

## Role of gadoxetic acid-enhanced 3T MRI combined with diffusion in small HCC diagnosis - case presentation

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**ABSTRACT:** We present the case of a patient with chronic viral hepatitis B and cirrhosis referred to the Gastroenterology Department for evaluation. The contrast-enhanced ultrasound and elastography revealed a nodule in the right liver lobe suggesting the diagnosis of dysplastic nodule. The patient performed contrast enhanced multi-detector computer-tomography, showing a subcapsular nodule with enhanced centre and lack of enhancement in the periphery, highly suspicious for HCC. The HCC final diagnosis was assessed by using 3T magnetic resonance imaging system along with hepatocyt specific contrast agents and diffusion sequences, pointing to the importance of state-of-the-art imaging techniques in the liver nodules assessment.

**KEYWORDS:** hepatocellular carcinoma, computer-tomography, magnetic resonance imaging

### Introduction

The advances in various imaging techniques, including contrast-enhanced ultrasonography (CEUS), elastography, multi-detector computer tomography (MDCT), diffusion weighted magnetic resonance imaging (DW-MRI), high field magnetic resonance imaging (MRI), along with the development of new contrast media have significantly improved detection of small hepatocellular carcinoma [1]. Early diagnosis of small hepatocellular carcinoma (HCC) is very important for successful therapeutic approach and for higher survival of patients. The new guidelines recommend the diagnosis of small HCC larger than 1cm on the basis of two imaging findings, including either CT, CEUS or MRI when they have typical features [2]. However the hypervascular nodules 2 cm in diameter have non-specific imaging features, therefore they are very difficult to characterize [3].

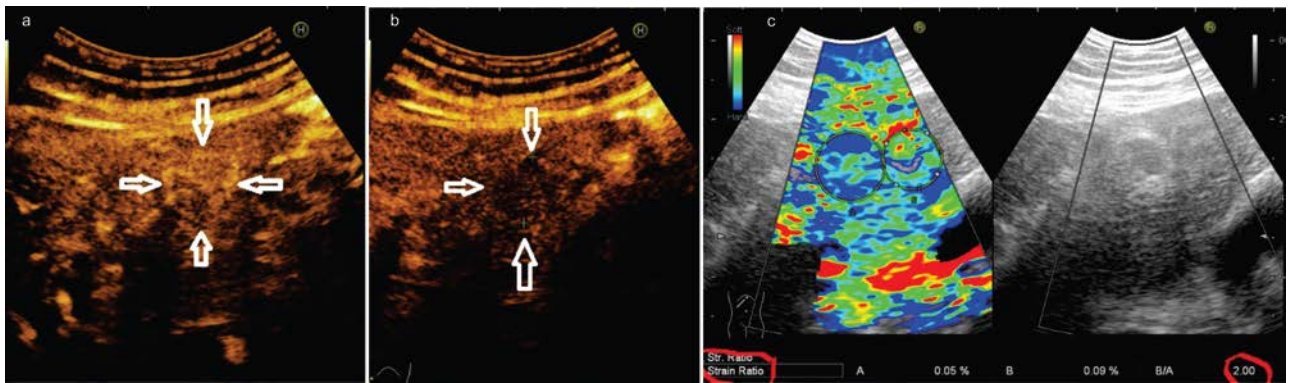
### Case report

A 65-year-old patient, alcohol consumer, with chronic viral hepatitis B diagnosed three years ago and cirrhosis one month ago, presented in the Gastroenterology Department for evaluation

and multiple investigation. His history includes multiple cardiovascular pathology (atrial fibrillation, inferior myocardial infarction, cardiac congestive failure), type 2 diabetes and stroke. The clinical exam included marked physical asthenia, fatigue, small efforts dyspnea and diffuse abdominal pain. Lab investigations showed normal values, including an alfa fetoprotein level of 1.68 UI/ml (normal values 0.00-5.80).

In the Gastroenterology Department the patient performed abdominal B-mode ultrasound which revealed in the right lobe, subcapsular, a round-shape mass, 2 cm in diameter with hyperechoic ring and hypoechoic centre, a bull's eye or target sign appearance.

The CEUS showed an inhomogeneous arterial enhancement, complete at 20 seconds (Figure 1a). In portal phase the enhancement was similar to surrounding parenchyma and wash-out in the late phase and at 5 minutes after enhancement (Figure 1b). The elastography performed revealed a hard tissue mass, with mixed structure, strain ratio 2 and C class ETLT (elasticity type of liver tumour) (Figure 1c). The diagnosis was suspected dysplastic nodule in the right liver lobe in cirrhotic context, without excluding a solitary metastasis,.



**Figure 1 a,b,c: CEUS showing a nodule in right liver lobe, with inhomogeneous arterial enhancement (a), wash-out complete at 5 minutes (b). In the elastography ultrasound mode the nodule has mixed structure (ETLT- C class) with a strain ratio of 2 (c);**

The patient was referred to the Imaging Department, University of Medicine and Pharmacy Craiova, for computer tomography and magnetic resonance imaging diagnosis. The MDCT investigation was made per-primam, for liver and other organs evaluation. The patient performed thorax, abdomen and pelvis 20 slices CT with and without contrast enhancement, in arterial, portal and interstitial phase, with bolus tracking. The imaging technique showed a

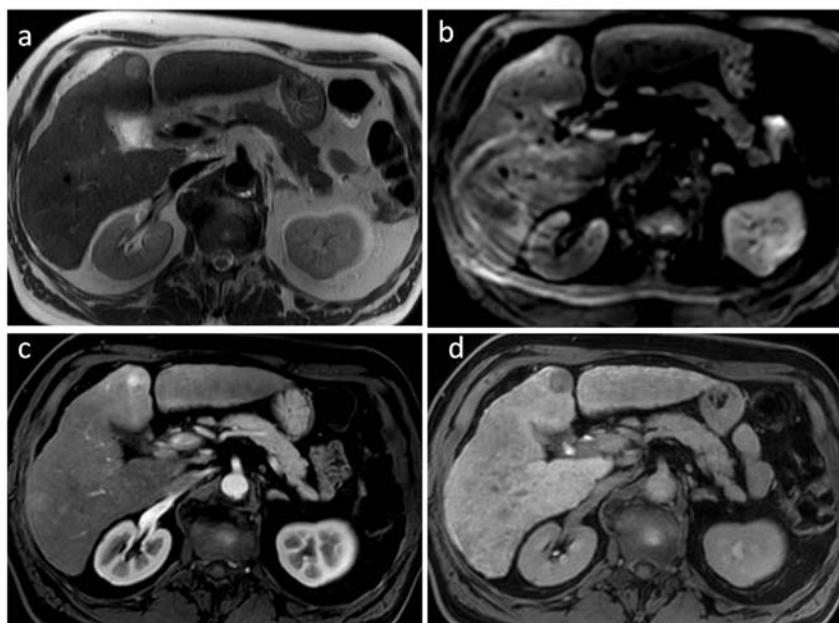
round-lesion, irregular delineated, in segment IVb, subcapsular, with an arterial enhanced foci in the centre and lack of enhancement in the periphery (Figure 2a). The lesion showed wash-out in the venous and late phase (Figure 2b) and a vascularized core in the perfusion reconstruction images (Figure 2c), pointing to a diagnosis of HCC with *nodule in nodule* appearance, without completely excluding a high-grade dysplastic nodule.



**Figure 2 a,b,c: Multidetector 20 slices CT revealing a nodule in the IVb liver segment, subcapsular, inhomogeneous, with focal enhancement and peripheral lack of uptake in the arterial phase (a) wash-out in the late phase (b) and the vascularized core in the perfusion reconstruction images (c);**

The next imaging technique performed was high resolution 3T MRI, with conventional T1, T2 weighted sequences before and after contrast media administration, including diffusion and fat suppression sequences. The contrast media used was hepatocyt specific (Gadolinium ethoxybenzyl dimeglumine-Gd-EOB-DTPA). This imaging technique revealed a 20.3 mm lesion in the IVb liver segment, with high signal in T2-weighted sequences (Figure 3a), low signal in T1 sequences in-phase and out-of-phase, inhomogenous, without fat inclusions. In

the diffusion sequence the lesions showed moderate nodular hiperintensity (Figure 3b). In the postcontrast phases the lesion revealed the same enhancement as in the other imaging techniques, nodular enhancement without peripheral enhancement in the arterial phase at 20 seconds (Figure 3c), wash-out in the venous phase at 70 seconds and interstitial phase at 180 seconds. At 20 minutes (hepatobiliary phase) after contrast uptake the lesion showed complete wash-out, which made the final diagnosis of small HCC (Figure 3d).



**Figure 3 a,b,c,d: Gd-EOB-DTPA enhanced 3T MRI technique which shows a 20.3 mm HCC with moderate high signal in T2-weighted sequences (a), focal hiperintensity in diffusion (b), inhomogeneous arterial enhancement (c) and complete wash-out in the hepatobiliary phase (d) ;**

Considering the patient clinical history the therapeutic decision was to follow-up the evolution of the lesion by imaging investigation.

## Discussion

HCC is a major health issue, as recognized by the World Health Organization (WHO), being the fifth most common tumor and responsible for a third of cancer-related deaths on a global scale, with an ever-increasing number of fatalities. As a result, there have been numerous attempts to establish a set of guidelines for an early liver cancer diagnosis and long-term prognosis [4].

The current diagnostic approach for hepatocellular carcinoma is adopted by the European Society for the Study of Liver (EASL) [5] and the American Association for the Study of Liver Disease (AASLD) [2]. According to the latest EASL guidelines, diagnosis of HCC is based on non-invasive criteria or pathology, the latter being used when imaging methods are inconclusive, especially in small lesions and possible borderline lesions (such as dysplastic liver nodules). Accurate pathological diagnosis, especially in early stages, is difficult even for an expert pathologist [6].

CE-US (contrast enhanced ultrasound) use is described as controversial in the latest EASL guideline, mainly due to the nature of contrast agents used in CE-US investigations, which are confined to blood vessels. The echographic contrast agent used in Europe (SonoVue) is

composed of small micro-bubbles, which can flow inside capillaries and generate a map of the intratumoral vascularization [7]. Nevertheless, CEUS is not recommended in current guidelines as it provides low specificity when compared to other imaging techniques [5], while standard biopsy is limited due to local complications such as bleeding and needle-track seeding [5,8]. The US elastography is a non-invasive promising method with a sensitivity between 50-78.9% and specificity of 92,2% in the diagnosis of early HCC [9]. The main limitation of US elastography is an observatory dependent assessment, being a highly subjective technique with absence of a standardized quantitative measurement. Also the fibrotic, hard, cirrhotic liver tissue may influence the imaging findings [9]. In our study the CEUS and elastography lesion imaging features suggested a possible dysplastic nodule in cirrhotic context.

Furthermore, as hepatic transplantation remains the only therapeutic option in certain cases, the 2013 Organ Procurement and Transplantation Network (OPTN)/United Network for Organ Sharing (UNOS) policy has established contrast-enhanced multi-detector computed tomography (MDCT) and contrast-enhanced magnetic resonance imaging (MRI) as diagnostic criteria for hepatic carcinomas larger than 1 cm [10].

Multidetector computer tomography is frequently the first diagnostic imaging technique used when a malignant hepatic lesion is

suspected and in the recent studies a more accurate characterization of this type of lesions can be obtained using multiphasic dynamic CT technology [11,12]. Despite optimal arterial phase imaging, a large number of small (<1.5 cm) HCCs remain isodense relative to the background and go undetected on CT. It is well known that to obtain the best conspicuity of lesions, thinner slices and late arterial phase images should be acquired [13]. It has been reported that the detection of hepatocellular carcinomas smaller than 2 cm, using three-phase helical dynamic CT, was 60% and the detection of those larger than 2 cm was 82% [14]. The computer tomography diagnosis in our case was small HCC with *nodule in nodule* appearance.

Currently, contrasted-enhanced MRI using gadolinium ethoxybenzyl dimeglumine (Gd-EOB-DTPA), a hepatocyte specific contrast agent commercially known as Primovist™ in Europe, is considered the option of choice in analyzing small hepatic lesions, due in part to the fact that gadoteric acid is excreted through the hepatobiliary system [15, 16]. The use of this contrast media is able to assess with the highest sensitivity rate certain features present only in early HCC, such as reduced signal intensity during the portal, late and hepatocyte phase, which are uncharacteristic for dysplastic nodules (DN). Although usually DNs also appear hypo- or iso-intense during portal phase, a 2013 prospective study has revealed that the combination of hypointensity in portal and hepatobiliary phase is an emerging standard for diagnosis of early hypovascular HCC [17]. Also in the case of focal hypervascular images during the arterial phase, the diagnosis of HCC is probable with a high degree of certainty, regardless of the tumor size [17]. There is also an open discussion regarding the *nodule in nodule* pattern which apparently is suggestive of dysplastic nodule comprising smaller early HCC [18]. The level of accuracy decreases to 40-50% for tumors less than 1 cm, especially if the liver has a dysmorphic architecture with multiple regenerative and DN, lacking normal tissue as a basis for comparison [19]. Use of high field strength 3T MRI with Primovist™ has been proposed in order to ensure a more accurate characterization of liver nodules, especially for those of small sizes [20]. Several studies have suggested that hyperintensity on diffusion weighted MRI (DW-MRI) can be proposed as an added criterion for nodule characterization in order to discriminate between DN and early HCC with benefits for long term prognosis. A

recent 2013 study supports the idea that the diagnosis of early HCC for small hypovascular lesions with hypointensity in hepatobiliary phase on Gd-EOB-DTPA MRI and hyperintensity on DW-MRI, has a high accuracy, sensibility and specificity ranging between 90% and 98%, respectively [21].

In the perfect concordance with the recent studies and EASL guidelines [5], in our case the final diagnosis was HCC, being possible through the use of two novel imaging techniques, MDCT and high field 3T MRI.

## Conclusion

The use of high field strength 3T MRI system, hepatocyt specific contrast agents and diffusion sequences together with multislice and multiphasic dynamic computer-tomography are an essential tool in the differential diagnosis between regenerative nodules, high-grade dysplastic nodules and early well-differentiated hepatocellular carcinoma. The existence of state-of-the-art infrastructure in a single centre can play an important role in the management of cirrhotic patients with small liver nodules.

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