Gadoxetic acid-based hepatobiliary MRI in hepatocellular carcinoma

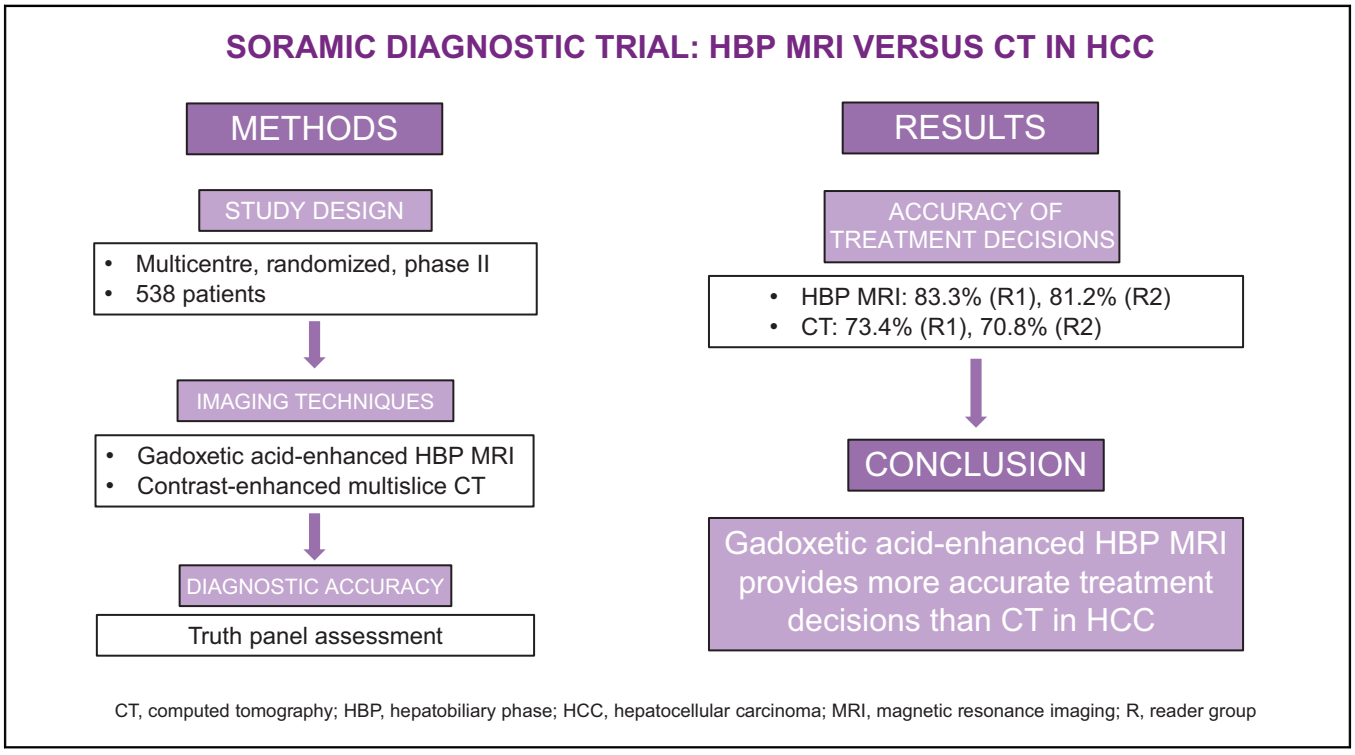
Authors

Jens Ricke, Ingo G. Steffen, Irene Bargellini, Thomas Berg, José Ignacio Bilbao Jaureguizar, Bernhard Gebauer, Roberto Iezzi, Christian Loewe, Musturay Karçaaltincaba, Maciej Pech, Christian Sengel, Otto van Delden, Vincent Vandecaveye, Christoph J. Zech, Max Seidensticker

Correspondence

jens.ricke@med.uni-muenchen.de (J. Ricke).

Graphical abstract



CT, computed tomography; HBP, hepatobiliary phase; HCC, hepatocellular carcinoma; MRI, magnetic resonance imaging; R, reader group

Highlights

- Comparison of gadoxetic acid-enhanced MRI *vs.* contrast-enhanced multi-slice CT to stratify patients with suspected HCC.
- Clinical decision-making was shown to be significantly more accurate with gadoxetic acid-enhanced hepatobiliary MRI than CT.
- To the best of our knowledge, this is the first study linking a clinical decision endpoint to hepatobiliary MRI criteria for HCC diagnosis.
- The results of our international multicentre trial could guide recommendations on the diagnostic management of HCC.

https://doi.org/10.1016/j.jhepr.2020.100173

Lay summary

Patients with hepatocellular carcinoma are allocated to curative or palliative treatment according to the stage of their disease. Hepatobiliary imaging using gadoxetic acid-enhanced MRI is more accurate than CT for treatment decision-making.

Research article

JHEP|Reports

Gadoxetic acid-based hepatobiliary MRI in hepatocellular carcinoma

Jens Ricke,[1,*] Ingo G. Steffen,[1] Irene Bargellini,[2] Thomas Berg,[3] José Ignacio Bilbao Jaureguizar,[4] Bernhard Gebauer,[5] Roberto Iezzi,[6] Christian Loewe,[7] Musturay Karçaaltincaba,[8] Maciej Pech,[9] Christian Sengel,[10] Otto van Delden,[11] Vincent Vandecaveye,[12] Christoph J. Zech,[13] Max Seidensticker[1]

[1]*Department of Radiology, Ludwig-Maximilians-University Munich, Munich, Germany;* [2]*Department of Interventional Radiology, Pisa University Hospital, Pisa, Italy;* [3]*Klinik und Poliklinik für Gastroenterologie, Sektion Hepatologie, Universitätsklinikum Leipzig AöR, Leipzig, Germany;* [4]*Department of Radiology, Clínica Universidad de Navarra, Pamplona, Spain;* [5]*Department of Radiology, Charité-Universitätsmedizin Berlin, Berlin, Germany;* [6]*Dipartimento di Diagnostica per Immagini, Radioterapia Oncologica ed Ematologia, Fondazione Policlinico Universitario A. Gemelli IRCCS, UOC di Radiologia, Rome, Italy;* [7]*Section of Cardiovascular and Interventional Radiology, Department of Bioimaging and Image-Guided Therapy, Medical University of Vienna, Vienna, Austria;* [8]*Department of Radiology, Hacettepe University School of Medicine, Ankara, Turkey;* [9]*Department of Radiology and Nuclear Medicine, University of Magdeburg, Magdeburg, Germany;* [10]*Radiologie interventionnelle vasculaire et percutanée, CHU de Grenoble, Grenoble, France;* [11]*Department of Radiology and Nuclear Medicine, Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands;* [12]*Department of Radiology, University Hospitals Leuven, Leuven, Belgium;* [13]*Radiology and Nuclear Medicine, University Hospital Basel, University of Basel, Basel, Switzerland*

JHEP Reports **2020.** https://doi.org/10.1016/j.jhepr.2020.100173

Background & Aims: SORAMIC is a prospective phase II randomised controlled trial in hepatocellular carcinoma (HCC). It consists of 3 parts: a diagnostic study and 2 therapeutic studies with either curative ablation or palliative Yttrium-90 radioembolisation combined with sorafenib. We report the diagnostic cohort study aimed to determine the accuracy of gadoxetic acid-enhanced magnetic resonance imaging (MRI), including hepatobiliary phase (HBP) imaging features compared with contrast-enhanced computed tomography (CT). The primary objective was the accuracy of treatment decisions stratifying patients for curative or palliative (non-ablation) treatment.

Methods: Patients with clinically suspected HCC underwent gadoxetic acid-enhanced MRI (HBP MRI, including dynamic MRI) and contrast-enhanced CT. Blinded read of the image data was performed by 2 reader groups (radiologists, R1 and R2). A truth panel with access to all clinical data and follow-up imaging served as reference. Imaging criteria for curative ablation were defined as up to 4 lesions <5 cm and absence of macrovascular invasion. The primary endpoint was non-inferiority of HBP MRI *vs.* CT in a first step and superiority in a second step.

Results: The intent-to-treat population comprised 538 patients. Treatment decisions matched the truth panel assessment in 83.3% and 81.2% for HBP MRI (R1 and R2), and 73.4% and 70.8% for CT. Non-inferiority and superiority (second step) of HBP MRI *vs.* CT were demonstrated (odds ratio 1.14 [1.09–1.19]). HBP MRI identified patients with >4 lesions significantly more frequently than CT.

Conclusions: In HCC, HBP MRI provided a more accurate decision than CT for a curative *vs.* palliative treatment strategy.

Introduction

Hepatocellular carcinoma (HCC) accounts for 80–90% of all liver cancers.[1–3] Curative treatment options, such as surgical resection, liver transplantation, or percutaneous ablation, are limited to early-stage cancers.[4] Global staging systems foresee only palliative treatment options in stages beyond local treatment, including transarterial chemoembolisation in intermediate and systemic treatment in advanced stages.[5–8]

The hallmark of HCC radiological imaging is the arterial enhancement of contrast media in the arterial phase, followed by washout during the portovenous or venous phase.[9] Lesions frequently missed are those with atypical features, such as arterial hyper-perfusion without washout, as well as early HCC with arterial hypoperfusion. In addition, high-grade dysplastic nodules (HGDNs) are of utmost interest for invasive treatment decisions, as they represent a distinct pre-malignancy and, depending on size, may frequently display HCC islets.[10,11]

Current diagnostic imaging recommendations in North America and Europe focus on arterial enhancement and washout criteria.[8,12] In addition to those perfusion patterns, current Asia Pacific guidelines recommend gadoxetic acid-enhanced hepatobiliary phase magnetic resonance imaging (HBP MRI) as a first-line tool for radiological workup.[13] Inclusion of additional HBP features enhancing sensitivity (*e.g.* hypo-intensity on HBP

Keywords: Gadoxetic acid; Hepatocellular carcinoma; Magnetic resonance imaging; SORAMIC trial.

Received 12 June 2020; received in revised form 6 August 2020; accepted 10 August 2020; available online 24 August 2020

* Corresponding author. Address: Department of Radiology, Ludwig-Maximilians-Universität München, Marchioninistrasse 15, 81377 Munich, Germany. Tel.: +49 4400 72750.

E-mail address: jens.ricke@med.uni-muenchen.de (J. Ricke).

imaging to replace washout on standard extracellular contrast media MRI) is justified by the greater use of resection or ablation in Asia, with a focus on enhancing sensitivity, whereas in North America and Europe, high focus on specificity ensures optimal compliance with regulations for organ allocation in liver transplantation.[8]

Sorafenib and Micro-Therapy Guided by Gadolinium-EOB-DTPA-Enhanced MRI (SORAMIC) (EudraCT2009-012576-27; NCT01126645) is a prospective study that comprises 3 sub-studies:

- Gd-EOB-DTPA (gadoxetic acid: Eovist® and Primovist®)-enhanced MRI *vs.* contrast-enhanced multi-slice computed tomography (CT) for the stratification of patients to a local ablation or palliative treatment group;
- Radiofrequency ablation (RFA) plus sorafenib *vs.* RFA plus matching placebo on time to recurrence; and
- Yttrium-90 (Y90) radioembolisation combined with sorafenib compared with sorafenib alone on overall survival.[14]

This paper reports on the outcomes of the diagnostic cohort, which has been designed to determine the value of HBP MRI employing gadoxetic acid for treatment decisions in patients with HCC.

Patients and methods

SORAMIC is a prospective phase II open-label, multicentre, randomised controlled trial. The study was conducted at 38 sites in 12 countries in Europe and Turkey. The study was approved by the institutional review boards of all participating centres. All patients gave written informed consent before entering the study.

Study objectives

The primary objective of the diagnostic cohort of SORAMIC was to confirm in a 2-step procedure that gadoxetic acid-enhanced HBP MRI is non-inferior (first step) or superior (second step) compared with contrast-enhanced multi-slice CT for the stratification of patients to a palliative *vs.* (curative intent) local ablation treatment strategy. A truth panel served as reference standard. Secondary endpoints included the number of detected lesions and the diagnostic confidence in gadoxetic acid-enhanced MRI *vs.* contrast-enhanced CT.

Patient selection

Patients with HCC confirmed by histology or non-invasive criteria underwent gadoxetic acid-enhanced MRI and contrast-enhanced CT. Barcelona Clinic Liver Cancer (BCLC) stages A, B, and C, as well as Child-Pugh A through B7, were eligible for inclusion.

Patient and public involvement statement

- At what stage in the research process were patients/the public first involved in the research and how?
  - Gadoxetic acid is an approved liver-specific contrast agent. This study was initiated to validate its potential for therapeutic decision in HCC. First public appearance was filing with authorities.
- How were the research question(s) and outcome measures developed and informed by their priorities, experience, and preferences?
  - Outcome measures are clinically oriented, defining the value of the experimental drug/approach for treatment decisions in hepatocellular cancer.
- How were patients/the public involved in the design of this study?
  - There was no involvement other than considering publicly available data.
- How were they involved in the recruitment to and conduct of the study?
  - There was no involvement.
- Were they asked to assess the burden of the intervention and time required to participate in the research?
  - All study examinations were based on clinical standard examinations. There was no extra burden for the patients.
- How were (or will) they be involved in the plans to disseminate the study results to participants and relevant wider patient communities (*e.g.* by choosing what information/results to share, when, and in what format)? If patients were not involved, please state this.
  - There was no involvement.

Assessments and imaging

All patients underwent contrast-enhanced CT and gadoxetic acid-enhanced MRI within 2 weeks following a standardised protocol, approved by the study Steering Committee. For details of the imaging parameters, see Information S6 and Table S1. The CT protocol consisted of a pre-contrast, an arterial, and a portovenous phase of the upper abdomen and a venous phase of the whole abdomen. The delay for the arterial and portovenous phases was 15 and 50 sec, respectively, after bolus tracking reached 100 HU in the descending aorta. The venous phase was obtained 120 sec after the start of injection. The independent read required arterial, portovenous, and venous phase image data.

The gadoxetic acid MRI protocol consisted of pre-contrast T1-weighted gradient echo (GRE) sequences (2D and 3D). After injection of gadoxetic acid (volume 0.1 ml/kg; injection rate 1.5 ml/sec), dynamic T1-weighted GRE 3D sequences were acquired in the late arterial phase (15 sec after bolus detected in the aorta), portovenous phase (60–70 sec after injection), and venous phase (120 sec after injection). T2-weighted turbo spin-echo 2D sequences with and without fat suppression were added, as well as diffusion-weighted imaging (DWI) (not mandatory). In the HBP at 20 min post-contrast injection, T1-weighted GRE 2D and 3D sequences were performed. Mandatory sequences for the independent read were T1-weighted GRE 3D pre-contrast, arterial phase, portovenous phase, venous phase, and HBP; coronal T1-weighted GRE 3D, HBP; and axial T2-weighted turbo spin echo (TSE) (Table S1; Information S6).

Clinical data recorded at study inclusion as well as at each follow-up included Eastern Cooperative Oncology Group, Child-Pugh score, bilirubin, albumin, international normalised ratio, platelets, alpha-fetoprotein, as well as standard laboratory investigations. Patients were followed at 2-month intervals for a minimum of 24 months or until death.

Definition of the study population

A total of 692 patients were included in the diagnostic study of the SORAMIC trial. Patients with both imaging modalities (contrast-enhanced CT and gadoxetic acid-enhanced MRI) and data sets fulfilling the mandatory criteria were defined as the

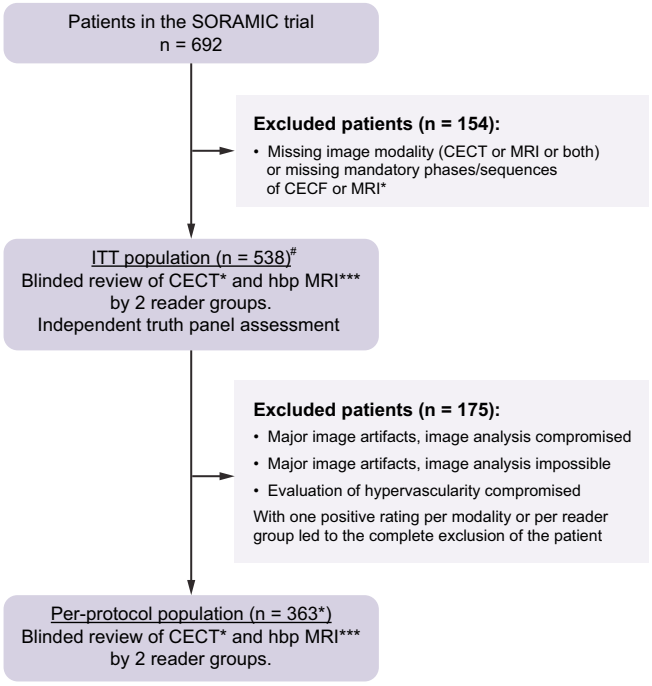


Fig. 1. CONSORT diagram. *Mandatory phases/sequences were arterial, portovenous, and venous phases for CECT and axial T1 3D pre-contrast, arterial, portovenous, venous, and HBP; coronal T1 3D HBP; and axial T2 TSE with or without fat saturation for MRI. **Imaging criteria for HCC in CECT and MRI: arterial enhancement and washout. ***Extended imaging criteria for HCC, including HBP MRI: arterial enhancement, no washout, and hypo- or hyperintensity in HBP; no arterial enhancement, washout, and hypo-intensity in the hepatobiliary phase; and no arterial enhancement, no washout, but hypointensity in the hepatobiliary phase. #Including 91 screening failures of the therapeutic study arms of the SORAMIC trial. +Including 60 screening failures of the therapeutic study arms of the SORAMIC trial. CECT, contrast-enhanced computed tomography; CT, computed tomography; HBP, hepatobiliary phase; ITT, intent to treat; MRI, magnetic resonance imaging; SORAMIC, Sorafenib and Micro-Therapy Guided by Gadolinium-EOB-DTPA-Enhanced MRI; TSE, turbo spin echo.

intent-to-treat (ITT) population (n = 538). The per-protocol (PP) population was defined by absence of major image artefacts (n = 363) (Fig. 1).

Blinded image read

CT and MRI images acquired at study inclusion were evaluated by 2 reader groups in blinded fashion. Reader group 1 (R1) consisted of 1 reader and reader group 2 (R2) of 6 readers. All readers were radiologists with >7 yr of experience in abdominal diagnostic imaging. The image read of each individual patient was performed in 2 separate reading sessions. In the first session, either a CT or an MRI image set was randomly presented to the readers. To minimise recall bias, the alternate image set of the patient was presented in a second session after a period of at least 2 weeks.

Truth panel assessment

Truth panel assessments were performed after study closure. The truth panel comprised a hepatologist with >10 yr of experience of management of patients with HCC and a radiologist at the same institution with >10 yr of experience in diagnostic and interventional radiology, responsible for CT and HBP MRI reads in the HCC unit. All decisions of the truth panel were taken by consensus. If no consensus was reached, an additional radiologist of similar experience assessed all available data, and the decision was taken by majority of votes. The truth panel had access to all CT and MRI images from baseline and all follow-up images obtained during the first year (complete follow-up image data available in n = 312 patients), as well as all clinical data. The panel determined the treatment recommendation for either ablation with curative intent, palliative treatment, or neither of these.

Criteria for diagnosing HCC and assignment to a treatment strategy

The imaging criteria for local ablation with curative intent were defined as up to 4 lesions <5 cm and absence of macrovascular invasion. For study inclusion and assessments, we allowed patients amenable for percutaneous as well as laparoscopic RFA, therefore including patients with peripheral and potentially difficult locations, such as adjacent to the heart or stomach. The imaging criteria for a palliative treatment strategy were tumour extent exceeding ablation criteria or presence of macrovascular invasion. The category 'neither' was chosen if no identifiable lesions were present, liver lesions identified did not show HCC characteristics, or tumour load of the whole liver was >70%. Extensive tumour load was added, as it represented an exclusion criterion from study arm III of SORAMIC (palliation study on Y90 radioembolisation).

The diagnostic criteria for HCC in the blinded read and truth panel were lesion diameter >1 cm and arterial enhancement and washout (typical HCC) for the dynamic image data set of both CT and MRI. The extended diagnostic criteria for HCC and HGDN in the HBP MRI data set are outlined in Fig. 2. Diagnosis of atypical HCC: arterial enhancement, no washout, and hypo- or hyperintensity in the HBP; early HCC: no arterial enhancement, but washout and hypo-intensity in the HBP; and HGDN: no arterial enhancement, no washout, but hypo-intensity in the HBP. A bright T2 signal intensity was used to exclude benign lesions, such as haemangioma.

Lesion number assessment was conducted for typical HCC, typical plus atypical HCC, as well as for typical plus atypical plus early HCC plus HGDN. The presence of hyper-vascularised lesions without washout as well as the number and size of early HCC and HGDN were assessed separately.

For details of the assessment of artefacts, macrovascular infiltration, added value of hepatobiliary imaging, and quality assurance, see Information S1 and Table S3.

Statistical analysis

Statistical analysis was performed using SAS (version 9.4; SAS Institute, USA) and the R Project (version 3.5.1; R Foundation for Statistical Computing, Austria). For sample size estimation, HBP MRI was assumed to show accuracies of 80–85% and CT of 80%, and the non-inferiority margin was set to −5% points, which is equivalent to an odds ratio (OR) of 0.75. If the lower limit of the 95% CI for the OR of the accuracies of HBP MRI and CT was above this limit, non-inferiority of HBP MRI was concluded. In the second step, the complete 95% CI for the OR had to be above 1 to show superiority of HBP MRI over CT. Simulation scenarios of generalised estimating equations (GEE) model with a 1-sided alpha of 2.5% revealed a power of 99.9% for the non-inferiority/superiority endpoint with the sample size of N = 519

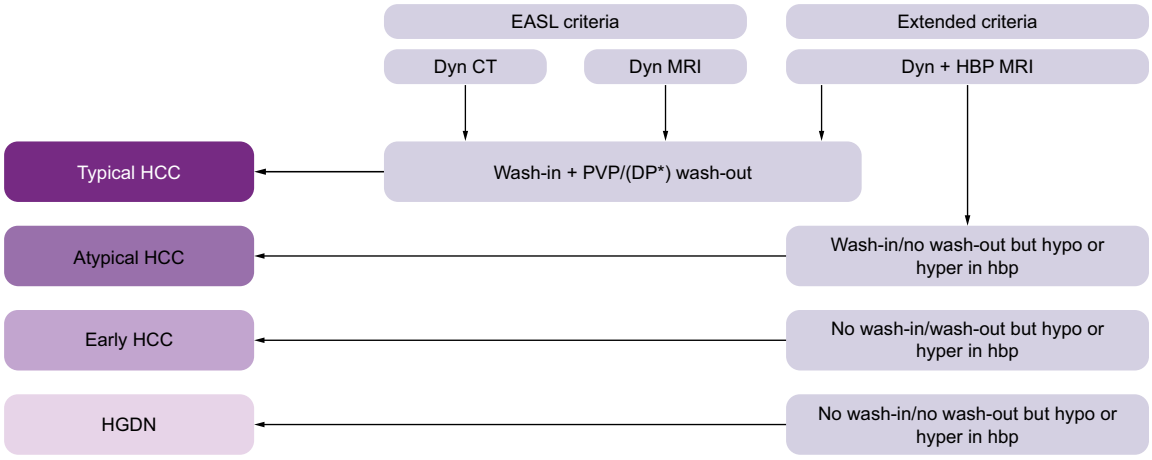


Fig. 2. Criteria for diagnosing HCC based on image data in both blinded read and truth panel. *Not in the HBP. CT, computed tomography; DP, delayed phase; Dyn, dynamic; EASL, European Association for the Study of the Liver; HBP, hepatobiliary phase; HGDN, high-grade dysplastic nodule; MRI, magnetic resonance imaging; PVP, portovenous phase.

(Information S2). Formally, this represents a non-inferiority design switched into a superiority design. The primary analysis of the primary efficacy variable was done with GEEs (SAS: PROC GENMOD) with independent working correlation matrix taking into account the correlations between readers and between modalities.

Descriptive statistics (n, mean, SD, median, minimum, and maximum) were calculated for each quantitative variable. Absolute and relative frequencies were determined for categorical data. Forest plots were used to depict ORs of accuracies among the data sets in association with confounding parameters. CIs for ORs are 2-sided in each case and provide 95% confidence.

The comparative analyses of the lesion detection rate, image artefacts, inter-reader agreement, as well as depiction of portal vein thrombosis or macrovascular invasion were not pre-planned, therefore were exploratory.

Results

Patients were recruited into the SORAMIC diagnostic study between January 5, 2011 and April 19, 2016. The ITT population comprised 538 patients. The baseline characteristics are displayed in Table 1, laboratory values in Table S2, PP population in Table S4, lesion characteristics in Table S6, and treatment allocation in Table S7. The PP population comprised 363 patients.

Primary endpoint

HBP MRI employing extended criteria for the diagnosis of HCC showed superiority of correct treatment decisions compared with contrast-enhanced CT employing perfusion criteria for the diagnosis of HCC. The results were 83.3% and 81.2% (R1 and R2) for HBP MRI and 73.4% and 70.8% for CT (OR 1.14 [1.09–1.19]). As the 2-sided 95% CI was completely above 1, non-inferiority and, consecutively, superiority were concluded.

Additional blinded read results

Inter-reader agreement in the ITT population is displayed in Table S5.

In the PP population, the accuracies of treatment decisions employing HBP MRI were 84.8% and 81.0% for R1 and R2, respectively. This compared to 76.6% and 71.6% when employing CT (OR 1.12 [1.07–1.17]). Imaging artefacts therefore had no impact on the accuracy of treatment decisions for HBP MRI (Tables 2–4; Fig. 3; Table S3).

Results of the GEE analysis, including factors with potential influence on the accuracy of treatment decisions, are shown in Fig. 3.

Lesion detection rate

Dichotomised assessment of the lesion number (0–4 *vs.* >4) showed 0–4 identified lesions in 65.8% (R1) and 62.6% (R2) of patients employing CT, in 65.6% (R1) and 62.1% (R2) employing HBP MRI (typical and atypical HCC), and in 61.3% (R1) and 52.2% (R2) employing HBP MRI (extended criteria covering typical and atypical HCC, as well as early HCC and HGDN; OR and CI displayed in Information S3).

Artefacts

The analyses of MRI artefacts included a separate analysis of MRI contrast dynamics and the HBP imaging added for HBP MRI. Image quality of CT (good *vs.* average and poor) was statistically superior compared with HBP MRI as well as with MRI contrast dynamics. Major artefacts compromising the analysis (*i.e.* exclusion criteria for the PP analysis) were less frequent in CT (R1 1.9%/R2 8%) compared with HBP MRI in R2 (R1 1.1%/R2 2.2%), and more frequent in MRI contrast dynamics compared with CT and HBP MRI (R1 7.6%/R2 22.1%), indicating that incorrect timing of the arterial phase and movement artefacts of the MRI contrast dynamics contributed mainly to relevant artefacts in MRI of the liver. For detailed information, see Table S3.

Portal vein thrombosis and macrovascular invasion

For results of portal vein thrombosis or macrovascular invasion, see Information S5.

Table 1. Baseline characteristics.

	Median	IQR	n	Valid (%)
Sex (17*)				
Women	–	–	69	13.2
Men	–	–	452	86.8
Age (yr) (17*)	66	59–73	–	–
≤65	–	–	249	47.8
>65	–	–	272	52.2
Race (38*)				
White	–	–	468	93.6
Other	–	–	32	6.4
Previous HCC treatment (19*)				
Yes	–	–	150	28.9
No	–	–	369	71.1
Previous HCC treatments in detail				
TACE or TAE	–	–	102	19.7
Resection	–	–	44	8.5
RFA	–	–	40	7.7
Other	–	–	15	2.9
Liver cirrhosis (23*)				
Yes	–	–	418	81.2
No	–	–	97	18.8
ECOG (31*)				
<2	–	–	498	98.3
≥2	–	–	9	1.7
HCC diagnosis by (19*)				
Histology	–	–	223	43
Imaging criteria	–	–	291	56.1
Other	–	–	5	0.9
Cause of disease†				
Alcohol abuse	–	–	225	41.8
Hepatitis B or C	–	–	185	34.4
NASH	–	–	49	9.1
NAFLD	–	–	27	5
Haemochromatosis	–	–	15	2.8
Other	–	–	56	10.4
Alcohol abuse only (no other cause)	–	–	182	33.8
Hepatitis B or C only (no other cause)	–	–	149	27.7
No hepatitis B or C; no alcohol abuse	–	–	125	23.2
Hepatitis B or C and alcohol abuse	–	–	25	4.6
Child-Pugh score (23*)				
A	–	–	458	88.9
B	–	–	55	10.7
C	–	–	2	0.4
BCLC stage (25*)				
0	–	–	6	1.2
A	–	–	93	18.1
B	–	–	144	28.1
C	–	–	269	52.4
D	–	–	1	0.2
Metastases (21*)				
Yes	–	–	90	17.4
No	–	–	427	82.6
Specified				
Lymph node	–	–	49	9.5
Bone	–	–	10	1.9
Other	–	–	31	6
Study arm				
Curative arm	–	–	95	17.7
Palliative arm	–	–	354	65.8
Screen failure	–	–	89	16.5

ITT population (n = 538).
BCLC, Barcelona Clinic Liver Cancer; ECOG, Eastern Cooperative Oncology Group; IQR, inter-quartile range; ITT, intent to treat; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; RFA, radio-frequency ablation; TACE, transarterial chemoembolisation; TAE, transarterial embolisation.
* Number of missing cases; reflect screening failures of the therapeutic study part of the SORAMIC study.
† Multiple answers possible.

Discussion

In the SORAMIC diagnostic study reported here, we demonstrate the capacity of HBP MRI to improve treatment decisions in patients suffering from early-stage *vs.* intermediate or advanced HCC. In comparison with state-of-the-art contrast-enhanced multi-slice CT, HBP MRI, including dynamic MRI, improved the accuracy of treatment decisions for curative ablation *vs.* a palliative treatment strategy based on the criteria of detecting up to 4 lesions <5 cm in diameter with an absence of macrovascular invasion. The accuracies of treatment decisions were 83.3% and 81.2% for HBP MRI by R1 and R2, and 73.4% and 70.8%, respectively, for CT (OR 1.14 [1.09–1.19]).

The properties of gadoxetic acid are different from those of extracellular MRI contrast agents, as, although both are gadolinium based and display similar perfusion properties, gadoxetic acid is taken up by hepatocytes and excreted via the biliary pathway.[15] Gadoxetic acid can therefore be used not only to display overt HCC by classic perfusion patterns, but also to display atypical HCC as well as lesions undergoing hepatocarcinogenesis, such as HGDN. Recently, Renzulli *et al.*[10] published a study involving 228 patients with 420 liver nodules undergoing HCC surveillance using gadoxetic acid-enhanced MRI. In total, 238 lesions were confirmed malignant by the American Association for the Study of Liver Diseases perfusion criteria; 3 by interval growth; and all other nodules, including 50 regenerative nodules and 19 HGDNs, were confirmed by histopathology. Similar to our definition, nodules failing to demonstrate arterial enhancement/washout were defined as

- atypical HCC: hyper-vascularity present in the arterial phase, no venous washout, but hypo-intensity in HBP MRI;
- early HCC: no arterial hyper-perfusion, but washout/hypo-intensity in HBP MRI and hyper-intensity in diffusion MRI; and
- HGDN: no arterial enhancement, but hypo-intensity in HBP MRI and no hyper-intensity in diffusion MRI.

Compared with perfusion criteria, Renzulli *et al.* reported an increased sensitivity of 96% *vs.* 76.4% (p <0.001), as well as a specificity of 91.8% *vs.* 98.6%, respectively (p = 0.063).[10] Golfieri *et al.* reported that, in gadoxetic acid-enhanced MRI, HBP hypo-intensity was the strongest indicator of malignancy in atypical liver lesions, with 88% sensitivity and 97% specificity.[16]

Controversy surrounding HBP MRI has revolved around uncertainties of depicting a clear washout signal in the venous phase. Gadoxetic acid uptake enhances the signal of liver parenchyma starting at approximately 90 sec after injection. Therefore, the lesion-to-liver contrast at some point during washout may not be true washout any longer.[17] The American College of Radiology (LI-RADS committee) recommends assessing washout with gadoxetic acid only during the portovenous phase.[18] In the Asian Pacific Association for the Study of the Liver (APASL) guideline, gadoxetic acid-enhanced MRI is accepted as a first-line diagnostic test. Hypo-intensity on the transitional phase or during HBP replaces washout on extracellular contrast-enhanced MRI.[13] In our own study, any signal decrease of a lesion during the portovenous or venous phase was considered positive for washout when assessing the dynamic MR image data set of gadoxetic acid. The full HBP data set allowed

Table 2. Accuracy of treatment decision and comparison of modalities (accuracy of treatment recommendation).

	CT		HBP MRI[†]	
	Reader 1 (%)	Reader 2 (%)	Reader 1 (%)	Reader 2 (%)
ITT (n = 538)[*]	73.4	70.8	83.3	81.2
PP (n = 363)[*]	76.6	71.6	84.8	81.0
Histological verified cases only (n = 223)[*]	78.5	74.0	87.0	87.4

CT, computed tomography; HBP, hepatobiliary phase; ITT, intent to treat; MRI, magnetic resonance imaging; PP, per protocol.
[*] Compared with truth panel.
[†] Employing extended HCC criteria.

Table 3. Accuracy of treatment decision and comparison of modalities (odds ratio by reader group).

	CT			
	Reader group 1		Reader group 2	
	OR	CI (LCI/UCI)	OR	CI (LCI/UCI)
ITT				
HBP MRI compared with	1.80	1.34/2.42	1.8	1.34/2.37
PP				
HBP MRI compared with	1.71	1.18/2.49	1.69	1.19/2.39
ITT histological verified cases only				
HBP MRI compared with	1.83	1.11/3.04	2.45	1.49/4.02

CT, computed tomography; HBP, hepatobiliary phase; ITT, intent to treat; LCI, lower CI; MRI, magnetic resonance imaging; OR, odds ratio; UCI, upper CI.

Table 4. Accuracy of treatment decision and comparison of modalities (odds ratio by modality).

	CT	
	OR	CI (LCI/UCI)
ITT		
HBP MRI compared with	1.14	1.09/1.19
PP		
HBP MRI compared with	1.12	1.07/1.17
ITT histological verified cases only		
HBP MRI compared with	1.14	1.08/1.21

Based on GEE with independent working correlation matrix. CT, computed tomography; GEE, generalised estimating equation; HBP, hepatobiliary phase; ITT, intent to treat; LCI, lower CI; MRI, magnetic resonance imaging; OR, odds ratio; PP, per protocol; UCI, upper CI.

for HCC diagnosis by adding hypo-intensity in the HBP, proving significant benefit over contrast-enhanced CT.

Image artefacts during arterial phase MR imaging were frequent in our study. At the time of study initiation, multi-arterial phase imaging was not established and therefore not included as part of the imaging protocol. Today, multi-arterial acquisition most likely would improve the number of non-diagnostic arterial phase scans.[19]

Gadoxetic acid uptake by hepatocytes may be altered by poor liver function.[20] The negative impact of a diminished liver function on the accuracy of treatment decisions was similar on HBP MRI compared with dynamic CT (Fig. 3). This finding suggests that even in Child-Pugh B7 or bilirubin-albumin score 2 patients, HBP MRI may be recommended. In addition, HBP MRI appeared to perform independently of the number and size of lesions, the presence of portal vein invasion/macrovascular invasion, or history of previous treatments. Although more patients showed significant imaging artefacts in MRI, the influence on treatment decision-making was not impaired and the diagnostic gain specifically with HBP MRI clearly outperformed this disadvantage.

The strength of our study is that its primary endpoint targets a clinical therapeutic decision rather than lesion count. The number of lesions detected with HBP MRI in our own study was increased over the CT count, in agreement with previous studies.[21–26] Two individual studies compared imaging techniques for staging and follow-up after intervention, respectively. A retrospective comparison against dynamic CT for staging HCC reported that gadoxetic acid-enhanced MRI provided significantly greater sensitivity (90.6% *vs.* 79.5%; p <0.0001) and more accurate BCLC staging (92.8% *vs.* 80.5%; p <0.0001). BCLC stage was correctly changed after gadoxetic acid-enhanced MRI in 13.8% patients.[27] Gadoxetic acid-enhanced MRI was also superior to CT for detecting intrahepatic recurrence post-curative surgery in patients with HCC. In a lesion-by-lesion analysis, the sensitivity was significantly higher for gadoxetic acid-enhanced MRI (100% for reviewer 1 and 97% for reviewer 2) than on multi-detector CT (44.4% and 66.6%) (p <0.005; both reviewers).[28]

Current HCC treatment guidelines in the Western world emphasise the highest possible specificity while accepting lower sensitivity caused by the apparent presence of HCCs without a typical perfusion pattern.[12] However, for optimal patient assignment to local ablative therapies or resection as preferred in Asia, a complete assessment of any HCC or borderline nodule is mandatory. This strategy may have motivated the inclusion of gadoxetic acid-enhanced MRI over extracellular contrast-enhanced MRI as a first-line diagnostic test in the APASL guideline.[13] For the same reason, the definition of target lesions in our study included atypical HCC, early HCC, and HGDN. Despite proven positive effects on early tumour recurrence and survival after ablation or resection, inclusion of such lesions in treatment strategies is still controversial.[29–34]

A trial limitation was that the truth panel assessment was not based on histopathology. In a study comprising non-transplant patients, this is unavoidable. However, given the extensive pre- and post-treatment data sets and the high patient number, the potential bias most likely had no impact on the study outcome. The criteria followed by the truth panel as well as the independent readers to allocate an individual to local ablation exceeded the established recommendations of all major guidelines by suggesting a maximum of 4 lesions up to 5 cm diameter for local ablation. These inclusion criteria for the local ablation arm of SORAMIC had been proposed during the study development; they reflect the heterogeneity of treatment decisions and clinical reality in a European setting before 2010. However, we propose that the deviation from current treatment recommendations regarding size and number of lesions eligible for local therapy does not affect the study outcome favouring HBI MRI over CT, with most treatment decision modifications resulting from additional lesions detected in MRI. HBP MRI did not employ DWI, which today is part of MRI standard protocols, but was not standardised at study initiation, and therefore not included. We hypothesise that the inclusion of DWI would have improved MRI performance in our study even further. Our study results were obtained in a population displaying pretreatments in 30%, potentially inducing a bias towards higher presence of multiple nodules. In addition, our data were obtained from a European cohort dominated by white males, as well as limited to Child-Pugh A and B patients. Participating institutions comprised

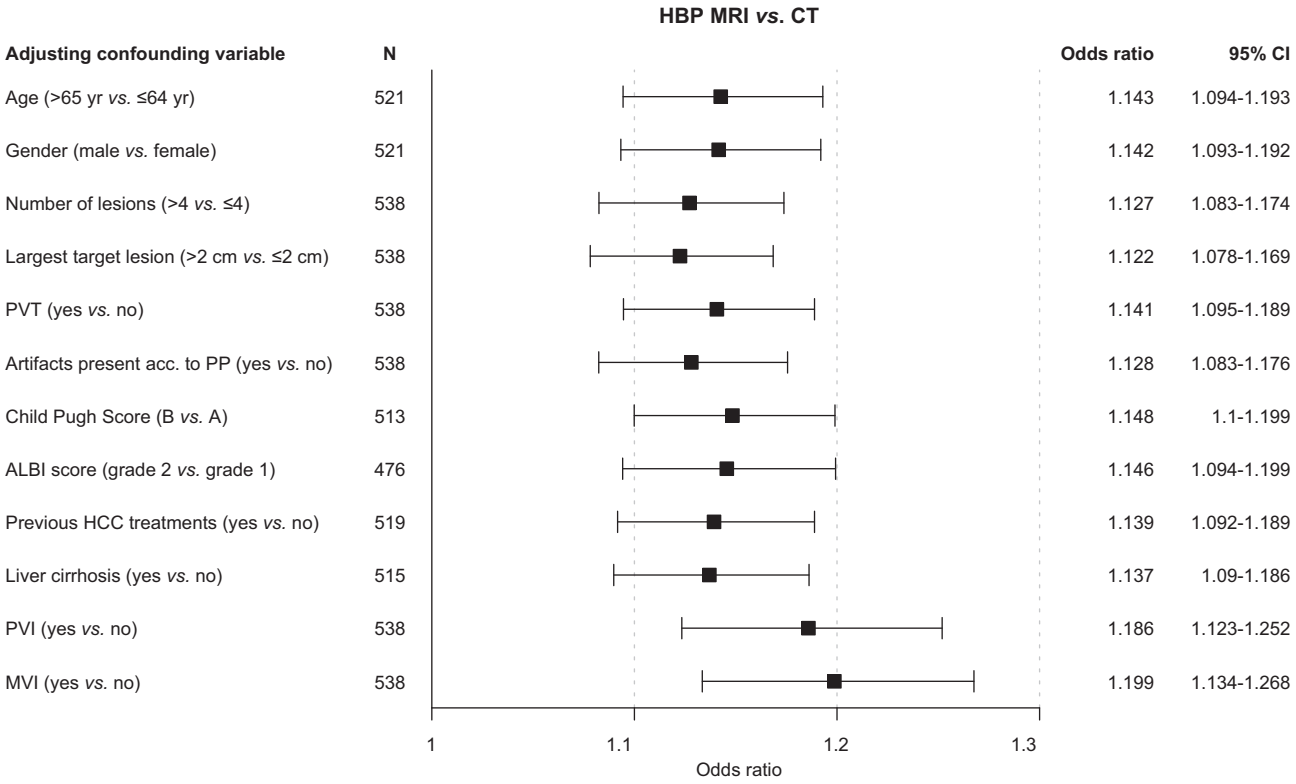


Fig. 3. Forest plots. Accuracy of the treatment decision, HBP MRI *vs.* CT (ITT population) based on GEE model, including confounding factors. Diagnostic items PVT, PVI, and MVI were evaluated in the dynamic MRI data set. CT, computed tomography; GEE, generalised estimating equation; HBP, hepatobiliary phase; ITT, intent to treat; MRI, magnetic resonance imaging; MVI, microvascular invasion; PVI, portal vein invasion; PVT, portal vein thrombosis.

high-volume centres with previous experience in HBP MRI in most cases.

HBP MRI employing extended criteria provided a more accurate decision than CT for curative *vs.* palliative treatments.

Abbreviations

APASL, Asian Pacific Association for the Study of the Liver; BCLC, Barcelona Clinic Liver Cancer; CT, computed tomography; DWI, diffusion-weighted imaging; GEE, generalised estimating equation; GRE, gradient echo; HBP, hepatobiliary phase; HCC, hepatocellular carcinoma; HGDN, high-grade dysplastic nodule; ITT, intent to treat; MRI, magnetic resonance imaging; OR, odds ratio; PP, per protocol; RFA, radio-frequency ablation; SORAMIC, Sorafenib and Micro-Therapy Guided by Gadolinium-EOB-DTPA-Enhanced MRI; TSE, turbo spin echo.

Financial support

SORAMIC is an investigator-initiated trial sponsored by the University of Magdeburg. Financial support was granted by Sirtex Medical and Bayer HealthCare, Germany.

Conflicts of interest

Jens Ricke reports grants and personal fees from Sirtex Medical and Bayer HealthCare. Ingo G. Steffen reports grants from Sirtex Medical and Bayer HealthCare. Irene Bargellini reports grants and personal fees from BTG Ltd, Sirtex Medical, Terumo Europe, GE Healthcare, and Bayer HealthCare. Thomas Berg currently acts as an advisor to AbbVie, Alexion, Bayer, Bristol Myers Squibb, Gilead, Intercept, Janssen, MSD/Merck, Merz, Novartis, and Sequana Medical. He has received speaking honoraria from AbbVie, Alexion, Bayer, Bristol Myers Squibb, Eisai, Gilead, Intercept, Ipsen, Janssen, MSD/Merck, Merz, Novartis, Sirtex, and Sequana Medical in the past 2 yr. He has received grant support from AbbVie, Bristol Myers Squibb, Gilead, Humedics, Intercept, Janssen, MSD/Merck, Merz, Novartis, and Sequana Medical. José Ignacio Bilbao Jaureguizar reports grants and personal fees from Sirtex Medical. Bernhard Gebauer reports personal fees and non-financial support from Sirtex Medical; personal fees and non-financial support from Bayer HealthCare; personal fees from Sirtex Medical, Pfizer, Merck, ICON, Parexel, BD/CR BARD, Roche, Guerbet, and Eisai. Roberto Iezzi reports grants and personal fees from Sirtex Medical. Musturay Karçaaltincaba reports personal fees from Bayer, GE Healthcare, and Pfizer. Maciej Pech reports grants from Bayer HealthCare, and grants and personal fees from Sirtex. Christoph J. Zech reports grants and personal fees from Bayer HealthCare. Max Seidensticker reports grants and personal fees from Sirtex and Bayer HealthCare. The other authors report nothing to disclose.

Please refer to the accompanying ICMJE disclosure forms for further details.

Authors' contributions

Study design: Jens Ricke, Max Seidensticker. Literature research: Jens Ricke, Max Seidensticker. Data collection: all authors. Data analysis: Jens Ricke, Musturay Karçaaltincaba, Max Seidensticker. Data interpretation: Jens Ricke, Ingo G. Steffen, Irene Bargellini, Thomas Berg, José Ignacio Bilbao Jaureguizar, Bernhard Gebauer, Roberto Iezzi, Christian Loewe, Musturay Karçaaltincaba, Maciej Pech, Otto van Delden, Vincent Vandecaveye, Christoph J. Zech, Max Seidensticker. Writing of paper: Jens Ricke, Max Seidensticker. Editing of paper: Jens Ricke, José Ignacio Bilbao Jaureguizar, Max Seidensticker. Review of paper: Ingo G. Steffen, Irene Bargellini, Thomas Berg, Bernhard Gebauer, Roberto Iezzi, Christian Loewe, Musturay Karçaaltincaba, Maciej Pech, Christian Sengel, Otto van Delden, Vincent Vandecaveye, Christoph J. Zech.

Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhepr.2020.100173.

References

[1] Perz JF, Armstrong GL, Farrington LA, Hutin YJ, Bell BP. The contributions of hepatitis B virus and hepatitis C virus infections to cirrhosis and primary liver cancer worldwide. J Hepatol 2006;45:529–538.

[2] Crissien AM, Frenette C. Current management of hepatocellular carcinoma. Gastroenterol Hepatol 2014;10:153–161.

[3] Balogh J, Victor 3rd D, Asham EH, Burroughs SG, Boktour M, Saharia A, et al. Hepatocellular carcinoma: a review. J Hepatocell Carcinoma 2016;3:41–53.

[4] Mazzaferro V, Llovet JM, Miceli R, Bhoori S, Schiavo M, Mariani L, et al. Predicting survival after liver transplantation in patients with hepatocellular carcinoma beyond the Milan criteria: a retrospective, exploratory analysis. Lancet Oncol 2009;10:35–43.

[5] Vogel A, Cervantes A, Chau I, Daniele B, Llovet JM, Meyer T, et al. Hepatocellular carcinoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2018;29(Suppl. 4):iv238–v255.

[6] Heimbach JK, Kulik LM, Finn RS, Sirlin CB, Abecassis MM, Roberts LR, et al. AASLD guidelines for the treatment of hepatocellular carcinoma. Hepatology 2018;67:358–380.

[7] Bruix J, Sherman M. Management of hepatocellular carcinoma. Hepatology 2005;42:1208–1236.

[8] European Association for the Study of the Liver. EASL Clinical Practice Guidelines: management of hepatocellular carcinoma. J Hepatol 2018;69:182–236.

[9] Forner A, Llovet JM, Bruix J. Hepatocellular carcinoma. Lancet 2012;379:1245–1255.

[10] Renzulli M, Biselli M, Brocchi S, Granito A, Vasuri F, Tovoli F, et al. New hallmark of hepatocellular carcinoma, early hepatocellular carcinoma and high-grade dysplastic nodules on Gd-EOB-DTPA MRI in patients with cirrhosis: a new diagnostic algorithm. Gut 2018;67:1674–1682.

[11] Bolondi L, Gaiani S, Celli N, Golfieri R, Grigioni WF, Leoni S, et al. Characterization of small nodules in cirrhosis by assessment of vascularity: the problem of hypovascular hepatocellular carcinoma. Hepatology 2005;42:27–34.

[12] American College of Radiology. CT/MRI LI-RADS v2018, 2019. https://www.acr.org/Clinical-Resources/Reporting-and-Data-Systems/LI-RADS/CT-MRI-LI-RADS-v2018. [Accessed 7 January 2020].

[13] Omata M, Cheng AL, Kokudo N, Kudo M, Lee JM, Jia J, et al. Asia-Pacific clinical practice guidelines on the management of hepatocellular carcinoma: a 2017 update. Hepatol Int 2017;11:317–370.

[14] Ricke J, Klumpen HJ, Amthauer H, Bargellini I, Bartenstein P, de Toni EN, et al. Impact of combined selective internal radiation therapy and sorafenib on survival in advanced hepatocellular carcinoma. J Hepatol 2019;71:1161–1174.

[15] Frydrychowicz A, Lubner MG, Brown JJ, Merkle EM, Nagle SK, Rofsky NM, et al. Hepatobiliary MR imaging with gadolinium-based contrast agents. J Magn Reson Imaging 2012;35:492–511.

[16] Golfieri R, Grazioli L, Orlando E, Dormi A, Lucidi V, Corcioni B, et al. Which is the best MRI marker of malignancy for atypical cirrhotic nodules: hypointensity in hepatobiliary phase alone or combined with other features? Classification after Gd-EOB-DTPA administration. J Magn Reson Imaging 2012;36:648–657.

[17] Forner A, Rimola J, Ayuso C. Conclusive HCC diagnosis with hepatocyte-specific contrast-enhanced magnetic resonance imaging? Not yet. J Hepatol 2016;65:648–649.

[18] Hope TA, Fowler KJ, Sirlin CB, Costa EA, Yee J, Yeh BM, et al. Hepatobiliary agents and their role in LI-RADS. Abdom Imaging 2015;40:613–625.

[19] Yoon JH, Lee JM, Yu MH, Kim EJ, Han JK. Triple arterial phase MR imaging with gadoxetic acid using a combination of contrast enhanced time robust angiography, keyhole, and viewsharing techniques and two-dimensional parallel imaging in comparison with conventional single arterial phase. Korean J Radiol 2016;17:522–532.

[20] Kanki A, Tamada T, Higaki A, Noda Y, Tanimoto D, Sato T, et al. Hepatic parenchymal enhancement at Gd-EOB-DTPA-enhanced MR imaging: correlation with morphological grading of severity in cirrhosis and chronic hepatitis. Magn Reson Imaging 2012;30:356–360.

[21] Lee YJ, Lee JM, Lee JS, Lee HY, Park BH, Kim YH, et al. Hepatocellular carcinoma: diagnostic performance of multidetector CT and MR imaging—a systematic review and meta-analysis. Radiology 2015;275:97–109.

[22] Liu X, Zou L, Liu F, Zhou Y, Song B. Gadoxetic acid disodium-enhanced magnetic resonance imaging for the detection of hepatocellular carcinoma: a meta-analysis. PLoS One 2013;8:e70896.

[23] Kim SH, Kim SH, Lee J, Kim MJ, Jeon YH, Park Y, et al. Gadoxetic acid-enhanced MRI versus triple-phase MDCT for the preoperative detection of hepatocellular carcinoma. AJR Am J Roentgenol 2009;192:1675–1681.

[24] Haradome H, Grazioli L, Tinti R, Morone M, Motosugi U, Sano K, et al. Additional value of gadoxetic acid-DTPA-enhanced hepatobiliary phase MR imaging in the diagnosis of early-stage hepatocellular carcinoma: comparison with dynamic triple-phase multidetector CT imaging. J Magn Reson Imaging 2011;34:69–78.

[25] Baek CK, Choi JY, Kim KA, Park MS, Lim JS, Chung YE, et al. Hepatocellular carcinoma in patients with chronic liver disease: a comparison of gadoxetic acid-enhanced MRI and multiphasic MDCT. Clin Radiol 2012;67:148–156.

[26] Di Martino M, Marin D, Guerrisi A, Baski M, Galati F, Rossi M, et al. Intraindividual comparison of gadoxetate disodium-enhanced MR imaging and 64-section multidetector CT in the detection of hepatocellular carcinoma in patients with cirrhosis. Radiology 2010;256:806–816.

[27] Choi SH, Byun JH, Kwon HJ, Ha HI, Lee SJ, Kim SY, et al. The usefulness of gadoxetic acid-enhanced dynamic magnetic resonance imaging in hepatocellular carcinoma: toward improved staging. Ann Surg Oncol 2015;22:819–825.

[28] Kim KA, Kim MJ, Choi JY, Park MS, Lim JS, Chung YE, et al. Detection of recurrent hepatocellular carcinoma on post-operative surveillance: comparison of MDCT and gadoxetic acid-enhanced MRI. Abdom Imaging 2014;39:291–299.

[29] Toyoda H, Kumada T, Tada T, Niinomi T, Ito T, Sone Y, et al. Non-hypervascular hypointense nodules detected by Gd-EOB-DTPA-enhanced MRI are a risk factor for recurrence of HCC after hepatectomy. J Hepatol 2013;58:1174–1180.

[30] Lee DH, Lee JM, Lee JY, Kim SH, Kim JH, Yoon JH, et al. Non-hypervascular hepatobiliary phase hypointense nodules on gadoxetic acid-enhanced MRI: risk of HCC recurrence after radiofrequency ablation. J Hepatol 2015;62:1122–1130.

[31] Kim HD, Lim YS, Han S, An J, Kim GA, Kim SY, et al. Evaluation of early-stage hepatocellular carcinoma by magnetic resonance imaging with gadoxetic acid detects additional lesions and increases overall survival. Gastroenterology 2015;148:1371–1382.

[32] Nault JC, Calderaro J, Di Tommaso L, Balabaud C, Zafrani ES, Bioulac-Sage P, et al. Telomerase reverse transcriptase promoter mutation is an early somatic genetic alteration in the transformation of premalignant nodules in hepatocellular carcinoma on cirrhosis. Hepatology 2014;60:1983–1992.

[33] Lee M, Kim K, Kim SY, Jung SH, Yoon J, Kim MS, et al. Genomic structures of dysplastic nodule and concurrent hepatocellular carcinoma. Hum Pathol 2018;81:37–46.

[34] Kumada T, Toyoda H, Tada T, Sone Y, Fujimori M, Ogawa S, et al. Evolution of hypointense hepatocellular nodules observed only in the hepatobiliary phase of gadoxetate disodium-enhanced MRI. AJR Am J Roentgenol 2011;197:58–63.