	Radiologic diagnosis	Method of pathologic diagnosis	Pathologic diagnosis
US	MS038	LR-M, 2.0cm	Resection	HCC, 1.9cm
	MS040	LR-5, 1.8cm	Resection	HCC, 1.8cm
	MS056	LR-5, 3.2cm	Resection	HCC, 2.4cm
	MS137	LR-5, 3.8cm	Resection	HCC, 3.5cm
		LR-5, 2.5cm		HCC, 2.5cm
	MS190	LR-5V, 3.2cm	Resection	5 HCC, <1cm
	MS395	LR-5, 2.5cm	Resection	HCC, 2.5cm
MRI	MS012	LR-5, 1.3cm	Resection	HCC, 1.8cm
		LR-2, 1.6cm		HCC, 1.8cm (early HCC)
	MS018	LR-M, 2.6cm	Resection	iCCA, 2.5cm
	MS039	LR-5, 2.2cm	Resection	HCC, 2.5cm
	MS060	LR-5, 1.6cm	Resection	HCC, 1.5cm
	MS087	LR-4, 0.8cm	Transplantation	5 early HCCs (2.0cm, 1.9cm,
		Multiple LR-3 lesions, up to 1.5cm		1.3cm, 1.2cm, 0.9cm)
	MS103	LR-5, 1.7cm	Resection	HCC, 2.1cm
	MS168	LR-M, 2.4cm	Resection	cHCC-CCA, 2.2cm
		LR-5, 1.4cm		HCC, 1.0cm (early HCC)
		LR-M, 1.3cm		cHCC-CCA, 1.0cm
	MS206	LR-5, 2.2cm	Resection	HCC, 2.2cm
	MS214	LR-M, 1.1cm	Resection	cHCC-CCA, 1.7cm
	MS245	LR-5, 1.4cm	Resection	HCC, 1.2cm
	MS262	LR-5, 1.5cm	Resection	HCC, 1.6cm
	MS309	LR-5, 1.8cm	Resection	HCC, 1.8cm
	MS346	LR-4, 2.0cm	Resection	HCC, 1.8cm
		LR-4, 1.7cm		Not identified
	MS357	LR-5, 1.9cm	Resection	HCC, 2.2cm

cHCC-CCA, combined hepatocellular-cholangiocarcinoma; iCCA, intrahepatic cholangiocarcinoma.

Supplementary Table 8. The Cause for Noncurative Treatment

Group	No.	Initial treatment	Cause of noncurative treatment	Notes
US	MS046	External beam radiation therapy and/or intraarterial chemotherapy	BCLC B or C	
US	MS057	External beam radiation therapy and/or intraarterial chemotherapy	BCLC B or C	
US	MS068	Transarterial chemoembolization	Unfavorable location for resection and ablation	Segment 4, close to the portal vein and middle hepatic vein, Size: 3.3 cm
US	MS090	Transarterial chemoembolization	Poor liver function, unfavorable location for ablation	Segment 8 dome area
US	MS097	Transarterial chemoembolization	Unfavorable location for resection and ablation	Three lesions scattered in left liver
US	MS171	Transarterial chemoembolization	BCLC B or C	
US	MS188	Transarterial chemoembolization	Unfavorable location for resection and ablation	Two lesions in segment 4/8 and segment 6
US	MS191	Transarterial chemoembolization	Unfavorable location for resection and ablation	Two lesions in segment 5 and segment 7/8
US	MS258	Transarterial chemoembolization	Poor liver function, large for ablation	Size: 3.1 cm
US	MS308	Transarterial chemoembolization	Poor liver function, unfavorable location for ablation	Segment 4, close to the left portal vein
US	MS321	Transarterial chemoembolization	Unfavorable location for resection and ablation	Two lesions in the contralateral lobes
US	MS372	Transarterial chemoembolization	Poor liver function, unfavorable location for ablation	Segment 5/6 subcapsular area
US	MS406	Transarterial chemoembolization	Unfavorable location for resection and ablation	Segment 1/2, abutment to inferior vena cava
MRI	MS150	External beam radiation therapy and/or intraarterial chemotherapy	Unfavorable location for resection and ablation	Segment 7/8 dome area
MRI	MS189	Transarterial chemoembolization	BCLC B or C	
MRI	MS280	Transarterial chemoembolization	Poor liver function, unfavorable location for ablation	Segment 8 dome area
MRI	MS351	Transarterial chemoembolization	Unfavorable location for resection and ablation	Two lesions in segment 4/8 and segment 6

cHCC-CCA, combined hepatocellular-cholangiocarcinoma; iCCA, intrahepatic cholangiocarcinoma.

Supplementary Table 9. Incidental Findings in Surveillance Exams

	US group (n = 207)	MRI group (n = 207)
Incidental findings in surveillance exams, n (%)		
Varix	4 (2)	18 (9)
GB adenomyomatosis	2 (1)	8 (4)
GB polyp(s)	40 (19)	1 (0.5)
GB stone(s)	26 (13)	34 (16)
CBD dilatation	9 (4)	5 (2)
Distal CBD stone	0 (0)	2 (1)
Pancreatic cyst(s)	7 (3)	19 (9)
Chronic pancreatitis	0 (0)	1 (0.5)
Adrenal adenoma	0 (0)	1 (0.5)
Renal cyst(s)	39 (19)	26 (13)
Operation or procedure related to incidental finding	None	Cholecystectomy for 3-cm GB stone (n = 1, 0.5%)

GB, gallbladder; CBD, common bile duct.