Digestive and Liver Disease 47 (2015) 775–782

Contents lists available at ScienceDirect

Digestive and Liver Disease

journal homepage: www.elsevier.com/locate/dld

Liver, Pancreas and Biliary Tract

Contrast-enhanced ultrasound for the differentiation of small atypical hepatocellular carcinomas from dysplastic nodules in cirrhosis

Seung Kak Shin [a], Yun Soo Kim [a,*], Seung Joon Choi [b], Young Sup Shim [b], Dong Hae Jung [c], Oh Sang Kwon [a], Duck Joo Choi [a], Ju Hyun Kim [a]

[a] Department of Internal Medicine, Gachon University Gil Medical Center, Incheon, Republic of Korea
[b] Department of Radiology, Gachon University Gil Medical Center, Incheon, Republic of Korea
[c] Department of Pathology, Gachon University Gil Medical Center, Incheon, Republic of Korea

ARTICLE INFO

Article history:
Received 17 December 2014
Accepted 4 May 2015
Available online 13 May 2015

Keywords:
Contrast-enhanced ultrasound
Dysplastic nodule
Hepatocellular carcinoma

ABSTRACT

Background: Contrast-enhanced ultrasound is highly accurate in depicting the vascularity of liver nodules. The aim of this study was to evaluate the usefulness of contrast-enhanced ultrasound for the differentiation of hepatocellular carcinomas from dysplastic nodules in cirrhotic patients with small liver nodules showing atypical or not coincidental typical vascular pattern on two dynamic imaging techniques (computed tomography and magnetic resonance imaging).
Methods: A total of 46 patients with cirrhosis and a liver nodule smaller than 3 cm showing an atypical or non-coincident typical vascular pattern on two dynamic imaging techniques, who underwent liver contrast-enhanced ultrasound and ultrasound-guided liver biopsy, were retrospectively reviewed. Contrast-enhanced ultrasound findings were compared with histopathological and clinical data, and with the two dynamic imaging findings.
Results: Significantly different contrast-enhanced ultrasound enhancement patterns were observed among dysplastic nodules, Edmondson grade I and grade II–III hepatocellular carcinomas. Ten out of 11 (90.9%) non-hypervascular hepatocellular carcinomas on two dynamic imaging techniques showed a hypervascular pattern on contrast-enhanced ultrasound, and these made it possible to distinguish hepatocellular carcinomas from dysplastic nodules.
Conclusion: Contrast-enhanced ultrasound is useful for the differentiation of hepatocellular carcinomas from dysplastic nodules in cirrhotic patients with small liver nodules.

1. Introduction

Hepatocellular carcinoma (HCC) is one of the most common cancers worldwide and the third leading cause of cancer-related death [1,2]. Chronic infection by hepatitis B virus (HBV) or hepatitis C virus are recognised important aetiological factors for HCC [2,3]. Unfortunately, the majority of patients who present with HCC are already at the intermediate or advanced stage according to the Barcelona Clinic Liver Cancer (BCLC) staging classification [4] and most have unresectable disease. Therefore, the detection of early-stage HCC, which may be more amenable to curative therapy, is an important therapeutic strategy.

Typically, HCC, especially moderately to poorly differentiated HCC, manifests as a hypervascular tumour with characteristic early arterial enhancement and venous or delayed phase wash-out during dynamic imaging, and these radiological features are highly specific for the diagnosis of HCC. On the other hand, well-differentiated, especially Edmondson grade I HCC, frequently shows atypical enhancement, such as arterial hypo-enhancement or arterial hyper-enhancement without wash-out during dynamic imaging in cirrhotic patients, because at this grade arterial vessels are not well developed and the tumour blood supply is mainly portal [5,6].

According to guidelines published in 2005, the non-invasive diagnosis of HCC was established by one imaging technique in nodules >2 cm showing the HCC radiological hallmark (arterial hyper-enhancement and delayed wash-out) and two coincident imaging techniques (computed tomography [CT] and magnetic

* Corresponding author at: Division of Gastroenterology, Department of Internal Medicine, Gachon University Gil Medical Center, 21, Namdong-daero 774 beon-gil, Namdong-gu, Incheon 405-760, Republic of Korea. Tel.: +82 32 460 3778; fax: +82 32 460 3408.
E-mail address: kimys@gilhospital.com (Y.S. Kim).

http://dx.doi.org/10.1016/j.dld.2015.05.001
1590-8658/

resonance imaging [MRI]) with nodules of 1–2 cm in recommendations reported by the European Association for the Study of the Liver (EASL) panel of experts and the American Association for the Study of Liver Diseases (AASLD) [7]. A recent updated AASLD guideline has proposed that one imaging technique (CT or MRI) showing the HCC radiological hallmark suffices for diagnosing tumours of 1–2 cm in diameter [8].

Recently, however, focal nodular hyperplasia-like lesions showing a radiological hallmark of HCC on CT or MRI have been reported in cirrhotic livers [9]. Therefore, it seems that pathological confirmation or another non-invasive method of diagnosis of HCC is necessary in cirrhotic patients with small liver nodules showing not only an atypical vascular pattern, but also a non-coincident typical vascular pattern on dynamic CT and MRI. However, percutaneous biopsy is not always feasible because of the location of the lesion, the presence of ascites or a bleeding tendency in patients with liver cirrhosis. Consequently, non-invasive imaging studies are required that facilitate the differentiation of early-stage HCCs from dysplastic nodules.

Contrast-enhanced ultrasound (CEUS), which is based on the use of a microbubble contrast agent, is a relatively new imaging method and has been shown to be useful for the characterisation of focal liver lesions. Thus, real-time CEUS might be useful for the differentiation of well-differentiated HCCs from dysplastic nodules in which it was difficult to clarify the difference owing to an atypical or non-coincident typical vascular pattern on dynamic CT and MRI.

This study was conducted to evaluate the usefulness of CEUS for the characterisation of dysplastic nodules, Edmondson grade I HCCs, and grade II–III HCCs in cirrhotic patients with liver nodules smaller than 3 cm showing an atypical or non-coincident typical vascular pattern on dynamic CT and MRI, and to assess the additional diagnostic value of CEUS in the differential diagnosis of non-hypervascular liver nodules on dynamic CT and MRI.

2. Patients and methods

2.1. Patients

We conducted a retrospective study including 116 cirrhotic patients with a single liver nodule smaller than 3 cm, suggestive of HCC that had been newly detected during conventional ultrasound surveillance, who underwent dynamic CT and MRI for imaging diagnosis of the focal nodule from August 2012 to December 2014. Of these, we evaluated 46 consecutive patients who underwent liver CEUS and ultrasound-guided liver biopsy for the differential diagnosis of the nodules showing an atypical or non-coincident typical vascular pattern on dynamic CT and MRI. An atypical vascular pattern of HCC is defined as not showing arterial hyper-enhancement followed by portal venous and delayed washout on dynamic CT and MRI, and this atypical vascular pattern was shown in 22 patients (arterial hypervascular nodule without portal/venous wash-out in 3 patients or arterial hypovascular nodule in 19 patients). All of the 22 nodules showed low signal intensity on the hepatobiliary phase of gadoxetic acid-enhanced MRI and 18 showed high signal intensity on T2-weighted images. A non-coincident typical vascular pattern of HCC is defined as a typical enhancement pattern of HCC with one dynamic imaging study (CT or MRI) and an atypical enhancement pattern with another imaging study, and this pattern was shown in 24 patients. These 24 patients agreed to validate the AASLD 2011 and EASL 2012 guidelines for the management of HCC and to undergo a CEUS for additional non-invasive information before liver biopsy because of the possibility of a false-positive diagnosis on a single imaging study [9].

We excluded 61 patients for a coincidental typical vascular pattern on dynamic CT and MRI, 6 patients for the location of the lesion or bleeding tendency that made it unsafe to perform the biopsy, and 3 patients who underwent transarterial chemoembolisation without liver biopsy. Cases of recurrent HCC after curative treatment, such as surgery or local ablation therapy, were not included.

Liver cirrhosis was diagnosed with liver biopsy or based on radiological findings such as coarse liver echo texture with nodularity and small liver size or the presence of features of portal hypertension (e.g. ascites, splenomegaly, varices) noted on liver imaging [10,11].

Clinical and laboratory parameters, CEUS, CT and MRI findings, and final pathological diagnoses were analysed. The study protocol was approved by the Institutional Review Border (IRB) of Gachon University Gil Medical Centre (IRB No. GCIRB2014-344).

2.2. CEUS

CEUS was performed using a convex transducer (4 MHz, LOGIQ E9, GE) after bolus injection of ultrasound contrast agent (SonoVue®; Bracco, Italy) with a low mechanical index (0.12) to avoid microbubble disruption. Target lesions and surrounding liver parenchyma were observed continuously after injecting SonoVue® (a 2.4-mL bolus was administered for each lesion to be characterised via a 20-gauge intravenous catheter placed in the left antecubital vein, and this was followed by a 10-mL saline flush) through the arterial (<30 s), portal-venous (30–120 s), and delayed phase (120–300 s). CEUS was performed by the same physician with over 18 years of experience of sonography. CEUS findings were compared with histopathological, clinical, and dynamic contrast-enhanced CT and MRI findings.

2.3. CT imaging

All CTs were performed on 64-channel multi-detector CT scanners (Somatom Sensation 64 and Definition; Siemens, Erlangen, Germany). Images of hepatic arterial, portal-venous, and equilibrium phases were obtained using delays of 20, 70, and 180 s respectively, after commencing the injection of 2 mL per kilogram of body weight (to a maximum of 100 mL) of non-ionic contrast agent (Iopromide, Ultravist 300, Schering, Berlin, Germany; or Iopamidol, Pamiray, Dongkook Pharmaceutical, Seoul, Korea) at a section thickness of 5 mm.

2.4. MRI

MRI images were obtained using a 3-T unit (Verio, Siemens Medical Solutions, Erlangen, Germany) or a 1.5-T unit (Avanto, Siemens Medical Solutions, Erlangen, Germany). The MRI sequence consisted of a breath-hold fat-saturated T2-weighted fast spin-echo or turbo spin-echo sequence, a breath-hold T1-weighted dual-echo (in-phase and opposed-phase) sequence, dynamic three-dimensional fat-saturated T1-weighted sequences, and free-breathing diffusion-weighted (DW) imaging by using a single-shot echo-planar imaging sequence. MR images were obtained using a T2-weighted single-shot fast spin-echo or a half-Fourier acquisition single-shot turbo spin-echo sequence (repetition time [TR]/echo time [TE], 700–980/90–100; flip angle, 90–150°; echo-train length, 1; matrix size, 320–380 × 256–305; slice thickness, 3.5–5 mm), a breath-hold T1-weighted gradient-recalled echo in-phase sequence (TR/TE 5–170/2.5–5.0; flip angle, 9–70°; echo-train length, 1; matrix size, 256–320 × 170–280; slice thickness, 3.5–5 mm) and an out-of-phase sequence (TR/TE 5–170/1.5–2.5; flip angle, 10–70°; matrix size, 256–320 × 170–280; slice thickness, 3.5–5 mm). Arterial phase images were acquired 7 s after contrast medium had arrived at the thoracic aorta, and portal-venous,