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LETTER TO THE EDITOR

Non-enhanced Magnetic Resonance Imaging Compared to Ultrasound as a Surveillance Tool for Hepatocellular Carcinoma. Not all that glitters is gold: the ultrasound hepatologist's point of view

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To the Editor,

In the April 2020 issue of the *Journal of Hepatology*, Park et al. reported the results of their study dealing with the value of non-enhanced MRI (ne-MRI) in the surveillance of HCC in cirrhosis compared with ultrasound (US) [1]. Park and colleagues retrospectively revised US results, comparing them to those obtained with ne-MRI during surveillance derived from Kim's prospective study using MRI with liver-specific contrast (e-MRI), which was conducted 8 years before [2]. While ne-MR images were revised by three experienced radiologists, US exams were not. Park et al. reported that ne-MRI showed higher performance than US in the detection of HCC nodules in high-risk patients during surveillance. According to the results of Park's study, the per-lesion sensitivity of ne-MRI in recognition of HCC was 77.1%, compared to only 25.0% of US, which was a very significant difference ($P < 0.001$) [1].

The criteria chosen by Park et al. in their paper for US detection of focal liver lesions were the following. Focal lesions ≥ 1 cm on US that met 1 or more of the following criteria were considered positive: (i) discrete focal mass distinguishable from the adjacent parenchyma; (ii) peripheral low echoic halo; (iii) mosaic pattern; and (iv) definite tumour thrombi visible on US. In our opinion, these criteria are questionable and may explain the high rate of false-positive lesions reported by Park et al. in their series.

As physicians who have been studying patients with chronic liver disease for years, we strongly disagree with this sonographic terminology for the following reasons [3]:

a. Early-stage HCC nodules > 1 cm usually appear *hypoechoic* [4]. What does "discrete focal mass distinguishable from the adjacent parenchyma" mean? Was the mass *hypoechoic*? Alternatively, was it *hyperechoic* (angioma-like) without halo sign? The latter US feature can be considered a *discrete focal mass* or simply haemangioma. However, it is well established that such a US finding in a cirrhotic patient has a great probability to be HCC, especially if it was not present at previous US examination [5, 6].

1 "Peripheral low echoic halo": Do the authors mean that the nodule was isoechoic with halo sign, allowing them to distinguish it from the surrounding US pattern? Alternatively, it was hyperechoic with fine halo sign. It is worth noting that it is rare to find a halo sign in early cancer.

2 ''mosaic pattern": This pattern is usually characteristic of large nodules, with steatosis and fibrosis.

The American College of Radiology Ultrasound Liver Imaging and Reporting Data System (US LI-RADS) has recently published guidelines on this issue, which are intended to emphasize and standardize the quality and usefulness of US for screening and surveillance of hepatocellular carcinoma [7].

In Park's study, most of the studied patients were HBsAg cirrhotics. On US, these patients frequently show a coarse nodular pattern [8]. How were these patients considered? In the paper by Park et al., the rate of patients with this US pattern is not specified, and this may have influenced the low sensitivity of US, considering the difficulty of identifying

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Table 1 Comparison of diagnostic imaging performance between Kim's and Park's study

Statistics	Liver-specific contrast MRI Kim et al. (N. 1031)		Non-enhanced MRI Park et al. (N. 1057)	
	Value (%)	95% CI	Value (%)	95% CI
Sensitivity	86.05%	72.07–94.70%	79.07%	63.96–89.96%
Specificity	96.97%	95.75–97.92%	97.93%	96.85–98.71%
Positive likelihood ratio	28.42	19.79–40.81	38.18	24.35–59.90
Negative likelihood ratio	0.14	0.07–0.30	0.21	0.12–0.38
Disease prevalence	3.91%	2.84–5.23%	4.07%	2.96–5.44%
Positive predictive value	53.62%	44.61–62.41%	61.82%	50.79–71.75%
Negative predicitve value	99.42%	98.79–99.72%	99.10%	98.41–99.50%
Accuracy*	96.55%	95.29–97.54%	97.16%	95.97–98.08%

CI confidence interval; *$P > 0.05$

early HCCs in this context. In addition, did HCV patients show this pattern? It is well known that the presence of a coarse nodular pattern represents a risk factor for the development of HCC [9, 10]. Furthermore, the most surprising finding for us is the very low sensitivity of US in recognition of HCC nodules > 2 cm: only 37.5%! How could that have been going on all the years we have been to monitoring cirrhotic patients with US [11]? Does it mean that we have failed to detect hundreds and hundreds of tumours? A recent metanalysis by Tzrartzeva et al. showed that the sensitivity of US for HCC detection during surveillance is suboptimal but certainly higher than that found by Park et al. (47% for early stages and 84% for all stages of HCC) [12]. The low US sensitivity reported in the latter study is even more surprising considering that most patients in it were infected with HBV and not overweight or affected by NASH [13, 14]. However, there are some other issues: (i) We have compared the results from Kim's prospective study using MRI with liver-specific contrast (e-MRI) and those from Park's retrospective study using reassessed ne-MR images (Table 1). The table shows the sensitivity, specificity, positive and negative likelihood ratio (± LR), positive and negative predictive values (PPV and NPV), and accuracy of the two methods. There is no statistically significant difference between the two procedures ($P > 0.05$). The diagnostic accuracy of e-MRI was found to be similar (indeed slightly lower) than that obtained by ne-MRI in the Park's retrospective study (96.6% vs 97.2%, respectively). This means that the ne-MRI method is more effective than the e-MRI method in the detection of HCC, and even that ne-MRI can provide simultaneous recognition and characterization of HCC. (ii) There is a discrepancy in the comparison between ne-MRI and US methods, as the first was made on images re-evaluated by two to three expert radiologists (in case of disagreement), while the US interpretation was exclusively derived from the previous study performed eight years ago [2]. It is not known what the agreement between the operators (K-index) was while the reassessment was carried out, and how many times the third radiologist was necessary. Therefore, a direct comparison between the two imaging procedures may be incorrect. (iii) In Kim's original study, 51 (10.8%) out of 474 participants refused to have e-MRI performed because of "logistical problems." Most likely this is because such patients could not be subjected to MRI for some contraindications (breathing difficulty, claustrophobia, metal prosthesis). This is an important issue affecting MRI and not US and, in our opinion, it represents a non-negligible percentage. Moreover, there is an important economic factor to be considered: US is inexpensive and MRI is much more expensive than US. Anyone understands the economic challenges of surveillance for HCC by MRI in populations at risk in countries that have universalistic health systems, given the high cost and the limited availability of technically adequate machines. Theoretically, non-enhanced MRI could be reserved for patients with US-related limitations that cannot be overcome.

In our opinion, at this time, robust prospective multicentre studies (including only patients who can be adequately examined with both methods) should be conducted to exclude a simple and well-accepted tool such US for the surveillance of HCC in high-risk patients in favour of other, more complicated machines.

Complaince with ethical standards

Conflict of interest Giorgio Antonio disclosed no relevant relationships. De Luca Massimo disclosed no relevant relationships. Gatti Pietro disclosed no relevant relationships. Giorgio Valentina disclosed no relevant relationships.

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