Authors' contributions

J Chen designed the study, received the grant supports and had full access to all data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. J Chen, QX Cai contributed to the writing and statistical analysis of the report. All authors contributed to data acquisition, data analysis, or data interpretation, and reviewed and approved the final version.

Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhep.2020.04.042.

References

Author names in bold designate shared co-first authorship

[1] **Cai Q**, **Huang D**, **Ou P**, Yu H, Zhu ZB, Xia Z, et al. COVID-19 in a designated infectious diseases hospital outside Hubei Province, China. Allergy 2020;75(7):1742–1752.

[2] Metlay JP, Waterer GW, Long AC, Anzueto A, Brozek J, Crothers K, et al. Diagnosis and treatment of adults with community-acquired pneumonia. An official clinical practice guideline of the American Thoracic Society and Infectious Diseases Society of America. Am J Respir Crit Care Med 2019;200(7):e45–e67.

[3] **Guan WJ**, **Ni ZY**, **Hu Y**, **Liang WH**, **Ou CQ**, **He JX**, et al. Clinical characteristics of coronavirus disease 2019 in China. N Engl J Med 2020;382(18):1708–1720.

[4] **Xu XW**, **Wu XX**, Jiang XG, Xu KJ, Ying LJ, Ma CL, et al. Clinical findings in a group of patients infected with the 2019 novel coronavirus (SARS-Cov-2) outside of Wuhan, China: retrospective case series. BMJ 2020;368:m606.

[5] **Wang D**, **Hu B**, Hu C, Zhu F, Liu X, Zhang J, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus–infected pneumonia in Wuhan, China. JAMA 2020;323(11):1061–1069.

[6] **Zhang C**, **Shi L**, Wang FS. Liver injury in COVID-19: management and challenges. Lancet Gastroenterol Hepatol 2020;5:428–430.

[7] Hikmet F, Méar Ln, Uhlén M, Lindskog C. The protein expression profile of ACE2 in human tissues. bioRxiv 2020. https://doi.org/10.1101/2020.03.31.016048 (preprints).

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Selection of MRI contrast agent and diagnostic criteria for HCC to maximize the advantages of contrast agents

To the Editor:

In the *Journal of Hepatology*, Paisant and colleagues[1] recently presented an interesting and timely study on comparisons between extracellular contrast agents (ECA) and hepatobiliary contrast agents (HBA) for the diagnosis of small hepatocellular carcinomas (HCCs), applying imaging criteria from different parts of the world. The authors should be congratulated for their results, especially as they performed this multicenter prospective study before the introduction of HBA into France. Even 10 years after the worldwide use of HBA and the active incorporation of HBA into the major clinical guidelines,[2–4] there remains a surprising paucity of studies comparing ECA and HBA in a head-to-head manner. The study of Paisant *et al.* took a step in the right direction by exploring the impacts of the choice of MRI contrast agent and diagnostic criteria. However, we would like to highlight some aspects requiring further consideration.

As this study found, restricting the timing of the "washout" appearance to the portal venous phase (PVP) on HBA-enhanced MRI significantly reduces the sensitivity of HCC diagnosis. This restriction seems unreasonable for HBA, as even with ECA, the washout appearance is more frequently depicted during the delayed phase than during the PVP.[5] Challenges in acquiring optimal arterial-phase gadoxetic acid-enhanced MRI could worsen the sensitivity further, although this can be mitigated by using multiple arterial phases or subtraction images. However, we find the authors' conclusion, claiming the superior performance of ECA over HBA, regardless of the applied criteria, to be concerning. Rather, it would be better to interpret the results as evidence that strict confinement of washout timing to the PVP on HBA-MRI, as endorsed by the western criteria, is not legitimate, given that the purpose of HBA-MRI is enhanced sensitivity. If hepatobiliary phase (HBP) hypointensity is not considered a major imaging feature, the main purpose of using HBA-MRI cannot be fully attained. In actual fact, in their study, the sensitivity of HBA-MRI (75.2%) considering HBP hypointensity as washout was higher than that of ECA-MRI (71.2%), although the difference was not statistically significant.

Considering HBP hypointensity as a major imaging feature can cost the specificity of HBA-MRI, in line with previous work.[6] Nevertheless, studies taking ancillary imaging features such as marked T2 hyperintensity or a targetoid appearance into account showed higher specificity (84.2–87.4%)[7,8] than a study not considering them (48.4%)[6] when washout timing

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was expanded. It was not described whether the authors considered ancillary imaging features to exclude common causes of false-positives such as hemangiomas or non-HCC malignancy. These ancillary imaging features have recently been added as exclusion criteria to the latest version of the Korean guidelines revised in 2018,[3] and are also included in the updated guidelines by the AASLD, although the European guidelines do not specifically describe their application. Given that modern liver MRI includes not only dynamic enhanced sequences, but also many other useful sequences, it is not possible to take full advantage of multi-parametric MRI information without considering ancillary imaging features. In addition, the specific details of false-positive cases diagnosed without pathologic diagnosis were not reported in the study. This information would be helpful to determine whether some false-positive cases would have been likely to be properly classified with consideration of ancillary imaging features.

It would be great if further details of the design of this study were to be clarified. This study was registered in ClinicalTrials.gov as NCT00848952; however, the study design, aim and the numbers at enrollment do not seem to exactly match that in the paper, which may require reasonable explanation. A previously published study[9] was also registered under the same identifier. Considering their importance, these studies are likely to be included in future meta-analyses. Thus, possible overlap with other study populations needs to be revealed in detail.

Lastly, we suppose that the performance of diagnostic tests for HCC should eventually be evaluated by the improvement of clinical outcomes including survival gain or reduction of mortality. Unlike those with end-stage liver disease in whom liver transplantation is the only curative treatment option, patients with preserved liver function and localized HCC may have a high chance of cure by surgical resection or image-guided ablation. The survival benefits of HBA over ECA in patients with localized HCC were demonstrated in a recent large scale cohort study including more than 30,000 patients,[10] and were attributed to the better sensitivity of HBA-MRI. Thus, the diagnostic criteria for HBA should be focused on boosting sensitivity with an acceptable loss in specificity, which can be countered by considering ancillary imaging features. In addition, appropriate diagnostic criteria should be applied according to the choice of MRI contrast agent to maximize the unique advantages of each agent.

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References
[1] Paisant A, Vilgrain V, Riou J, Oberti F, Sutter O, Laurent V, et al. Comparison of extracellular and hepatobiliary MR contrast agents for the diagnosis of small HCCs. J Hepatol 2020;72:937–945.
[2] EASL Clinical Practice Guidelines: Management of hepatocellular carcinoma. J Hepatol 2018;69:182–236.
[3] 2018 Korean Liver Cancer Association-National Cancer Center Korea practice guidelines for the management of hepatocellular carcinoma. Korean J Radiol 2019;20:1042–1113.
[4] Marrero JA, Kulik LM, Sirlin CB, Zhu AX, Finn RS, Abecassis MM, et al. Diagnosis, staging, and management of hepatocellular carcinoma: 2018 practice guidance by the American Association for the Study of Liver Diseases. Hepatology 2018;68:723–750.
[5] Jang HJ, Kim TK, Khalili K, Yazdi L, Menezes R, Park SH, et al. Characterization of 1-to 2-cm liver nodules detected on hcc surveillance ultrasound according to the criteria of the American Association for the Study of Liver Disease: is quadriphasic CT necessary? AJR Am J Roentgenol 2013;201:314–321.
[6] Joo I, Lee JM, Lee DH, Jeon JH, Han JK, Choi BI. Noninvasive diagnosis of hepatocellular carcinoma on gadoxetic acid-enhanced MRI: can hypointensity on the hepatobiliary phase be used as an alternative to washout? Eur Radiol 2015;25:2859–2868.
[7] Kim DH, Choi SH, Kim SY, Kim MJ, Lee SS, Byun JH. Gadoxetic acid-enhanced MRI of hepatocellular carcinoma: value of washout in transitional and hepatobiliary phases. Radiology 2019;292:270.
[8] Joo I, Lee JM, Lee DH, Jeon JH, Han JK. Retrospective validation of a new diagnostic criterion for hepatocellular carcinoma on gadoxetic acid-enhanced MRI: can hypointensity on the hepatobiliary phase be used as an alternative to washout with the aid of ancillary features? Eur Radiol 2019;29:1724–1732.
[9] Aube C, Oberti F, Lonjon J, Pageaux G, Seror O, N'Kontchou G, et al. EASL and AASLD recommendations for the diagnosis of HCC to the test of daily practice. Liver Int 2017;37:1515–1525.
[10] Kang TW, Kong SY, Kang D, Kang MW, Kim YK, Kim SH, et al. Use of gadoxetic acid-enhanced liver MRI and mortality in more than 30 000 patients with hepatocellular carcinoma: a nationwide analysis. Radiology 2020;295:114–124.

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