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.

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 [1-2]. Therefore, if 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 [3].

The extensively described washout phase, defined as negative enhancement in the tumor 75 s after injection of the microbubble contrast agent, is being used to differentiate between benign and malignant liver lesions [4]. 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 [5]. However, the frequency of the presence of features for HCA and FNH on CEUS and its capacity to differentiate between HCA and FNH have the diagnosis is firmly established, treatment is rarely indicated [2] [6]. HCA, on the other hand, has a risk of hemorrhage, rupture and malignant transformation, and treatment might be indicated [7].

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 [6]. 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 [8]. 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 [9-10]. However, recent US Food and Drug Administration approval of capacity to differentiate between HCA and FNH have only been described in a few small series [11-13]. A metaanalysis concluded that a detailed evaluation of HCA by CEUS was not possible because of the low numbers of patients with HCA [11]. 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 [12-13] 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 [13].

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 nontypical FNH [5].

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 [9]. For example, the central scar, which is more commonly described in FNH, was also found in 21% of confirmed HCA cases [8] [10].

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 grayscale, contrast-tuned imaging and a 2.5- 25.0-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).

Ultrasound examination was performed in a standardized fashion. First, all patients underwent unenhanced abdominal and hepatic sonography using the fundamental color/power Doppler technique. The location, number, size and sonographic features of the focal liver lesions were recorded. In case of significant hepatic steatosis, the identification of a specific liver mass with ultrasound (US) might be more difficult. However, when the examination was done using the CEUS mode, specific features appear, which can be used to differentiate the different liver masses. Three phases can be observed with CEUS because of the unique network of the hepatic artery and the portal vein [14-17]. CEUS was performed during the hepatic arterial (10–40 s post-injection), portal venous (40–120 s post-injection) and late parenchymal phases (120 s, bubble disappearance), according to the standardized EFSUMB protocol [18]. The vascularity and enhancement pattern of the lesions were compared with the adjacent liver parenchyma. Accordingly, CEUS was performed 5 min after application of the contrast agent. The flash-replenishment technique was applied when needed.

Still images and digital cineloops were saved and later reviewed. Central arteries were defined by the presence of enhanced central arteries with a spoke-wheel appearance. A central scar was defined as a central stellate hypoechogenic area without contrast enhancement in the portal venous phase. Necrosis or a thrombus caused by previous bleeding was defined as an irregular area without contrast filling. Late

contrast-enhancement (contrast agent retention) was defined as the presence of hyperechogenic filling (mostly fine) compared with adjacent liver parenchyma in the late portal phase.

STATISTICAL ANALYSIS

All statistical analyses were performed using SPSS (version 16.0, SPSS Inc., Chicago, IL, USA). Normality of continuous data was checked by inspecting the distribution. Parametric tests were used for continuous data, as these were all normally distributed. Continuous variables are presented as means with standard deviations and categorical variables as numbers and percentages.

First, a univariate analysis was performed by comparing characteristics between HCA and FNH. All p-values < 0.05 (two-sided) were considered as statistically significant.

Next, a multivariable logistic regression analysis was performed to investigate the association between the different covariates and the definitive diagnosis of HCA. A stepwise regression model with backward elimination was used. All items included in the univariate analysis were initially included as a covariate in the initial model. After each step, the covariate with the worst predictive value was removed until the best-fit model remained. The classification cut-off for elimination was set as p 5 0.05. The coefficients of the final multivariate model were used to create a formula for the prediction of the probability that the lesion was HCA.

RESULTS

A total of 324 CEUS examinations were performed in patients diagnosed with FNH or HCA. Patients and lesion characteristics of the CEUS examinations of FNH and HCA are summarized in Table 1. Of the 324 patients, 311 patients (96%) were women and 143 (44%) patients had an HCA. The median age at diagnosis for all patients with HCA was 41 y (range 4–63 y). The median age of the 181 (56%) patients with FNH was 37 y (range 17–61 y). The lesions had a mean diameter of 56 mm (range 10–180 mm).

Steatosis in a nontumorous parenchyma was observed in 47% of the patients with HCA compared with 23% in patients with FNH. Necrosis or thrombus formation was observed in 18% of the patients with HCA compared with 3% necrosis or thrombus formation in the patients with FNH. No acute bleeding or thrombus formation was observed.

Results from the univariate analysis of possible patient-related predictors combined with features on CEUS between the group of patients with HCA and FNH are shown in Table 1. HCA and FNH patients differed significantly with respect to age

Table 1. Univariate analysis of possible predictors for HCA and FNH*

	HCA (n = 143) n (%)	FNH (n = 181) n (%)	p value
Patient Age, y (range)	40.6 (18–77)	40.6 (18–77)	0.001
Size lesion (mm)	54 (10–180)	59 (15–175)	0.04
Liver Steatosis	67 (47)	41 (23)	< 0.001
Ultrasound before contrast Echogenicity (M = 1)			< 0.001
Hypo	48 (34)	31 (17)	
Iso	59 (42)	137 (76)	
Hyper	35 (25)	13 (7)	
Homogenicity (homo)	107 (75)	156 (86)	0.009
Central scar	34 (24)	145 (80)	< 0.001
Central artery (M = 1)	46 (32)	150 (83)	< 0.001
CEUS arterial phase Enhancement pattern (M = 16)			< 0.001
Fugal	14 (11)	98 (56)	
Mixed	19 (14)	40 (23)	
Petal	99 (75)	38 (22)	
Necrosis or bleeding (M = 1)	26 (18)	6 (3)	< 0.001
CEUS portal venous phase (M = 3) Sustained/retention	20 (14)	73 (40)	< 0.001
Iso	92 (66)	95 (53)	
Hypo	21 (15)	8 (4)	
Hetero	7 (5)	5 (3)	

HCA = hepatocellular adenoma; FNH = focal nodular hyperplasia; CEUS = contrast-enhanced ultrasound.

* Univariate analysis results for various comparisons for HCA and FNH. $p < 0.05$ was considered statistically significant.

Data were analyzed using a t-test or Pearson's c^2 test where appropriate. Values in parentheses are percentages unless otherwise noted.

and the CEUS features of steatosis, echogenicity, homogeneity, central scar, central artery, arterial enhancement pattern, necrosis or thrombus, and enhancement in the late portal phase (contrast agent retention).

In a multivariable analysis, the subsequent items were eliminated in the following order: homogeneity ($p = 0.888$), enhancement in the late venous phase (contrast retention) ($p = 0.797$), necrosis or thrombus caused by previous bleeding ($p = 0.527$), echogenicity ($p = 0.108$) and steatosis ($p = 0.193$). The regression coefficients of the final regression model are given in Table 2. Using these coefficients, the predicted probability of HCA was calculated using the following formula:

Predicted Probability (P) =1/(1+e(0.778+(0.36 *Age) + (-1.251*central scar) +(-1.198*central artery) +(0.541*enhancement mixed) +(1.157*enhancement petal))

A receiver operating characteristic (ROC) curve was plotted and showed an area under the curve (AUC) of 0.854 (Figure 1). Figure 2 shows the predicted probability that the definitive diagnosis is HCA for increasing age and visualization of a central scar and central artery for different enhancement patterns.

Table 2. Multivariable logistic regression analysis for the prediction of HCA based on patient characteristics and CEUS

	p value	Regression coefficient	95% confidence interval
Age	0.015	1.037	1.007–1.067
Central scar	0.020	0.286	0.129–0.634
Central artery	0.010	0.302	0.148–0.615
Enhancement pattern Fugal	0.056		
Mixed	0.221	1.718	0.722–4.090
Petal	0.017	3.182	1.229–8.239

HCA = hepatocellular adenoma; CEUS 5 contrast-enhanced ultrasound.
Central artery and enhancement pattern

DISCUSSION

Liver Steatosis

Currently, fatty liver disease is the most common chronic liver disease with an estimated incidence of 30% in Western countries [19]. Liver steatosis is often accompanied by obesity. HCA seems to also be associated with obesity, explaining why significantly more people with HCA have liver steatosis (47%) compared to patients with FNH (23%). Identifying a specific liver mass with US might be more difficult in obese patients. However, specific features can be depicted using CEUS, which can aid in differentiating the various liver masses.

HCA can be hyperechogenic in an otherwise normal liver during ultrasound without the use of contrast ("fat-containing HCA"); however, we also found that 7% of FNHs were hyperechogenic. This rare hyperechogenicity of FNH could be explained by the occasional presence of fat in FNH, which has been previously described and should be considered in ultrasound and imaging diagnostics [20]. When other classical FNH findings are seen, the presence of fat in the lesion can occasionally make the diagnosis less robust.

Central scar

A classic FNH is composed of nodules surrounded by radiating fibrous septa originating from a central scar [21] [8]. The central scar in FNH is a collection of blood vessels, bile ducts and fibrosis stroma [22]. With CT and MRI, the central scar has been reported in 22% – 85% of FNH cases [23-24]. On CEUS, in which the central scar appears as a hypoechogenic area in the delayed phase [16-17], or on B-scan ultrasound, where it appears as a white fibrotic stripe, we identified a central scar in 80% of the FNH cases. However, fibrotic stripes similar to a central scar have been observed in 24% of HCA cases as well. Recently, fibrotic scars have also been described in 21% of HCAs on MRI [9-10]. The central scar is characterized on MRI by a T2 weighted late enhancement in the delayed phase. As a central scar could also be visible in HCA: Differentiation between HCA and FNH should not be based on the rare, but can be present and is not exclusively diagnostic for HCA on US.

As expected, a central artery with centrifugal (stellate) filling was more common in FNH, and a petal appearance of the central scar alone, fibrotic stripes could have the same appearance.

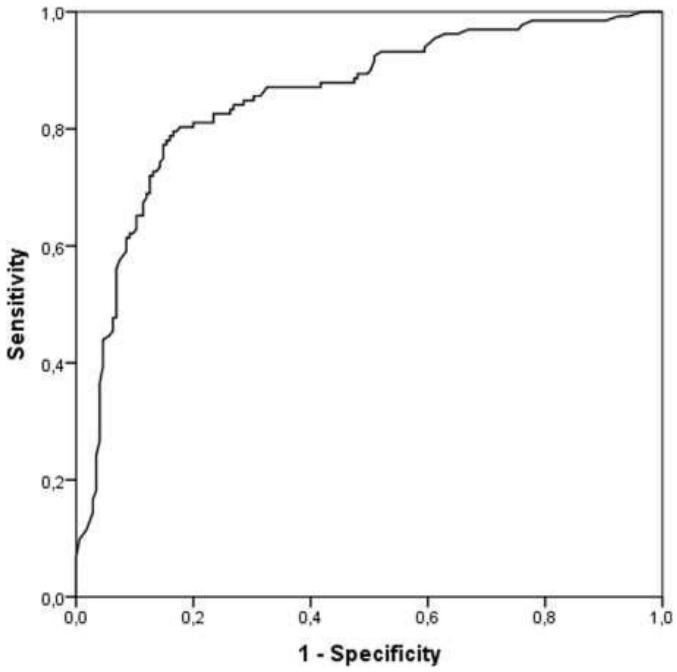

Fig. 1. ROC curve for the prediction of HCA using the formula 1/(1 1 e(0.778 1 (0.36 *Age)) 1 (central scar) (central artery) (enhancement mixed) (enhancement petal)), showing an area under the curve value of 0.854. ROC 5 receiver operating characteristic; HCA 5 hepatocellular adenoma.

Necrosis or thrombus

A thrombus caused by previous bleeding was present in 18% of the HCA and 3% of the FNH in this study. Thrombus caused by bleeding in HCA is fairly common, with an average overall frequency of 27.2% and a maximum reported frequency of 64% [25-26]. It should be noted that if an irregular area without contrast enhancement is observed on CEUS, no differentiation among necrosis, thrombus from an old bleeding, or a large central scar can be made [1-27]. The presence of an avascular area (necrosis/thrombus) in FNH is very rare, but can be present and is not exclusively diagnostic for HCA on US.

Central artery and enhancement pattern

As expected, a central artery with centrifugal (stellate) filling was more common in FNH, and a petal filling was most common in HCA [28]. Arteries in FNH can be abnormally large for the region of the liver they perfuse and in some nodules color Doppler examination can be diagnostic. It may sometimes be difficult to localize the central part of the arterial tree with single plane US because it can be located eccentrically and not centrally. A subset of patients has not one, but two or more centers with stellate arterial projections. In these cases, the centers probably tend to be faint and not robust. Further technological development, such as the regular use of 3-D CEUS, could be of benefit here.

Contrast-agent retention in the late portal phase

This US sign (contrast-agent retention in the late portal phase) was confirmed to be predominant in FNH but was found only in 40% of FNH patients. This level was statistically significant but not exclusive; up to 14% of adenomas were hyperechogenic in the late phase. Contrast-agent retention can be confusing because 25% of adenomas are already hyperechogenic on B-scan US. The sonographer should carefully differentiate between an already hyperechogenic tumor background that already exists and an influence of the presence of contrast agent. Some atypical FNHs may show a washout-like image in late phase — in our series 4%, which is usually seen in hepatocelullar carcinoma and also in some HCAs (15% in this study).

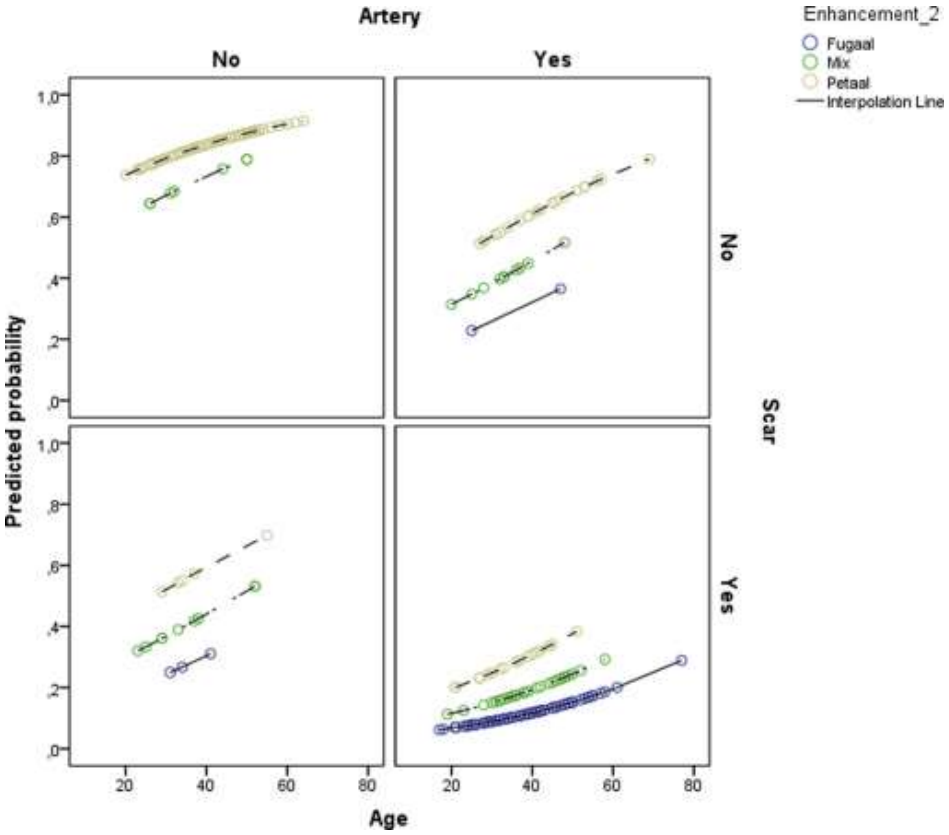

Fig. 2. HCA diagnosis. The predicted probability that the definitive diagnosis is HCA. The visualization of a central scar and a central artery on CEUS indicates which quadrant of the figure should be used. The colored lines in each quadrant represent the various enhancement patterns (blue, fugal; green, mixed; yellow, petal). By using the age of the patient at the time of diagnosis on the corresponding colored line, the predicted probability that the definitive diagnosis is HCA can be determined. HCA = hepatocellular adenoma; CEUS = contrast-enhanced ultrasound.

Limitations

Our study has limitations. First, the final diagnoses were not all histologically validated. In those cases, combined imaging was used as the reference method for the final diagnosis, which was made after consensus was reached within our multidisciplinary tumor board committee. If we had only selected patients with a histologically proven diagnosis, a bias would have been introduced because a biopsy is only approved in our hospital if the diagnosis is in doubt or radiologic examinations are incongruent. Second, because the lesions were not biopsied, it was impossible to link the specific features to the Bordeaux classification of HCA subtypes and their ultrasonographic appearance.

The aim of this study was to differentiate FNH and HCA, two solid benign liver tumors. In clinical practice, it is also of the utmost importance to exclude hepatocellular carcinoma. The most important feature to differentiate benign and malignant liver lesions on CEUS is the presence of washout [29], [4]. However, this feature showed no additional value in differentiating between FNH and HCA. It is essential to first rule out a malignancy before using this model, which givesinsight intothe predicted probability of HCA.

CONCLUSIONS

In conclusion, increased age and CEUS features of liver steatosis, tumor echogenicity, homogeneity, thrombus presence, filling pattern and central scar, central artery, arterial enhancement pattern and absence of enhancement in the portal venous phase were found to be predictive in distinguishing between HCA and FNH. A reliable model using age and the presence of a central scar, central artery and enhancement pattern can predict the probability that the definitive diagnosis is HCA. If the diagnosis of HCA or FNH is equivocal on MRI, CEUS can be used to differentiate the two lesions, as a combination of the two methods provides the highest diagnostic accuracy [30]. This study gives insight about the reliability of the features on CEUS and helps clinicians to decide whether further liver mass biopsy is needed.

BIBLIOGRAPHY

[1] M. Behrend, P. Flemming and H. Halbfass, "Spontaneous Bleeding of Focal Nodular Hyperplasia as a Rare Cause of Acute Abdomen", *Chirurg,* pp. 1201-4, 72(10) Oct 2001.

[2] J. Belghiti, F. Cauchy, V. Paradis and V. Vilgrain, "Diagnosis and Management of Solid Benign Liver Lesions," *Nat Rev Gastroenterol Hepatol,* pp. 737-49, 11(12) Dec 2014.

[3] M. Claudon, C. Dietrich, B. Choi, D. Cosgrove, M. Kudo, C. Nolsoe, F. Piscaglia, S. Wilson, R. Barr, M. Chammas, N. Chaubal, M.-H. Chen, D. Clevert, J. Correas, H. Ding, F. Forsberg, J. Fowlkes, R. Gibson, B. Goldberg, N. Lassau, E. Leen, R. Mattrey, F. Moriyasu, L. Solbiati, H.-P. Weskott, H.-X. Xu, World Federation for Ultrasound in Medicine and European federation of Societies for Ultrasound, "Guidelines and Good Clinical Practice Recommendations for Contrast Enhanced Ultrasound (CEUS) in the Liver - Update 2012: A WFUMB-EFSUMB Initiative in Cooperation With Representatives of AFSUMB, AIUM, ASUM, FLAUS and ICUS," *Ultrasound Med Biol,* pp. 187-210, 39(2) Feb 2013.

[4] D. Bhayana, T. Kim, H.-J. Jang, P. Burns and S. Wilson, "Hypervascular Liver Masses on Contrast-Enhanced Ultrasound: The Importance of Washout," *AJR Am J Roentgenol,* pp. 977-83, 194(4) Apr 2010.

[5] N. Alberti, N. Frulio, P. Bioulac-Sage, H. Laumonier, C. Balabaud, J.-T. Perez, F. Teixeira Jr, N. Harbonnier and H. Trillaud, "Interest of Contrast-Enhanced Sonography to Identify Focal Nodular Hyperplasia With Sinusoidal Dilatation," *Diagn Interv Imaging,* pp. 77-83, 95(1) Jan 2014.

[6] T. Terkivatan, S. Hussain, R. De Man and J. IJzermans, "Diagnosis and Treatment of Benign Focal Liver Lesions," *Scand J Gastroenterol,* pp. 102-15, (243) Suppl 2006.

[7] European Association for the Study of the Liver, (EASL), "EASL Clinical Practice Guidelines on the Management of Benign Liver Tumours," *J Hepatol,* pp. 386-98, 65(2) Aug 2016.

[8] S. Hussain, T. Terkivatan, P. Zondervan, E. Lanjouw, S. de Rave, J. IJzermans and R. de Man, "Focal Nodular Hyperplasia: Findings at State-Of-The-Art MR Imaging, US, CT, and Pathologic Analysis," *Radiographics,* pp. 3-17, discussion 18-9, 24(1) Jan-Feb 2004.

[9] M. Thomeer, M. Broker, Q. de Lussanet, K. Biermann, R. Dwarkasing, R. de Man, J. IJzermans and M. de Vries, "Genotype-phenotype Correlations in Hepatocellular Adenoma: An Update of MRI Findings," *Diagn Interv Radiol,* pp. 193-9, 20(3) may-Jun 2014.

[10] S. van Aalten, M. Thomeer, T. Terkivatan, R. Dwarkasing, J. Verheij, R. de Man and J. IJzermans, "Hepatocellular Adenomas: Correlation of MR Imaging Findings With Pathologic Subtype Classification," *Radiology,* pp. 172-81, 261(1) Oct 2011.

[11] M. Friedrich-Rust, T. Klopffleisch, J. Nierhoff, E. Herrmann, J. Vermehren, M. Schneider, S. Zeuzem and J. Bojunga, "Contrast-Enhanced Ultrasound for the Differentiation of Benign and Malignant Focal Liver Lesions: A Meta-Analysis," *Liver Int,* pp. 739-55, 33(5) May 2013.

[12] W.-T. Kong, W.-P. Wang, B.-J. Huang, H. Ding, F. Mao and Q. Si, "Contrast-enhanced Ultrasound in Combination With Color Doppler Ultrasound Can Improve the Diagnostic Performance of Focal Nodular Hyperplasia and Hepatocellular Adenoma," *Ultrasound Med Biol,* pp. 944-51, 41(4) Apr 2015.

[13] V. Roche, F. Pigneur, L. Tselikas, M. Roux, L. Baranes, M. Djabbari, C. Costentin, J. Caldararo, A. Laurent, A. Rahmouni and A. Lusiani, "Differentiation of Focal Nodular Hyperplasia From Hepatocellular Adenomas With Low-Mechanical-Index Contrast-Enhanced

Sonography (CEUS): Effect of Size on Diagnostic Confidence," *Eur Radiol,* pp. 186-95, 25(1) Jan 2015.

[14] M. Claudon, D. Cosgrove, T. Albrecht, L. Bolondi, M. Bosio, F. Calliada, J.-M. Correas, K. Darge, C. Dietrich, M. D'Onofrio, D. Evans, C. Filice, L. Greiner, K. Jager, N. de Jong, E. Leen, R. Lencioni, D. Lindsell, A. Martegani, S. Meairs, NolsoeC, F. Piscaglia, P. Ricci, G. Seidel, B. Skjoldbye, L. Solbiati, L. Thorelius, F. Tranquart, H. Weskott and T. Whittingham, "Guidelines and Good Clinical Practice Recommendations for Contrast Enhanced Ultrasound (CEUS) - Update 2008," *Ultraschall Med,* pp. 28-44, 29(1) Feb 2008.

[15] H.-J. Jang, T. Kim and S. Wilson, "Imaging of Malignant Liver Masses: Characterization and Detection," *Ultrasound Q,* pp. 19-29, 22(1) Mar 2006.

[16] F. Piscaglia, R. Lencioni, E. Sagrini, C. Dalla Pina, D. Cioni, G. Vidili and L. Bolondi, "Characterization of Focal Liver Lesions With Contrast-Enhanced Ultrasound," *Ultrasound Med Biol,* pp. 531-50, 36(4) Apr 2010.

[17] F. Piscaglia, A. Venturi, M. Mancini, F. Giangregorio, G. Vidili, F. Magnolfi, M. Mirarchi, F. Fornari and L. Bolondi, "Diagnostic Features of Real-Time Contrast-Enhanced Ultrasound in Focal Nodular Hyperplasia of the Liver," *Ultraschall Med,* pp. 276-82, 31(3) Jun 2010.

[18] F. Piscaglia, C. Nolsoe, C. Dietrich, D. Cosgrove, O. Gilja, M. Bachmann Nielsen, T. Albrecht, L. Barozzi, M. Bertolotto, O. Catalano, M. Claudon, D. Clevert, J. Correas, M. D'Onofrio, F. Drudi, J. Eyding, M. Giovannini, M. Hocke, A. Ignee, E. Jung, A. Klauser, N. Lassau, E. Leen, G. Mathis, A. Saftoiu, G. Seidel, P. Sidhu, G. ter Haar, D. Timmerman and H. Weskott, "The EFSUMB Guidelines and Recommendations on the Clinical Practice of Contrast Enhanced Ultrasound (CEUS): Update 2011 on Non-Hepatic Applications," *Ultraschall Med,* pp. 33-59, 33(1) Feb 2012.

[19] J. Browning, L. Szczepaniak, R. Dobbins, P. Nuremberg, J. Horton, J. Cohen, S. Grundy and H. Hobbs, "Prevalence of Hepatic Steatosis in an Urban Population in the United States: Impact of Ethnicity," *Hepatology,* pp. 1387-95, 40(6) Dec 2004.

[20] A. Burt, B. Portman and L. Ferrell, MacSween's Pathology of the Liver, 6th edition, London: Churchill Livingstone, 2012.

[21] Y. Fukukura, O. Nakashima, A. Kusaba, M. Kage and M. Kojiro, "Angioarchitecture and Blood Circulation in Focal Nodular Hyperplasia of the Liver," *1998,* pp. 470-5, 29(3) Sep J Hepatol.

[22] K. Elsayes, C. Peterson and C. Menias, "The Central Scar: Pathophysiology and Imaging Features," *Curr Probl Diagn Radiol,* pp. 247-57, 36(6) Nov-Dec 2007.

[23] T. Bartolotta, A. Taibbi, G. Brancatelli, D. Matranga, M. Tumarello, M. Midiri and R. Lagalla, "Imaging Findings of Hepatic Focal Nodular Hyperplasia in Men and Women: Are They Really Different?," *Radiol Med,* pp. 222-30, 119(4) Apr 2014.

[24] K. Mortelé, M. Praet, H. Van Vlierberghe, M. Kunnen and P. Ros, "CT and MR Imaging Findings in Focal Nodular Hyperplasia of the Liver: Radiologic-Pathologic Correlation," *AJR Am J Roentgenol,* pp. 687-92, 175(3) Sep 2000.

[25] M. Bieze, S. Phoa, J. Verheij, K. van Lienden and van Gulik, "Risk Factors for Bleeding in Hepatocellular Adenoma," *Br J Surg,* pp. 847-55, 101(7) Jun 2014.

[26] S. van Aalten, R. de Man, J. IJzermans and T. Terkivatan, "Systematic Review of Haemorrhage and Rupture of Hepatocellular Adenomas," *Br J Surg,* pp. 911-16, 99(7) Jul 2012.

[27] B. Nguyen, J. Flejou, B. Terris, J. Belghitti and C. Degott, "Focal Nodular Hyperplasia of the Liver: A Comprehensive Pathologic Study of 305 Lesions and Recognition of New Histologic Forms," *Am J Surg Pathol,* pp. 1441-1454, 23(12) Dec 1999.

[28] T. Kim, H.-J. Jang, P. Burns, J. Murphy-Lavallee and S. Wilson, "Focal Nodular Hyperplasia and Hepatic Adenoma: Differentiation With Low-Mechanical-Index Contrast-Enhanced Sonography," *AJR Am J Roentgenol,* pp. 58-66, 190(1) Jan 2008.

[29] T. Bernatik, K. Seitz, W. Blank, A. Schuler, C. Dietrich and D. Strobel, "Unclear Focal Liver Lesions in Contrast-Enhanced Ultrasonography--Lessons to Be Learned From the DEGUM Multicenter Study for the Characterization of Liver Tumors," *Ultraschall Med,* pp. 577-81, 31(6) Dec 2010.

[30] M. Soussan, C. Aube, S. Bahrami, J. Boursier, D. Valla and V. Vilgrain, "Incidental Focal Solid Liver Lesions: Diagnostic Performance of Contrast-Enhanced Ultrasound and MR Imaging," *Eur Radiol,* pp. 1715-25, 20(7) Jul 2010.