Liver Magnetic Resonance Imaging for Hepatocellular Carcinoma Surveillance

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Hepatocellular carcinoma (HCC) surveillance is recommended when the annual incidence of HCC exceeds 1.5%. In 2018, several international guidelines included alternative surveillance modalities, such as computed tomography and magnetic resonance imaging (MRI), as alternatives for patients with inadequate surveillance with an ultrasound. Currently, abbreviated MRI selectively includes several key sequences and is emerging as an effective tool for HCC surveillance with reduced cost and scan time and the required diagnostic performance. The incidence of HCC substantially impacts the benefits of surveillance in terms of cost-effectiveness. Therefore, we need to individualize imaging surveillance of HCC, tailor screening, and determine risk-stratified strategies. The purpose of this article was to present a brief overview of the diagnostic performance and cost-effectiveness of liver MRI as an HCC surveillance tool. (*J Liver Cancer* 2020;20:25-31)

Keywords: Hepatocellular carcinoma; Liver; Magnetic resonance imaging; Surveillance

INTRODUCTION

Hepatocellular carcinoma (HCC) is the fifth most common type of cancer and a leading cause of cancer-related deaths worldwide.^{1,2} It imposes a heavy annual economic burden that reached 454.9 million United States dollars from 1991 to 1999.³ The most common risk factor for HCC is liver cirrhosis caused by viral hepatitis, followed by alcoholic liver disease and nonalcoholic fatty liver disease.² To reasonably detect HCCs at an early and potentially curable stage, guidelines by the European Association for the Study of the Liver (EASL), American Association for the Study of Liver Diseases

(AASLD), Asian Pacific Association for the Study of the Liver (APASL), and Korean Liver Cancer Association-National Cancer Center Korea (KLCA-NCC) currently recommend a surveillance program for HCC through biannual ultrasonography (US) with or without serum alpha fetoprotein (AFP).^{1,4-6} This strategy is largely supported by a randomized controlled trial in which biannual screening of patients with AFP and US resulted in a 37% decrease in mortality from HCC.⁷ Although US is an affordable and accessible modality for screening, meta-analyses reveal that it has an unsatisfactory 60-65% per-patient sensitivity for HCC detection in the cirrhotic liver,^{8,9} which is low for a screening test. The accuracy of US could further reduce in patients with obesity, advanced cirrhosis, or subcapsular lesions.^{10,11} For HCCs smaller than 2 cm, the sensitivity of US is 20% or less.¹²⁻¹⁴ Thus, failed or suboptimal US surveillance seems to contribute to an advanced-stage tumor presentation.¹⁵

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Because detecting HCC at an early stage provides a wider range of options for curative treatments, a feasible and robust screening tool is required. To overcome limited efficacy of US, several guidelines updated in 2018 included alternative surveillance modalities, such as computed tomography (CT) or magnetic resonance imaging (MRI) in patients with inadequate US surveillance (Fig. 1).^{1,4,6} The purpose of this review was to present an overview of the diagnostic performance and cost-effectiveness of liver MRI as an HCC surveillance tool.

LIVER MRI FOR HCC SURVEILLANCE

1. Full-protocol gadoxetic acid-enhanced liver MRI: diagnostic performance

Gadoxetic acid (Primovist or Eovist, Bayer Schering Parma, Berlin, Germany) is a gadolinium-based, hepatocyte-specific MRI contrast agent that provides dynamic enhancement profile of the focal lesion as well as functional and structural information of the hepatobiliary system. Unlike conventional extracellular contrast media (ECCM), which

only distributes in the extracellular space, gadoxetic acid enters the functioning hepatocyte and is then excreted into the biliary system approximately 20 minutes after injection.¹⁶ T1-weighted imaging obtained in this specific temporal window is referred to as the hepatobiliary phase (HBP). On images obtained in HBP, most malignant focal liver lesions, including HCC, are hypointense compared to the strongly enhancing liver parenchyma, increasing the sensitivity for detecting such nodules.¹⁷ Additionally, T1-weighted dual gradient-echo in-phase and out-of-phase image (Dual-GRE), T2-weighted image (T2WI) and diffusion-weighted image (DWI) are obtained as part of the full-protocol liver MRI to preserve both the specificity and sensitivity for the diagnosis of HCC.¹⁷ A meta-analysis revealed that gadoxetic acid-enhanced liver MRI was superior to dynamic contrast-enhanced CT or MRI using other types of ECCM and hepatocyte-specific contrast agents for detecting and characterizing liver lesions during the intrahepatic staging workup of HCC.¹⁸ Owing to the high sensitivity and superior tissue contrast, gadoxetic acid-enhanced MRI could be a potential screening tool for HCCs. Kim et al. hypothesized that gadoxetic acid-enhanced MRI would show a significantly higher

HCC Surveillance Strategies in 2018 Guidelines

Figure 1. Guidelines in 2018 on alternative surveillance modalities. HCC, hepatocellular carcinoma; EASL, European Association for the Study of the Liver; US, ultrasonography; CT, computed tomography; MRI, magnetic resonance imaging; AASLD, American Association for the Study of Liver Diseases; AFP, alpha fetoprotein; NAFLD, non-alcoholic fatty liver disease; KLCA & NCC, Korean Liver Cancer Association-National Cancer Center Korea.

sensitivity compared to US for the detection of early-stage HCC in patients with cirrhosis at high risk of developing HCC.¹¹ Of the 423 patients at risk, 48 HCCs were diagnosed in 43 patients during 1,057 screening rounds using paired US and MRI at 6-month intervals, with most HCCs belonging to a very early stage or an early stage according to the Barcelona Clinic Liver Cancer (BCLC) staging system. The overall HCC detection rates of US and MRI were 27.9% and 86.0%, respectively. The false-positive rate was 5.6% (59/1,057) for US and 3.0% (32/1,057) for MRI, showing a notable difference. This study highlights the superior performance of gadoxetic acid-enhanced MRI compared to US in detecting very-early-stage HCCs in patients at a high risk for HCC, which in turn is associated with a higher probability of curative treatment and patient survival. However, the cost of gadoxetic acid-enhanced MRI is high, and concerns regarding how cost-effective this surveillance scheme is should be considered. The issue of cost-effectiveness will be addressed later in this article.

2. Abbreviated liver MRI (AMRI): suggested sequences and diagnostic performances

AMRI is a shortened version of the full-sequence dynamic contrast-enhanced MRI, and is emerging as a practical screening modality for HCC. Advantages of AMRI are reduced scan time and cost in addition to an acceptable diagnostic performance, which are achieved by selectively including several key sequences. AMRI can be primarily divided into three categories (Table 1): noncontrast AMRI, HBP added to noncontrast AMRI (EOB-AMRI), and dynamic AMRI using an ECCM.¹⁹⁻²³ In prior studies, two to five key sequences were selected for each AMRI protocol to yield a fairly high per-patient sensitivity of 80-89.6% for the diagnosis of HCC.¹⁹⁻²⁴ Particularly, for noncontrast AMRI, the per-patient sensitivity and specificity ranged from 82.9-89.6% and 76.4-87.5%, respectively.^{21,23} For EOB-AMRI, the sensitivity and specificity ranged from 80.6-83.7% and 90.6-91.6%, respectively.^{19,22} Although these were heterogeneous studies carried out at different centers, all showed promising

Table 1. Summary of abbreviated magnetic resonance imaging sequences and studies

Study	No. of patients	No. of HCCs	Field strength	AMRI	MRI sequence	Per-patient sensitivity	Per-patient specificity	Inter-reader agreement
Kim et al. ²⁵	135	116	3T	Noncontrast-AMRI	T2WI, Dual-GRE, and DWI	91.7%*	77.5%	k=0.615-0.733
Han et al. ²¹	247	175	3T	Noncontrast-AMRI	T2WI, Dual-GRE, and DWI	82.9-86.3%	76.4-87.5%	k=0.668
Kim et al. ²³	226	173	3T	Noncontrast-AMRI	T2WI and DWI vs. T2WI, Dual-GRE, and DWI	84.4-87.3% vs. 87.3-89.6%	86.8 vs. 79.2-81.1%	k=0.77-0.78
Marks et al. ¹⁹	298	49	1.5T 3T	EOB-AMRI	T2WI and HBP vs. T2WI, HBP, and DWI	82.6% vs 83.7%	91.6%	k=0.72
Besa et al. ²²	174	62	1.5T 3T	EOB-AMRI	Various combinations using HBP and DWI vs. dynamic enhancement	80.6%†	90.6%	k=0.79-0.82
Tillman et al. ²⁰	79	27	1.5T 3T	EOB-AMRI	T2WI and HBP	85.2%‡	N/A	k=0.75
Lee et al. ²⁴	164	N/A	3T	ECCM-AMRI	Pre-, arterial, portal, 3-min-delayed MRI (only dynamic phase AMRI) vs. full-sequence MRI	5% of cases with changes in LI-RADs	N/A	k=0.508

HCC, hepatocellular carcinoma; AMRI, abbreviated magnetic resonance imaging; MRI, magnetic resonance imaging; T2WI, T2-weighted images; Dual-GRE, dual gradient-echo in-phase and out-of-phase image; DWI, diffusion-weighted imaging; EOB-AMRI, gadoxetic acid-enhanced AMRI; HBP, hepatobiliary phase; N/A, not available; ECCM-AMRI extracellular contrast media-enhanced AMRI; LI-RAD, Liver Imaging Reporting and Data System.

*Per-patient sensitivity for detection of malignancy; †Sensitivities of DWI and HBP sequences; ‡Per-lesion sensitivity for HCC.

results for AMRI as a screening tool for HCC.

Noncontrast AMRI was tested to detect HCC or other liver malignancies in several retrospective studies, mainly performed in South Korea (Fig. 2).^{21,23,25} Advantages of noncontrast AMRI are cheaper cost, safer study free of contrast agents, and simplicity in execution: If enough sequences are selected to preserve the sensitivity for HCC detection without the use of contrast agents, the risk of contrast agent-related adverse events is eliminated, and both the cost and examination time can be reduced. Han et al. found three effective key sequences: Half-Fourier Acquisition Single-shot Turbo spin Echo (HASTE) T2WI, Dual-GRE, and DWI.²¹ During a reduced scan time of 12-15 minutes, the AMRI protocol showed per-patient sensitivities of 86.3% and 82.9% for HCC as evaluated by two independent readers. In the same study, per-lesion sensitivity ranged from 70.5-75.9% for detecting tumors within Milan criteria.

There is an ongoing prospective, multicenter clinical trial evaluating the use of noncontrast AMRI as an HCC surveillance tool in patients with liver cirrhosis in South Korea.²⁶ The study aims to assess the detection rate of HCC using US at 6-months intervals compared to yearly noncontrast liver MRI over a 3-years follow-up.²⁶ In this trial, the AMRI protocol uses five sequences: HASTE T2WI, fast-spin-echo T2WI, Dual-GRE, DWI, and T1-weighted images. This trial might provide more solid evidence to support the utility of noncontrast MRI for HCC surveillance. Noncontrast AMRI has sev-

eral great advantages as a surveillance tool for HCC; however, issues regarding sensitivity for detecting small lesions and its performance with a 1.5T system require further assessment. The prospective study might resolve some of these issues.

EOB-AMRI for HCC surveillance has been evaluated in several retrospective studies mostly conducted in the United States of America.^{19,20,22} These studies were designed to detect HCC greater than 1 cm using the tested sequences. The protocol is based on the hypothesis that AMRI consisting only of HBP and T2WI, essentially, and/or DWI could provide adequate per-patient sensitivity and negative predictive values for HCC surveillance. The rationale for the protocol was that most HCCs are hypointense in contrast to the liver parenchyma in HBP so that HCCs could be easily detected even in the absence of the dynamic contrast-enhanced studies. Additionally, T2WI in this protocol is useful in differentiating HCCs from cysts and hemangiomas showing a distinctively high T2 signal intensity. In EOB-AMRI, gadoxetic acid is hand-injected to the patient in the waiting room 20 minutes prior to the scan in order to save 20 minutes of time interval required to image HBP. If there is a suspicious lesion on EOB-AMRI, the patient is called back to undergo dynamic contrast-enhanced MRI. The main advantage of this protocol is its high sensitivity for detecting HCCs while remarkably reducing the scan time. Several studies have assessed the optimized sequence combination: Mark et al. found that the per-patient sensitivity of the T2WI sequence plus HBP did

Figure 2. A representative case of hepatocellular carcinoma in a treatment-naïve 60-year-old woman with hepatitis B-associated cirrhosis. Abbreviated magnetic resonance imaging shows a 1.3 cm, positive nodule (arrows) for hepatocellular carcinoma in segment 5. The lesion shows (A) mild high signal intensity on T2-weighted image, (B) diffusion restriction, and (C, D) fat-containing lesion on T1-weighted dual gradient-echo in-phase and out-of-phase images.

not improve even after adding DWI (82.6% vs. 83.7%).¹⁹ Besa et al. compared the sensitivity of HCC detection among several combinations of sequences, and per-patient sensitivity was reported to be 80.6% when T2WI, HBP, and DWI combination was used. The sensitivity was higher at 90.6% when dynamic contrast enhancement and T2WI were used.²² Tillman et al. reported that the per-lesion sensitivity was 85.2% when the combination of T2WI and HBP was used.²⁰ Although the studies reported a satisfactory sensitivity, these were retrospective in nature and were based on simulated sets built from a full-sequence gadoteric acid-enhanced MRI. Other unresolved issues are the need to optimize noncontrast sequences to balance the sensitivity, cost, and scan time. A high rate of false-positives should also be addressed. Additionally, the most effective confirmative dynamic contrast-enhanced study of suspicious lesions detected on AMRI should be identified.

A retrospective study using AMRI that only included dynamic enhancement using ECCM agents for HCC surveillance was conducted in the USA.²⁴ In this study, the AMRI protocol obtained pre-, arterial, portal, and 3-minutes-delayed phase images requiring approximately 7-10 minutes to perform. The authors compared AMRI utilizing only dynamic contrast-enhanced images to full-sequence liver MRI and reported that only 5% of cases would require modification in the Liver Imaging Reporting and Data System (LI-RADS) category because of ancillary features on T2WI and DWI. The limitation of this study was its retrospective design based on a simulated set without a reference standard for the diagnosis of HCC. Advantages of dynamic AMRI are the short scan time, reduced cost, and ability to confirm the diagnosis.

COST-EFFECTIVE ANALYSIS OF LIVER MRI FOR HCC SURVEILLANCE

The choice of a surveillance tool requires consideration of key factors, including the cost, sensitivity, and specificity for the disease, incidence of the disease, and increase in survival rates with the treatment.²⁷⁻²⁹ HCC surveillance should be performed for patients whose risk for HCC development is high enough to make it cost-effective. Surveillance is considered

effective if it increases the life expectancy by more than 3 months and cost-effective if 1 quality-adjusted life year is increased for less than \$50,000.³⁰ Therefore, the incidence of HCC is the primary determinant of cost-effectiveness of surveillance.

The risk of developing HCC is not uniform across all patients even in the presence of risk factors. The annual risk of developing HCC ranges from 0.2% to over 10%. Therefore, it is necessary to stratify the risk and determine the target distribution. In patients with Child-Pugh A cirrhosis, HCC surveillance becomes cost-effective if the annual incidence of HCC exceeds 1.5%.³¹ In patients with chronic hepatitis B without cirrhosis, surveillance is considered cost-effective if the incidence of HCC is greater than 0.2%.³² When the incidence of HCC is greater than 3%, MRI surveillance is an acceptable, cost-effective option.³³

PERSPECTIVES ON FUTURE RESEARCH

1. Most effective confirmation study for an AMRI-detected lesion

Because AMRI protocols are designed to detect suspicious lesions, further testing is required to confirm the diagnosis. Currently, the proposed scheme is to call the patients back for an additional dynamic contrast-enhanced study.¹⁹ However, if the patient underwent a recent dynamic contrast-enhancement study, it may be a substitute and avoid a repeated scan. Park et al. reported that AMRI combined with recently performed multiphasic CT demonstrated a diagnostic performance similar or superior to a full-sequence gadoteric acid-enhanced MRI for HCC using LI-RADS.³⁴ Therefore, in patients at risk for HCC, multiphasic CT could be potentially used as a sequential examination to confirm an AMRI-detected hepatic nodules.

2. Prospective comparison of the diagnostic capability of US and variable combinations of liver MRI sequences for HCC surveillance

A prospective comparison of the diagnostic capability of

US and other AMRI protocols should be performed because there have only been simulated retrospective studies so far. Many of these studies compared several different combinations of sequences to improve the sensitivity, but finding the best combination still requires further research. A recent study reported expected savings of up to 49% on a simulated cost-effective analysis when AMRI replaced full-sequence MRI.²² This has been further emphasized in an estimated cost-effective analysis based on the medical cost of US: EOB-AMRI was more cost-effective in patients at a high or intermediate risk for HCC.²² A more detailed cost-effective analysis may provide evidence for tailored screening and a risk-stratified approach.

3. Role of serum markers combined with liver MRI for HCC surveillance

Another consideration is to evaluate the possible benefit of combining serum marker results with AMRI findings.

4. Inter-reader agreement of liver MRI for HCC surveillance

Inter- and intra-reader agreements should be validated since assessments could vary depending on the combination of sequences.

CONCLUSION

Several protocols of AMRI are under investigation to aid unsatisfactory performance of the currently recommended HCC surveillance using US. Yang et al. recently reported that the incidence of HCC and stage of progression of cirrhosis was associated with the strongest cost-effectiveness of surveillance,³⁵ remarking that the incidence of HCC in the population and sensitivity of the surveillance tool substantially impact the benefits of HCC surveillance. Therefore, we need to individualize HCC surveillance through assessments of patients' risk for HCC, diagnostic accuracy of the imaging tool, and costs of examinations.

Conflicts of Interest

The authors declare no conflicts of interest relevant to this article.

FINANCIAL DISCLOSURE

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