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● *Original Contribution*

A MODEL-BASED PREDICTION OF THE PROBABILITY OF HEPATOCELLULAR ADENOMA AND FOCAL NODULAR HYPERPLASIA BASED ON CHARACTERISTICS ON CONTRAST-ENHANCED ULTRASOUND

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Abstract—Contrast-enhanced ultrasound (CEUS) is an emerging imaging technique that is increasingly used to diagnose liver lesions. It is of the utmost importance to differentiate between the two most common solid focal liver lesions (*i.e.*, hepatocellular adenoma [HCA] and focal nodular hyperplasia [FNH]), because their management and follow-up differ greatly. The main objective of this study was to determine how frequently the specific CEUS features of HCA and FNH are visible on CEUS and to define their predictive value for discrimination between HCA and FNH. We included 324 CEUS examinations performed on patients with FNH (n = 181) or HCA (n = 143). Patients with HCA and FNH significantly differed with respect to age and CEUS features of steatosis, echogenicity, homogeneity, the presence of a central scar, central artery, arterial enhancement pattern, necrosis or thrombus and enhancement in the late venous phase. (E-mail: j.ijzermans@erasmusmc.nl) © **2017 World Federation for Ultrasound in Medicine & Biology.**

Key Words: **Hepatocellular adenoma, Focal nodular hyperplasia, Contrast-enhanced ultrasound.**

INTRODUCTION

Abdominal ultrasound examination is readily available and frequently used in virtually every hospital. Consequently, during examination of complaints that are not directly related to the liver, many patients are misdiagnosed with a focal lesion in the liver on ultrasound. Most of these lesions are of benign origin, such as hemangiomas, simple cysts, focal nodular hyperplasia (FNH) or hepatocellular adenoma (HCA). Some lesions, such as simple cysts, can be diagnosed on ultrasound. However, solid liver lesions, such as FNH and HCA, need further characterization. Accurate diagnosis is of the utmost importance because treatments for the conditions differ greatly. FNH is a benign lesion with no malignant transformation, symptoms that may resolve during follow-up and a very low incidence of bleeding (Behrend et al. 2001; Belghiti et al. 2014). Therefore, if the diagnosis is firmly established, treatment is rarely indicated (Belghiti et al. 2014; Terkivatan et al. 2006). HCA, on the other hand, has a risk of hemorrhage, rupture and malignant transformation, and treatment might be indicated (European Association for the Study of the Liver 2016).

Macroscopically, FNH tends to be lobulated and in most cases it has a central stellate scar (central element) that radiates into nodules of normal hepatocytes (Terkivatan et al. 2006). The central scar contains a fibrous stroma and malformed vascular structure, the central artery. From this anomalous central artery, the arterial blood often flows centrifugally (stellate-type contrast agent distribution), which is in contrast to HCA (Hussain et al. 2004). HCA tends to have peripheral subscapular vessels that cause diffuse homogenous arterial filling. These characteristics can be used to discriminate the two conditions.

Until recently, magnetic resonance imaging (MRI) or needle biopsy were needed for characterization (Thomeer et al. 2014; van Aalten et al. 2011). However, recent US Food and Drug Administration approval of

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the contrast agent Lumason (Sonovue, Bracco Diagnostics, Monroe Township, NJ, USA) will increase interest in and use of contrast-enhanced ultrasound (CEUS) in clinical medicine.

CEUS is an emerging imaging technique that is increasingly used to diagnose solid focal liver lesions. The use of microbubble ultrasound contrast agents allows detailed assessment of vasculature patterns. The detection and characterization of solid liver tumors has improved considerably using CEUS (Claudon et al. 2013).

The extensively described washout phase, defined as negative enhancement in the tumor 75 s after injection of the microbubble contrast agent, is used to differentiate between benign and malignant liver lesions (Bhayana et al. 2010). Furthermore, a centrifugal hypervascular enhancement pattern (FNH), diffuse arterial enhancement in the arterial phase (HCA), a central scar (FNH), contrast-enhancement in the late phase (FNH) and the presence of thrombus or necrosis (adenoma) are CEUS characteristics that help to differentiate between FNH and HCA. Moreover, a centrifugal hypervascular enhancement pattern in the arterial phase may be an essential feature for the diagnosis of non-typical FNH (Alberti et al. 2014). However, the frequency of the presence of features for HCA and FNH on CEUS and its capacity to differentiate between HCA and FNH have only been described in a few small series (Friedrich-Rust et al. 2013; Kong et al. 2015; Roche et al. 2015). A meta-analysis concluded that a detailed evaluation of HCA by CEUS was not possible because of the low numbers of patients with HCA (Friedrich-Rust et al. 2013). Thereafter, 28 patients with FNH and 10 patients with HCA have been described and showed 66% of the lesions using CEUS were correctly diagnosed compared with 40% of the lesions using color Doppler ultrasound (Kong et al. 2015). Roche et al. (2015) described 40 patients (31 patients with only FNH, 7 patients with only HCA and 2 patients with both FNH and HCA) and suggests that CEUS is a useful adjunct tool, especially in assessing smaller lesions, with an almost perfect interobserver agreement (Roche et al. 2015).

Guidelines outline steps for diagnosing benign solid liver tumors with CEUS and indicate that the specific feature in FNH is a centrifugal hypervascular enhancement pattern in the arterial phase. This specific feature can be used to differentiate FNH from HCA and could even be an essential step for the diagnosis of non-typical FNH (Alberti et al. 2014).

HCA, on the other hand, should have a diffuse arterial enhancement in the arterial phase. Other known patterns include central scar (in B-mode as a CEUS late phase), contrast enhancement in the late phase (both patterns described in FNH) or the presence of thrombus or necrosis (adenoma).

According to the literature that describes the characteristics of FNH and HCA in MRI some findings are more typical than others (Thomeer et al. 2014). For example, the central scar, which is more commonly described in FNH, was also found in 21% of confirmed HCA cases (Hussain et al. 2004; van Aalten et al. 2011).

The frequency that the specific features described for HCA and FNH are present and visible on CEUS has not been satisfactorily described. Therefore, the main objective of this study was to determine how frequently the specific features of HCA and FNH are displayed on CEUS. We also sought to define the predictive value of features for the discrimination between HCA and FNH on CEUS.

MATERIALS AND METHODS

The study was performed in accordance with the ethical guidelines of the 1975 Declaration of Helsinki and approved by the local Institutional Review Board and Ethical Committee from the Erasmus MC University Medical Center, Rotterdam, The Netherlands. The need for written informed consent was waived.

Patients

We included 324 CEUS examinations performed between 2007 and 2014 in patients with confirmed FNH or HCA for review in this study. CEUS findings were only included if the diagnosis of the lesion had been confirmed using at least 2 radiologic modalities, including at least 1 MRI examination with the use of a liver-specific contrast agent. Consensus on the diagnosis was reached after discussion within our multidisciplinary tumor board committee or if the lesion was histologically confirmed (by biopsy or surgical resection). Patient characteristics were collected from the electronic hospital records.

CEUS

CEUS was introduced in our hospital as an additional radiologic modality. CEUS was performed by various sonographers, but all examinations were reviewed by a specialist with more than 20 y of experience in liver ultrasound and more than 9 y of experience in CEUS. The sonographers were blinded to the patients' pre-existing imaging (computed tomography [CT] and MRI) information. CEUS was performed using the Hitachi 900 and Hitachi Preirus ultrasound platforms (Hitachi Medical Systems, Tokyo, Japan) with real-time gray-scale, contrast-tuned imaging and a 2.5- −5.0-MHz probe. The contrast agent used was SonoVue (Bracco Diagnostics, Monroe Township, NJ, USA; dose range 1.0–2.4 mL; repeated if needed and flushed by isotonic saline).