Editorial

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Non-enhanced MRI surveillance for HCC: A new tool for all, none or selected patients at risk?

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Despite the absence of high-quality randomized controlled trials, the results of meta-analyses and large prospective cohort studies suggest that ultrasound (US) surveillance for hepatocellular carcinoma (HCC) confers clinical benefit, with improved overall survival through detection of very early or early stage HCC leading to increased eligibility for potentially curative local treatments and transplantation.[1,2] Moreover, the cost-effectiveness of periodical HCC surveillance was reported in patients with cirrhosis in France and the United States.[3] In keeping with such results, hepatic US is currently the standard modality for periodical surveillance of cirrhosis and HCC screening,[4,5] with an optimum surveillance interval of 6 months, based on the median doubling time of HCC ranging from 3 months to 9 months. Studies showed that the 6-month interval is equivalent in efficacy to 3-month to 4-month intervals[6] and is better than a 12-month surveillance interval.[7] However, while US alone detects any stage HCC with 84% sensitivity, a recent meta-analysis highlights its suboptimal sensitivity for detection of HCC at an early stage, with sensitivity as low as 47%.[8] In addition, subgroups of patients, including obese individuals, patients with non-alcoholic steatohepatitis (NASH) or alcohol-related liver disease with severe fatty infiltration, and those with Child-Pugh B or C cirrhosis with a markedly coarse echotexture, may be particularly prone to suboptimal US quality and potential surveillance failure for early stage HCC,[9,10] leading to increasing use of contrast-enhanced CT- or MRI-based surveillance strategies in clinical practice. The benefit of adding periodic assays of alpha fetoprotein (AFP) to US has been investigated extensively, but results have proven inconclusive[4,8] and better surveillance modalities remain to be found.

Some studies have shown the potential benefit of using contrast-enhanced CT, but radiation hazards prevent any possible systematic use in a surveillance setting. More recently, studies have shown that the combination of the most sensitive MRI sequences – diffusion-weighted imaging (DWI) and gadoxetic-enhanced MRI sequence at the hepatobiliary phase – had high pooled sensitivity and specificity for any HCC detection, up to 83.1% (95% CI 72.0%–90.5%) and 89.1% (95% CI 86.5%–91.3%), respectively,[11,12] and early data suggest an abbreviated MRI protocol may retain high accuracy.[13–15] However, gadolinium was shown to accumulate in the brain,[16] although any possible clinical consequence remains to be demonstrated and it may also induce nephrogenic systemic fibrosis,[17] so the safety of periodic injections for years is unknown. Moreover, the use of contrast agents, especially with a hepatospecific phase, prolongs examination time and costs, hampering its possible application for universal surveillance. Indeed, the choice of surveillance modality must balance sensitivity to optimize early HCC detection, specificity to minimize surveillance-related harms, and costs to remain cost effective. In addition, surveillance modalities must not only be cost effective according to Porok's postulates, but also acceptable to patients.[18]

In this issue of the *Journal*, Park *et al.*[19] aimed to evaluate the diagnostic accuracy of non-enhanced MRI, consisting of DWI and T2-weighted imaging, and US for HCC in a series of 382 patients with high-risk HCC enrolled in a prospective cohort.[12] This study showed that non-enhanced MRI outperforms US in terms of sensitivity (per exam: 79% *vs.* 28%) and specificity (98% *vs.* 94.5%), with higher positive and negative predictive values (62% *vs.* 18% and 99% *vs.* 97%, respectively).

To our knowledge, this is among the first attempts to compare US with non-enhanced MRI in a systematic fashion. Although non-randomized, this study provides high-quality data emphasizing the performance of non-enhanced MRI as a surveillance tool for patients with cirrhosis at high risk of developing HCC. The main strength of the study is the double-blinded nature of non-enhanced MRI sequences. Conversely, the study suffers from some methodological limitations, worth noting before jumping to the conclusion that non-enhanced MRI should be immediately implemented as a surveillance imaging tool for every patient at risk of HCC. The most important limitation is its *post hoc* retrospective design (ancillary study to the prospective trial of Kim *et al.*[12]). Additional limitations are that i) all patients underwent MRI and US but comparison between the modalities is not exactly fair because US interpretation comes from initial examinations while MR examinations were all reviewed for research

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purposes by experts; indeed, this is a classical limitation with US that has to be pointed out. ii) The sensitivity of US in this study (by examination 28%; by lesion 25%) is much lower than the results of the meta-analysis by Tzartzeva *et al.*[8] (47% for early stages *vs.* 84% for all stages of HCC); this is all the more surprising since patients included in this study were lean (median body mass index 24.6 kg/m^2) and mainly infected by HBV in 72% of cases, corresponding to rather favorable conditions for US – HBV-related chronic liver disease is not known to be specifically associated with heterogeneity of the hepatic parenchyma or fatty infiltration unlike alcohol-related liver disease and NASH.[20] iii) The target population is highly selected, including patients with an annual risk of HCC over 5%; in addition, the results observed in this Asian population mainly infected by HBV preclude generalization of the results to Western populations. iv) There is a low proportion of biopsy-proven HCC (28%), the vast majority of diagnosis being made using CT scanning (72%) – a modality closer to MRI than to US. v) The clinical benefits of periodical surveillance with fast MRI is not obvious here as the number of patients amenable to curative treatment is surprisingly low (67.4%) for a screening study with such an accurate imaging tool, while far beyond the proportion described by Trinchet *et al.*[6] in their randomized control trial comparing 3- to 6-month US surveillance in patients with cirrhosis (61%). vi) Moreover, improvement in survival was not assessed and overall there is no evaluation of the cost-effectiveness of this strategy.

Additional issues limiting the possible universal replacement of US with non-enhanced MRI are: vii) the missing information about positive (hepatic and extrahepatic) findings in the study by Park,[19] which might translate into unnecessary additional investigations (*e.g.* detection of small intraductal pancreatic mucinous neoplasms, leading to costs and unjustified patient anxiety after a positive clinically low impact finding, since cirrhotic patients with portal hypertension are poor candidates for pancreatic prophylactic surgery). viii) The limited availability of MRI scanners given the longer equipment occupancy requested for MRI (even unenhanced) compared with US. Actually, not just the scanning time must be considered, but also the time from patient entrance to exit in the scanning room, which is obviously significantly longer with MRI than US. ix) The unknown performance of MRI in older patients who are expected to be less performant in following the equipment commands in breath holding. x) The rate of patients unsuitable for MRI because of contraindications (*e.g.* claustrophobia, magnetic sensitive devices, obesity, *etc.*). xi) The acceptability of the technique by the at-risk population outside of experimental studies like the present one.

Therefore, these results must be considered very cautiously, although similar findings were recently reported by other groups.[15] The clinical benefits of abbreviated MRI remain to be assessed, although alternative surveillance strategies to US alone may be warranted. Furthermore, the intention-to-diagnose performance of MRI for surveillance, specifically in patients prone to US failure, such as those with obesity, is unknown. Thus, although appealing, further investigations are required to make definitive recommendations about the role of unenhanced MRI, even in patients with suboptimal US liver explorability. There is also a place for prospective studies, ideally randomized (MRI *vs.* US), with medico-economic evaluation.

In conclusion, non-enhanced MRI cannot be considered a standard modality for HCC surveillance for all patients at risk of HCC, but it has potential, especially as it appears to be almost as sensitive but more applicable than contrast-enhanced liver imaging. It might therefore become a tool for selected patients, whose definition requires further studies.

Moreover, non-enhanced MRI can be easily and immediately complemented with contrast, in case of a positive finding, producing an accelerated recall strategy and diagnostic work up.

Conflicts of interest

NGC: (honoraria for speaker bureau, consultancy or advisory board) Abbvie, Bayer, Gilead, IPSEN, Shionogi. Research contract with Echosens. FP: (honoraria for speaker bureau, consultancy or advisory board) Alkermes, Astrazeneca, Bayer, Bracco, BMS, EISAI, GE, IPSEN, La Force Guerbet, Roche, Siemens Healthcare, Tiziana Life Sciences. Research contract with ESAOTE.

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

Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhep.2020.01.006.

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