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Evolving strategies in the diagnosis of hepatocellular carcinoma

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COMMENTARY ON:

The diagnostic and economic impact of contrast imaging techniques in the diagnosis of small hepatocellular carcinoma in cirrhosis. Sangiovanni A, Manini MA, Iavarone M, Romeo R, Forzenigo LV, Fraquelli M, Massironi S, Della Corte C, Ronchi G, Rumi MG, Biondetti P, Colombo M. Gut, 2010 May;59(5):638–44. Copyright (2010). Abstract reproduced with permission from BMJ Publishing Group Ltd.

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Abstract Background: *Contrast-enhanced ultrasound (CE-US), contrast CT scan and gadolinium dynamic MRI are recommended for the characterization of liver nodules detected during surveillance of patients with cirrhosis with US.*

Aim: *To assess the sensitivity, specificity, diagnostic accuracy and economic impact of all possible sequential combinations of contrast imaging techniques in patients with cirrhosis with 1–2 cm liver nodules undergoing US surveillance.*

Methods: *Sixty four patients with 67 de novo liver nodules (55 with a size of 1–2 cm) were consecutively examined by CE-US, CT, MRI, and a fine-needle biopsy (FNB) as a diagnostic standard. Undiagnosed nodules were re-biopsied; non-malignant nodules underwent enhanced imaging follow-up. The typical radiological feature of hepatocellular carcinoma (HCC) was arterial phase hypervascularisation followed by portal/venous phase washout.*

Results: *HCC was diagnosed in 44 (66%) nodules (2, <1 cm; 34, 1–2 cm; 8, >2 cm). The sensitivity of CE-US, CT and MRI for 1–2 cm HCC was 26%, 44% and 44%, repectively, with 100% specificity; the typical vascular pattern of HCC being identified in 22 (65%) by a single technique versus 12 (35%) by at least two techniques carried out at the same time point ($p = 0.028$). Compared with the cheapest dual examination (CE-US + CT), the cheapest single technique of stepwise imaging diagnosis of HCC was equally expensive (euro 26,440 versus euro 28,667) but led to a 23% reduction of FNB procedures ($p = 0.031$).*

Conclusions: *In patients with cirrhosis with a 1–2 cm nodule detected during surveillance, a single imaging technique showing a typical contrast pattern confidently permits the diagnosis of HCC, thereby reducing the need for FNB examinations.*

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Until 2000, the only accepted method to diagnose hepatocellular carcinoma (HCC) was a positive biopsy finding. Unfortunately, image-guided biopsy of nodular lesions in cirrhosis has limitations. Obtaining an adequate sample may not be technically feasible in lesions that are very small in size or in difficult location for percutaneous targeting. In addition, histologic differentiation between HCC and non-malignant hepatocellular entities, especially high-grade dysplastic nodule, may be challenging on fine-needle biopsy specimens, since stromal invasion, one of the most relevant criteria, is difficult to recognize [1]. Last but not least, biopsy involves the risk of serious complications, including bleeding and tumor seeding along the needle track [2].

In 2000, a panel of experts on HCC convened in Barcelona on behalf the European Association for the Study of the Liver (EASL) and developed for the first time non-invasive criteria for HCC based on a combination of imaging and laboratory findings [3]. The non-invasive criteria were restricted to cirrhotic patients undergoing surveillance and included either (a) the detection of a focal lesion larger than 2 cm showing evidence of arterial hypervascularization in two coincident imaging techniques or (b) the detection of a focal lesion larger than 2 cm showing evidence of arterial hypervascularization in only one imaging technique but in association with an alpha-fetoprotein (AFP) value exceeding 400 ng/ml. Biopsy, however, was still recommended for lesions smaller than 2 cm, particularly those ranging 1–2 cm. For the tiny lesions below the 1 cm threshold, the consensus was to schedule an enhanced follow-up, given that most of such focal abnormalities detected by ultrasound in a cirrhotic liver are not HCC, and that obtaining a definitive diagnosis of HCC was anyway considered unfeasible in the majority of the cases.

In 2005, the guidelines for the clinical management of HCC issued by the American Association for the Study of Liver Diseases (AASLD) amended the EASL non-invasive criteria, acknowledging that the newest imaging techniques – including contrast-enhanced ultrasound, multidetector computed tomography (CT), and thin-section dynamic magnetic resonance imaging (MRI) – allowed for better exploration of the vascular pattern of focal hepatic lesions. The AASLD guidelines recommended

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dropping the use of AFP and to rely on a more comprehensive enhancement pattern of HCC, including not only the detection of hypervascularization in the arterial phase but also the evidence of contrast washout in the venous or the late phase. While for lesions above 2 cm a single imaging technique showing such characteristic vascular profile of HCC was considered adequate to confidently establish the diagnosis, in lesions ranging 1–2 cm, AASLD guidelines recommend that typical imaging findings are confirmed by two coincident dynamic imaging modalities [4].

Prospective studies aimed at validating the AASLD guidelines have confirmed that these criteria are highly specific for the diagnosis of HCC. In a trial conducted in a series of consecutive patients with a solitary focal lesion smaller than 2 cm detected during ultrasound surveillance, the AASLD criteria achieved 100% specificity for the diagnosis of HCC [5]. Unfortunately, such absolute specificity had the downside of very low sensitivity. As a result, biopsy was still needed in about two thirds of the cases [5].

In the article "The diagnostic and economic impact of contrast imaging techniques in the diagnosis of small hepatocellular carcinoma in cirrhosis", Sangiovanni et al. suggest a different approach to the diagnosis of HCC [6]. They propose a sequential – rather than combined – application of imaging techniques. They show that in the setting of surveillance, a single imaging technique showing a typical contrast enhancement pattern enables a confident diagnosis of HCC even in nodules ranging 1–2 cm. The use of a sequential algorithm maintains an absolute specificity (100%) but increases the sensitivity from 35% (two imaging techniques showing coincident typical vascular pattern at the same time point, as per AASLD guidelines) to 65%, with significant savings in terms of liver biopsy procedures. In addition, the stepwise imaging diagnosis was shown not to increase costs with respect to the dual examination.

The paper by Sangiovanni et al. is a major contribution to the diagnostic management of HCC. Correct characterization of nodules ranging 1–2 cm in diameter is a key issue, since such small lesions are the true target of surveillance programmes [2]. On the other hand, the specificity of imaging diagnosis is crucial to prevent therapeutic mistakes due to false positive diagnoses of HCC. In this regard, an important caveat is the recent demonstration that intrahepatic colangiocellular carcinoma (ICC) in cirrhosis may show a similar enhancement pattern as HCC at contrast ultrasound (arterial uptake followed by wash-out) [7]. Fortunately, this overlap does not occur with MRI, since ICC, contrary to HCC, does not show contrast washout in delayed phases [8]. Such a difference can be explained with the different pharmacokinetic of ultrasound contrast agents with respect to iodinated contrast agents for CT and gadolinium chelates for MRI. Ultrasound microbubbles are blood-pool agents, confined to the intravascular space, whereas the majority of currently approved contrast agents for CT and MRI are rapidly cleared from the blood into the extracellular space [9].

In conclusion, the ongoing progress in imaging techniques requires continuous updates of diagnostic algorithms. In fact, new approaches have been proposed at 5-year intervals during the last decade (Table 1). At the same time, it is crucial that every new approach is externally validated before its implementation on a large scale is recommended. In this regard, it is important to point out that, despite the ability of state-of-the-art imaging to assess tumor vascularity, neither the absence of arterial hypervascularization nor the absence of contrast wash-out is the criterion for ruling out HCC. It is well established that early stage HCC tumors may not exhibit the characteristic vascular features of overt HCC. Delaying the diagnosis of HCC until imaging detection of arterial hypervascularization or wash-out could reduce the chances of a radical cure, since the incidence of microscopic vascular invasion and satellite nodules significantly increases when a tumor develops imaging-detectable neoangiogenetic changes [10]. Alternate approaches – particularly the use of liver-specific MRI contrast agents – are expected to improve the ability to characterize small lesions. However, prospective investigation, with meticulous imaging-pathology correlations on explanted livers, is warranted before any alternate criterion is endorsed by scientific societies as the standard diagnostic approach for HCC.

Table 1. Evolving criteria for imaging diagnosis of HCC in cirrhosis.

Author, year	Diagnostic criteria	
	1-2 cm	>2cm
Bruix *et al.*, 2001 [3]	*Imaging pattern: arterial-phase hypervascularization*	
	Biopsy confirmation required	Two coincident imaging techniques One technique + AFP > 400 ng/ml
Bruix and Sherman, 2005 [4]	*Imaging pattern: hypervascularization with venous / late phase washout*	
	Two coincident imaging techniques	One imaging technique
Sangiovanni *et al.*, 2010 [6]	*Imaging pattern: hypervascularization with venous / late phase washout*	
	One imaging technique (sequential application)	One imaging technique (sequential application)

HCC, hepatocellular carcinoma. AFP, alpha-fetoprotein.

Conflict of interest

The author who have taken part in this study declared that he does not have anything to disclose regarding funding or conflict of interest with respect to this manuscript.

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