HCCR-1 for detecting small hepatocellular carcinoma latent in a cirrhotic liver: a prospective cohort study

We read with great interest the leading article by Tremosini and coworkers in *Gut* (2012 doi:10.1136/gutjnl-2011-301951) on the prospective validation of an immunohistochemical panel (glypican 3, heat shock protein 70 and glutamine synthetase) in liver biopsies for diagnosis of very early hepatocellular carcinoma (HCC).¹ In this prospective study which included nodules <2 cm, this panel had 60% sensitivity and 100% specificity when at least two of the markers (regardless of which) were positive. These data establish the clinical usefulness of this panel of genetic biomarkers for the histological diagnosis of early HCC.¹ The distinction between early HCC changes and dysplastic nodules among cirrhotic patients is challenging even in expert hands. Therefore, further prospective studies with a predominant inclusion of HCC lesions of <2 cm in diameter are needed for the final validation and confirmation of the conclusions of this interesting study.

Screening programmes have been developed for the surveillance of patients at risk of HCC (mainly liver cirrhosis) for detection at an early stage.² Regrettably, a large proportion of small HCC does not meet the non-invasive diagnosis criteria (US, CT or MRI), and a biopsy should be requested for confirmation of HCC.² Although a biopsy is usually considered the gold standard, it is also flawed by an excessive rate of false negative results.¹

Despite the large number of studies devoted to the immunohistochemistry of HCC, the absolute positive and negative markers for HCC are still lacking, and even those characterised by very high sensitivity and specificity do not have a universal diagnostic usefulness. So far, serum biomarkers such as AFP, AFP-L3, DCP, AFU, GGT, GP-73, MUC-1, SCCA, GPC-3, and a new generation of IgM-immunocomplexes have significant diagnostic limitations, and in fact they are not particularly precise for the early diagnosis of HCC. Simultaneous determination of these markers in various combinations could improve the accuracy in differentiating HCC from non-malignant hepatopathy.

It has been reported that HCCR-1 is elevated according to disease progression from liver cirrhosis to HCC, and it is more frequently positive in patients with early small HCC.^{3,4} The aim of this study is to assess, prospectively, the diagnostic accuracy of AFP, DCP and HCCR-1 for the diagnosis of early HCC in a cirrhotic background. A total of 2040 subjects, including 612 patients with HCC, 608 patients with liver cirrhosis, 402 patients with chronic hepatitis and 418 normal volunteers were investigated between 2004 and 2010 through the

Table 1 Sensitivity, specificity, PPV, NPV, accuracy, youden index ($J = Se + Sp - 1$) of AFP, DCP and HCCR-1 when combined

Serum marker	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)	Youden index	AUC
AFP	65.4%	80.2%	58.6%	84.4%	75.8%	0.456	0.791
DCP	44.3%	86.7%	58.7%	78.4%	74.0%	0.31	0.678
HCCR-1	41.6%	87.4%	58.6%	77.7%	73.7%	0.29	0.643
AFP+DCP	67.7%	82.9%	62.8%	85.7%	78.3%	0.506	0.824
AFP+HCCR-1	75.2%	75.8%	57.1%	87.7%	75.6%	0.51	0.830
DCP+HCCR-1	55.9%	84.7%	61.0%	81.8%	76.1%	0.406	0.746
AFP+DCP+HCCR-1	75.4%	79.3%	60.8%	88.3%	78.1%	0.547	0.891

prospective cohort study in China and Korea. The sensitivity, specificity and positive predictive value for HCCR-1 were 41.6%, 87.4% and 58.6%; for AFP, 65.4%, 80.2% and 58.6%; and for DCP, 44.3%, 86.7% and 58.7%, respectively (table 1). A combination of three biomarkers yielded an improved sensitivity of 75.4% for detecting HCC. When only those with early HCC were evaluated, the AUC for AFP and HCCR-1 was almost identical, while that of DCP was rather low (figure 1). In addition, the sensitivities of AFP, DCP and HCCR-1 in small HCC (<2 cm) were 39.7%, 11.5% and 51.9%, respectively, using the currently recommended cut-offs for AFP (20 ng/ml), DCP (40 mAU/ml) and HCCR-1 (10 ng/ml) (data not shown). The one-year cumulative incidence rates of HCC for cirrhosis patients positive for AFP or HCCR-1 were 15.0% and 20.4%, respectively. HCCR-1 was also detected in 35.9% (52/145) of HCC-negative both for AFP and DCP. Therefore, our study suggests that the HCCR-1 could be a useful biomarker for the detection of small HCC (<2 cm), for the detection of HCC latent in a cirrhotic liver, and for the diagnosis of both AFP- and DCP-negative HCC.

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Figure 1 ROC curves comparing AFP, DCP and HCCR-1 in patients with HCC (Panel A) or small HCC (Panel B) versus those with non-malignant liver disease. The curves show the optimal cut-off value for AFP of 10 ng/ml, for DCP of 22 mAU/ml, and for HCCR-1 of 1.96 ng/ml. The area under the ROC curve is shown with its 95% confidence. AFP is blue, DCP is brown, HCCR-1 is green, and AFP + HCCR-1 + and DCP is purple. The number of cases for each group used in this ROC curve analyses is 612 (HCC), 131 (early HCC) and 1010 (those with non-malignant disease). AUC, Area Under the Curve.

and drafted the report. Jin Zhongtian, Cui Zhuqingqing, Youn Soo Lee, Gi Hwan Gong, Joo Hee Yoon, Hae Nam Lee, Sa Jin Kim, Tae Eung Kim, Eun Young Song and Yun Kyung Lee investigated the patients and obtained, processed and documented clinical samples. Seon-Ah Ha, Hyun Kee Kim, Jinah Yoo, Sanghee Kim, Guoxin Zhang, Peng Jirun and Jin Woo Kim wrote the manuscript. Seon-Ah Ha, Hyun Kee Kim, Jinah Yoo, Sanghee Kim, Guoxin Zhang, Peng Jirun, Jin Zhongtian, Cui Zhuqingqing, Youn Soo Lee, Joo Hee Yoon, Hae Nam Lee, Sa Jin Kim, Tae Eung Kim, Eun Young Song, Yun Kyung Lee, Yong Gyu Park and Jin Woo Kim approved the final manuscript.

Competing interests None.

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