Research Article

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Lack of arterial hypervascularity at contrast-enhanced ultrasound should not define the priority for diagnostic work-up of nodules <2 cm

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Background & Aims: Current guidelines recommend diagnostic work-up for nodules >1 cm detected during screening for hepatocellular carcinoma (HCC). This implies that patients with benign conditions may undergo unnecessary evaluation and those with small nodules may be intervened too early, leading to overdiagnosis. Since increased arterial vascularization is the hallmark of malignancy, its detection by contrast-enhanced ultrasound (CEUS) could become the signal to proceed with diagnosis confirmation. The aim was to assess if HCCs <2 cm without arterial hyperenhancement by baseline CEUS have a benign evolutionary profile, suggesting that diagnosis and invasive treatment could be delayed until detection of an overt malignant profile, associated with increased vascularization.

Methods: We prospectively included 168 cirrhotic patients with a newly detected solitary nodule of 5–20 mm by screening ultrasonography. MRI, CEUS and fine needle biopsy (FNB) were performed and if no confident diagnosis was obtained, patients were closely followed to rule out HCC. Final diagnosis was: HCC (n = 119), cholangiocarcinoma (n = 3), neuroendocrine tumour (n = 1) and benign lesions (n = 45).

Results: CEUS did not detect contrast hyperenhancement in the arterial phase in 55 cases (34%). Eighteen out of these 55 nodules were diagnosed as HCC. Non-CEUS hyperenhanced HCCs were more frequently well-differentiated than CEUS-hyperenhanced HCCs (p <0.004). Fourteen patients were treated with ablation and 4 with resection. Ten (55.6%) patients experienced tumour recurrence after treatment, mostly distant, confirming their overt malignant profile.

Conclusions: Absence of contrast hyperenhancement on CEUS during the arterial phase in nodules <2 cm in a cirrhotic liver does not predict a less malignant profile. Accordingly, priority for diagnostic work-up and treatment should not differ according to contrast profiles on CEUS.

Introduction

Clinical practice guidelines for hepatocellular carcinoma (HCC) recommend screening patients with cirrhosis with the aim to detect tumours at an early stage, particularly when they are smaller than 2 cm [1–6]. Between 1 and 2 cm the malignant nodules gain arterial blood supply and this coincides with an increasing prevalence of microvascular invasion and/or satellite nests. This pathology profile marks the risk of dissemination and implies a potential impairment of long-term disease-free survival after therapy [7]. Current recommendations suggest starting diagnostic techniques when a nodule, detected at screening ultrasound, exceeds 1 cm [1,2], since at that point the likelihood of being an HCC is higher than 50% [8]. If dynamic imaging techniques such as MRI or CT show a specific profile for HCC, the diagnosis is established, but this is registered in less than 60% of patients with nodules smaller than 2 cm [8–11]. Accordingly, in a relevant proportion of patients, diagnosis should be obtained by biopsy. This is known to bear some risks (bleeding, tumour seeding) that despite their reduced prevalence should be taken into account, and even more, if it is recalled that in such small nodules, biopsy has a reduced sensitivity. This fact results in the need to perform repeated biopsy samplings in a relevant proportion of patients [8]. These comments expose that the diagnostic work-up to diagnose HCC in such small lesions and then to

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Abbreviations: AASLD, American Association for the Study of Liver Diseases; CEUS, contrast enhanced ultrasound; CT, computed tomography; FNB, fine needle biopsy; HCC, hepatocellular carcinoma; MRI, magnetic resonance imaging; US, ultrasonography.

decide treatment is not free of risks and in some instances could give place to overdiagnosis. This is defined by a lack of survival benefit and increased risks, associated with the willingness to diagnose a malignancy as early as possible without being associated with improved survival at all [12,13]. Clearly, overdiagnosis would mostly affect patients with nodules that do not have developed an extensive arterial network, responsible for the diagnostic imaging profile. Since this lack of vascularization would imply a less malignant profile, it could be argued that the invasive procedures for diagnosis and treatment of an initially hypovascular nodule at contrast-enhanced ultrasound (CEUS) could exceed the benefits of early diagnosis and treatment. If this would be the case, all interventions could be delayed until arterial vascularization would be recognized.

CEUS has been excluded from the diagnostic process for HCC [1,2] as it may raise false positive HCC diagnosis in patients with intrahepatic cholangiocarcinoma [14–18], a neoplasm with increasing incidence worldwide and for which cirrhosis is a major risk factor [19]. However, as CEUS is able to detect increased arterial vascularization that reflects malignancy [20], it was suggested that if CEUS does not detect increased arterial vascularization in a nodule <2 cm, detected during US screening, it would not be worth to engage in further examinations, or they could be considered of low priority [21,22].

In 2003 we started a prospective study to assess the diagnostic accuracy of MRI, CEUS, fine needle biopsy, and tumour markers for diagnosing HCC in solitary nodules smaller than 2 cm, detected in cirrhotic patients by US screening. The protocol has kept prospectively recruiting patients, aiming to further refine and improve the imaging criteria. In prior studies we established the diagnostic accuracy of MRI and CEUS, using biopsy as gold standard [8]. We exposed the false positive results of CEUS in intrahepatic cholangiocarcinoma [14] and we evidenced the limited value of intratumoural fat or a peritumoural capsule in the diagnostic accuracy of MRI [23]. This study assessed the outcome of patients with HCC, detected by screening ultrasound (US) within this prospective protocol, selecting those for whom baseline CEUS did not detect increased arterial vascularization. If the evolution and treatment response of these nodules would not differ from those for whom hyperenhancement was detected at baseline CEUS, the use of CEUS in establishing urgency and priority criteria for the diagnostic work-up of such nodules would not be supported.

Patients and methods

Patients

Between November 2003 and April 2011, we prospectively included asymptomatic patients with Child-Pugh class A-B cirrhosis with no history of HCC, in whom a new, solitary, well-defined, solid nodule between 5 and 20 mm was detected by screening ultrasonography (US). After reporting that nodules <10 mm rarely correspond to a malignant nodule [8], the cut-off for inclusion was set at 10 mm. Patients with contraindications to perform MRI or fine-needle biopsy were excluded. This study was approved by the Institutional Ethics Committee for Clinical Research.

The diagnostic algorithm is described elsewhere [8]. Upon initial detection of hepatic nodule at screening ultrasound (US) and after signing informed consent, we registered all clinical data. Patients were examined by dynamic MRI and CEUS with a second-generation contrast agent (SonoVue, Bracco, Italy), and finally submitted to fine-needle biopsy (FNB). Biopsy result was considered the gold standard and was repeated if a conclusive diagnosis was not achieved. Since non-invasive criteria by MRI have been externally validated [8–10] and adopted as a criteria for HCC diagnosis [1], we considered after 2007 also the specific vascular profile by MRI as gold standard for HCC diagnosis, and if this was not present a positive biopsy was requested. Nodules with neither pathological confirmation nor specific vascular pattern by MRI were followed with CEUS/3 months and MRI/6 months and a new FNB was performed only in case of growth or acquisition of hypervascularization during the follow-up.

Image acquisition: CEUS

US studies were performed by four experienced radiologist (RV, LB, AGC, and CB), using a Sequoia 512 equipment (Acuson, Mountain View, CA) and following the methods recommended by the European Federation of Societies for Ultrasound in Medicine and Biology (EFSUMB) [20]. Baseline hepatic US was performed with a multifrequency 4C1 convex and a 4V1 sectorial array probe to identify the target nodule. Upon identifying the lesion, CEUS was performed using contrast coherent imaging (CCI, Siemens). A low mechanical index (<0.2) was selected to avoid microbubble disruption. CEUS explorations were performed after the administration of 2.4 ml of SonoVue. This bolus was repeated if the first evaluation was not evaluable. Enhancement patterns were studied during the vascular phase up to 3.5 min, including the arterial (0–35 s), portal (36–120 s) and late phase (>120 s) [20]. Explorations were recorded and baseline appearance, presence of halo and the echographic characteristics after contrast injection were registered.

Image acquisition: MRI

MRI was performed in all patients with a 1.5-T MRI system (Symphony, Siemens Medical Systems, Erlangen, Germany; and SIGNA CVi, General Electric Medical System, Milwaukee, WI) using a phased-array coil for signal detection. All MRIs were done with gadodiamide 0.5 mmol/L (Omniscan-Amersham Health, Madrid, Spain). The technical aspects for imaging acquisition are summarized in Supplementary Table 1.

Fine-needle biopsy

FNB was performed using a 20-gauge needle (Yale Spinal BD medical, NJ). When technically feasible because of location and accessibility, a core-biopsy was performed using an 18-gauge needle (Monopty; Bard Inc, Covington, UK). Specimens were routinely processed and stained with Haematoxylin & Eosin. Stains for reticulin and CD34 were applied when necessary. Diagnosis of HCC was made according to the International Working Party criteria [24].

According to the results of the FNB, lesions were divided in two groups: HCC and non-HCC lesions, which included all hepatic lesions except HCC, independently of their aetiology (benign or malignant).

Statistical analysis

Baseline characteristics of the patient were expressed as median and range, or count and proportion. A comparison of patients with HCC and patients with non-HCC nodules was done, using the Student *t* test or the Mann-Whitney *U* test for continuous variables and the χ^2 test or Fisher's exact test for categorical variables. A *p* value of less than 0.05 was considered significant. The diagnostic accuracy was described by sensitivity, specificity and positive/negative predictive values and expressed with their 95% confident interval. Calculations were done with the SPSS package version 18 (SPSS, Inc. 1989–2006, Chicago, IL).

Results

A total of 168 patients with a solitary liver nodule $\leqslant$20 mm explored by CEUS and MRI were included. Their main patient and echographic characteristics are summarized in Supplementary Tables 2 and 3, respectively. In 5 patients (3%) the echographic pattern after contrast administration was not evaluable due to a poor sonographic window that prevented a reliable evaluation; 4 out of these 5 nodules were finally categorized as HCC. In 119 nodules the final diagnosis was HCC (70.8%). The main echographic characteristics of these 119 HCC nodules are summarized in Table 1 and in Supplementary Table 4. In fourteen