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MRI Using Gadoxetic Acid in the Work-Up of Liver Nodules Not Conclusively Benign in Budd-Chiari Syndrome: A Prospective Long-Term Follow-Up

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Keywords
Hepatocellular carcinoma · Liver-specific contrast agents · Vascular disorders · Hepatic vein obstruction

Abstract
Introduction: The incidence of hepatocellular carcinoma (HCC) in Budd-Chiari syndrome (BCS) is unknown and there is no validated diagnostic work-up to define the liver nodules with arterial phase hyperenhancement (APHE), suggesting malignancy. This prospective study evaluates HCC incidence in a Western cohort of patients with BCS and assesses the performance of MRI with hepatobiliary contrast (HB-MRI) for nodule characterization. ***Methods:*** Patients with BCS followed in our hospital were prospectively evaluated by MRI with extracellular contrast (EC-MRI). Nodules with APHE categorized as non-conclusively benign by 2 radiologists were studied by HB-MRI and reviewed by 2 radiologists blinded to the EC-MRI results. A new EC-MRI 1 year later and clinical, analytical, and sonographic follow-up every 6 months for a median of 10 years was performed. ***Results:*** A total of 55 non-conclusively benign nodules with APHE were detected at EC-MRI in 41 patients. While 32 of them were suggestive of HCC by EC-MRI, all the 55 nodules showed increased uptake of hepatobiliary contrast. An unequivocal central scar was seen in 12/55 nodules at HB-MRI regardless of it was not detected on the EC-MRI. None of the nodules was hypointense in the hepatobiliary phase (HBP). HCC was not detected during a median of 10 years of follow-up. ***Conclusions:*** Detection of nodules with APHE is frequent in patients with BCS, but HCC is rare in Western patients with

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BCS. While EC-MRI may detect nodules suggesting malignancy, the identification of contrast uptake in the HBP at HB-MRI may help categorize them as benign.

Introduction

Budd-Chiari syndrome (BCS) is an uncommon condition caused by obstruction of hepatic venous outflow at any level from the small hepatic veins to the junction of the inferior vena cava. The most frequent cause is the thrombosis of the hepatic veins due to an underlying prothrombotic state.

In patients with BCS, the development of hypervascular benign hepatocellular nodules [1–3] referred to as "focal nodular hyperplasia-like" (FNH-like) is frequent. BCS related to a membranous obstruction of the inferior vena cava is also a recognised risk factor in developing hepatocellular carcinoma (HCC) [4–6]. Although far less frequent, some cases of HCC in patients with BCS secondary to thrombosis of the hepatic veins in Western countries have also been described [7]. However, the magnitude of risk is not well defined and only isolated reported cases and a retrospective study [7] have been published about it. The lack of prospective studies makes the incidence of HCC in BCS in Western countries unknown.

The radiological characteristics of benign hepatic nodules associated with BCS usually allow the differential diagnosis with HCC to be established [3, 8, 9]. However, there are occasionally benign nodules that have an imaging behaviour indistinguishable from HCC. It has been noted that the non-invasive diagnostic criteria established for HCC by MRI in patients with cirrhosis cannot be applied to patients with BCS [10]. In these cases, a biopsy would be necessary to obtain a conclusive diagnosis. This is particularly risky in a population with thrombotic disorders and almost universally under anticoagulation treatment although it would be feasible if anticoagulation is previously stopped following the recommendations [11]. The high incidence of benign nodules in these patients, frequently multiple, would imply to perform a large number of biopsies during follow-up. The risk of dissemination outside the liver along the needle track in case of hypervascular malignant tumours could be also a limitation for biopsy [12].

Gadoxetic acid (GA) or Gd-EOB-DTPA (Primovist®, Bayer Schering Pharma) is a hepatocyte-specific MRI contrast agent that is progressively taken up into the hepatocytes [13] via the organic anion transporter polypeptides. FNH and FNH-like nodules revealed equal or stronger organic anion transporter polypeptide expression than the surrounding liver tissue [14], resulting in hepatobiliary phase (HBP) hyperintensity [15, 16]. Until now, only a few case reports [17, 18] and recently, a retrospective study [19] have reported the application of MRI with hepatobiliary contrast (HB-MRI) in the characterization of focal liver lesions in BCS. The lack of knowledge of the true incidence of HCC in patients with BCS combined with the absence of prospective studies using HB-MRI, make that the role of this contrast agent in the diagnostic algorithm of patients with BCS has not been established.

The aim of this prospective and long-term follow-up study was to evaluate the incidence of HCC in a Western cohort of patients with BCS and to assess the performance of HB-MRI for the non-invasive diagnosis of liver nodules associated to BCS, focused on those that do not show conclusive characteristics of benignity by MRI with extracellular contrast (EC-MRI).

Materials and Methods

A prospective study including all patients with primary BCS followed in our hospital between February 2010 and June 2012 was designed and approved by the Institutional Ethics Committee for Clinical Research (HCB 2010/6155). Written informed consent was obtained from participants (or their parent/legal guardian) to participate in the study.

Patients

We invited all patients with the diagnosis of primary BCS followed in our hospital to participate in the study. Patients with other concomitant causes of chronic liver disease as hepatitis C, hepatitis B virus infection, ethanol abuse, non-alcoholic steatohepatitis, or others were excluded. After signing the written informed consent, demographic, laboratory, and clinical data were collected. Underlying disease-causing BCS, time elapsed since the diagnosis of BCS, history of transjugular intrahepatic portosystemic shunt (TIPS), and time since their placement were recorded. Alpha-feto-protein (AFP) determination was also performed.

An EC-MRI was carried out in all patients included in the study and the presence of liver nodules was registered. Patients were classified into two groups according to the presence or absence of liver nodules. All demographic, laboratory, and clinical data were evaluated for each group. A HB-MRI was performed within 4–5 months to all patients with nodules ≥1 cm in the EC-MRI.

Follow-Up

A clinical, analytical, and ultrasound follow-up was carried out every 6 months for a very extended period, until July 2021, in all patients included (patients with and without liver nodules). In addition, a new EC-MRI and AFP determination was scheduled after 1 year of the first MRI in all patients.

MRI Technique

Examinations were performed on a 1.5-T MR: Signa HDxt, GE Healthcare, Milwaukee, Wi, USA or Magnetom Aera, Siemens Medical Solutions, Erlangen by using multichannel-phased array coils for signal detection. The supplementary material (for all online suppl. material, see https://doi.org/10.1159/000533598) reports the MRI acquisition protocols in detail.

Image Analysis

MRI with Extracellular Contrast

The initial EC-MRI examination performed was evaluated by two radiologists with more than 10 years of experience in liver imaging (J.R. and A.G.) and differences were solved in consensus. Patients were classified into two groups based on the presence or absence of liver nodules. Patients with nodules ≥1 cm with arterial phase hyperenhancement (APHE) were selected, and the profile of the nodules was registered as follows: (1) nodules with conclusive characteristics of benignity including nodules with presence of a central scar (either central hyperintense signal on T2-weighted images or central enhancement on delayed phase of gadolinium-enhanced imaging) [20] and any other considered to have imaging characteristics of benignity (i.e., haemangioma) and (2) nodules without conclusive characteristics of benignity. This last group represents the final study group, and these nodules were considered as target lesions.

Nodules with APHE and without conclusive characteristics of benignity were classified as (1) nodules suspicious of HCC when they showed characteristic behaviour pattern of HCC according to the non-invasive criteria accepted for the diagnosis of HCC in cirrhotic patients: non-rim APHE and venous washout, without central scar or (2) indetermined nodules when they showed any other imaging pattern. To further characterize the suspicious and indetermined nodules on EC-MRI, the following items were recorded: (1) size, (2) location according to the Couinaud classification, (3) signal intensity on T2-weighted sequences, (4) signal intensity on T1-weighted sequences of dynamic study (presence of rim enhancement or non-rim enhancement), (5) presence of fat in mass determined by signal loss on out-of-phase sequences, (6) presence of enhancing "capsule" on delayed venous phase. Finally, as exploratory analysis, we also collected the presence of signal restriction detected on diffusion-weighted imaging (DWI) sequences on high b-value (600 and 800 s/mm^2).

MRI with Hepatobiliary Contrast

Lecture of HB-MRI was carried out independently by two radiologists (AD and EB with more than 15 and 5 years of experience in liver imaging, respectively). With the aim to determine the contribution of HBP in the diagnosis of non-conclusive nodules, only the HBP of the nodules with APHE without conclusive characteristics of benignity were evaluated, and the two radiologists were blinded to the findings of EC-MRI and HB-MRI, except for the HBP. Imaging parameters registered on HB-MRI were (1) signal intensity of the lesion on the HBP: hypointense, isointense, or hyperintense compared to liver parenchyma, (2) presence of unequivocal central area of low signal intensity on the HBP, indicative of central scar. Any discrepancies during image analysis were solved by consensus discussion between the two readers. Additional data on the presence of hypoenhancing lesions on HBP of all HB-MRI performed were also recorded by a senior radiologist (CA) not involved in the previous lectures.

Follow-Up EC-MRI

Nodules considered as indeterminate or suspicious for malignancy on the first EC-MRI were revaluated at the 1-year follow-up EC-MRI by a single radiologist (A.G.). The analysis included (1) size compared with the first EC-MRI and categorization as stability, growth, or reduction, (2) pattern of enhancement and categorization as similar or different compared with the first EC-MRI.

Statistical Analysis

Quantitative variables were expressed as median and interquartile range (IQR 25th–75th percentiles). Categorical variables were described as absolute frequencies and percentages (%). The Fisher's exact test was used to compare categorical variables and U of Mann-Whitney test was used to compare quantitative or ordinal variables.

Agreement between readers (inter-reader agreement) for washout identification in EC-MRI study and for uptake in HBP and detection a central scar in HB-MRI was assessed with Kappa statistic for binary response parameters. When kappa was low despite high observed agreement when the marginals are imbalanced (first kappa paradox [21]), we used Bangdiwala's B-statistic [22]. A board certified statistician performed all statistics analysis using SAS software v9.4®. The level of significance was set at 5% (two-sided).

Results

Patient Characteristics

A total of 43 patients with the diagnosis of BCS were eligible for the study. Two patients declined to be enrolled. Finally, 41 patients were included in the prospective study. Table 1 reports patients' characteristics. Six patients had thrombosis of two out of the three hepatic veins while the remaining 35 patients had the three hepatic veins involved, four of them had associated a thrombosis of the inferior cava vein.

The EC-MRI demonstrated the presence of any size liver nodule in 25/41 patients (60.9%): two had one nodule (8%), 4 patients had 2–5 nodules (16%), 7 patients had 6–10 nodules (28%), 4 patients had 11–20 nodules (16%), and 8 patients had >20 nodules (32%). As shown in Table 1, patients with liver nodules had a significantly lower age than those without (p = 0.02). Indeed, all patients under the age of 35 years at inclusion in the study had liver nodules on the EC-MRI.

A significantly greater proportion of patients with a previous TIPS stenting was observed in the group of patients with nodules: 18/25 (72%) versus 5/16 (31.3%) (p = 0.02). In the majority of cases (n = 19/23), the TIPS had been placed >2 years ago. In order to avoid a possible confounding factor, an analysis excluding patients with TIPS stenting was also performed: the age remained significantly lower in the group of patients with liver nodules than those without (p = 0.02).

Table 1. Characteristics of the patients

	All	Patients w/o nodules	Patients w nodules	*p* value
Patients, *n*	41	16	25	
Age at inclusion, years, median [IQR]	41 [35–51]	46 [38–54.5]	37 [32–48]	0.02
Gender (female), *n* (%)	26 (63.4)	9 (56.3)	17 (68)	0.5
Median years from diagnosis of BCS, median [IQR]	5.7 [1.8–9.8]	7.2 [3.3–11.8]	4.3 [1.8–7.1]	0.17
Age at diagnosis, years, median [IQR]	36 [30–41]	39 [33–43.5]	34 [28–40]	0.06
Etiology of BCS (7 patients had more than one etiologic factor)				
Myeloproliferative neoplasm	27	7	20	
Factor V Leiden	3	2	1	
Protein C deficiency	1	0	1	
Protein S deficiency	1	1	0	
Antiphospholipid antibodies	5	1	4	
Paroxysmal nocturnal haemoglobinuria	3	2	1	
Behçet's disease	2	1	1	
Systemic lupus erythematosus	2	1	1	
Idiopathic	4	3	1	
TIPS (yes), *n* (%)	23 (56.1)	5 (31.3)	18 (72)	0.02
Years with TIPS, median [IQR]	6.1 [3.3–10.8]	9.8 [9.5–10.8]	5.5 [2.4–8.6]	0.16
AFP, ng/mL, median [IQR]	3 [2–4]	3 [2–3.5]	3 [3–5]	0.16

AFP, alpha-feto-protein.

AFP value was determined in all but 2 patients at baseline. The AFP value was normal in all cases with a median of 3 ng/mL (IQR: 2–4), and no patient had an AFP >15 ng/mL.

Figure 1 shows the flow chart of patients and MRI through the study. Twenty-two out of 41 patients (53.6%) had at least one nodule ≥10 mm in size. A HB-MRI was performed in 19 of them. HB-MRI was not performed in 3 cases for different reasons: 1 patient was lost for the follow-up. 2 patients were followed-up and treated in another institution (one of them was transplanted 12 months after inclusion in the study and had no evidence of malignancy in the explant. The other had a follow-up EC-MRI 1 year after inclusion in the study, and a clinical and sonographic follow-up for 9 years without evidence of HCC).

Suspicious and Indeterminate Liver Nodules

Figure 2 shows the flow chart of suspicious and indeterminate liver nodules, and Table 2 summarizes their MRI characteristics.

Characteristics on EC-MRI

A total of 55 liver nodules with APHE ≥10 mm without specific characteristics of benignity were identified in 10 of the 22 patients with nodules ≥10 mm. All showed non-rim APHE and 32/55 (58.2%) had washout appearance in the portal or delayed phase (further categorized as suspicious nodules) (Fig. 3). The remaining 23/55 nodules with APHE (41.8%) appeared isointense in the portal and delayed phases (further categorized as indeterminated nodules) (Fig. 4). No nodules showed signal restriction on DWI at time of diagnosis or during the follow-up.

Interestingly, all patients with suspicious nodules carried a TIPS (7/7) (all placed more than 2 years ago), while this was the case in only 12/20 (60%) of the patients with nodules without washout (benign and indeterminated nodules).

Characteristics on the HBP of HB-MRI

A HB-MRI was performed in 19 out of 22 patients with liver nodules ≥1 cm including all 10 patients with suspicious or indeterminate nodules. The median time elapsed between HB-MRI and EC-MRI was 3 months (IQR 1.1–4.5). Most indeterminate and suspicious liver nodules were homogeneously hyperintense on the HBP (54/55, 98.1%). Only one lesion was isointense related to the surrounding liver parenchyma on the HBP. It corresponded to a nodule considered as indetermined on EC-MRI. No hypointense nodules on the HBP were detected in any of the patients. An unequivocal central hypointensity interpreted as a central scar was detected in 12/55 lesions (21.8%). It was present in 6/32 (18.8%) of suspicious nodules and in 6/23 (26.1%) indetermined

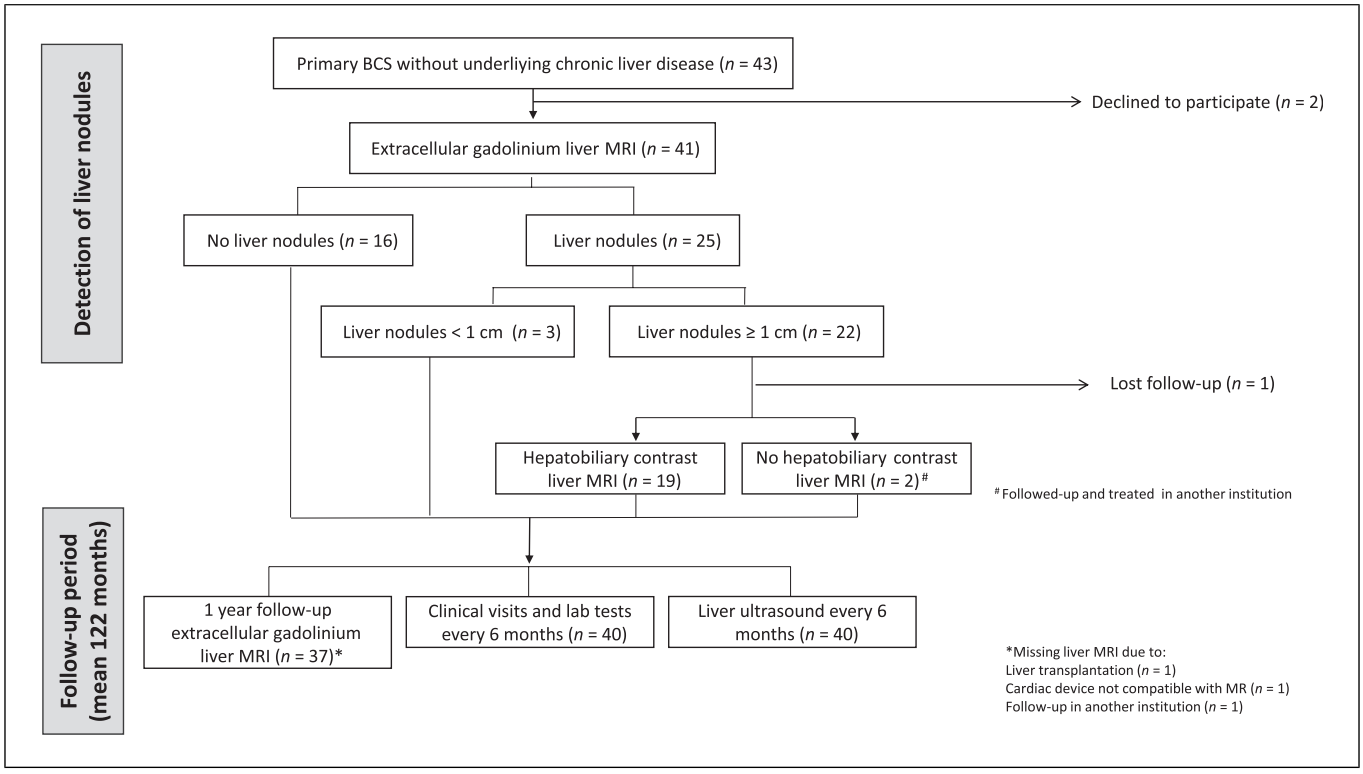

Fig. 1. Flow chart of patients and MRI studies.

nodules. The central scar had not been detected on the EC-MRI study (T1- or T2-weighted images or dynamic study) (Fig. 5).

Inter-Reader Agreement

The inter-reader agreement for washout on EC-MRI was substantial with a kappa value of 0.694 (95% CI: 0.50–0.88). The inter-reader agreement for contrast uptake in the HBP was almost perfect: 0.96 (95% CI: 0.91–1) (Bangdiwala's B-statistic). A high inter-reader agreement (kappa = 0.81; 95% CI: 0.63–0.99) for the detection of central scar on the HBP was also evidenced.

Follow-Up MRI

Patients

A follow-up EC-MRI was carried out 10–21 months (median 12.8 [IQR: 11.9–15.0]) after the first EC-MRI in 37 patients. In 4 patients, it was not done: 1 patient was lost for the follow-up. Another patient received a liver transplantation 12 months after inclusion in the study (no HCC was evidenced in the explant). A third patient, without suspicious or indeterminate nodules at baseline MRI, received a cardiac device not compatible with MRI during the follow-up and the fourth patient was followed-up outside our hospital and the follow-up MR was not available. The previous 2 patients had no evidence of HCC at clinical and sonographic follow-up performed for more than 9 and 10 years, respectively.

Suspicious and Indeterminate Nodules

Nine out of 10 patients with suspicious or indetermined nodules were followed with EC-MRI. The last patient (with one suspicious and one indetermined nodule) had a clinical and sonographic follow-up for more than 10 years without evidence of HCC. Therefore, the follow-up involved 53 nodules previously detected at EC-MRI (31 suspicious and 22 indetermined). The time elapsed since the first EC-MRI was 15.1 months (IQR: 14.5–17.7).

Changes in size detected in the follow-up MRI are showed in Figure 2. Concerning the pattern of enhancement on the follow-up EC-MRI, in 9 out of the 31 suspicious nodules (29%), the washout was not detected (7 were isointense compared to surrounding liver parenchyma in venous phase and 2 were hyperintense). Two out the 22 nodules classified as indetermined showed washout appearance in the follow-up, but not associated to changes in size. In one of these patients, three more

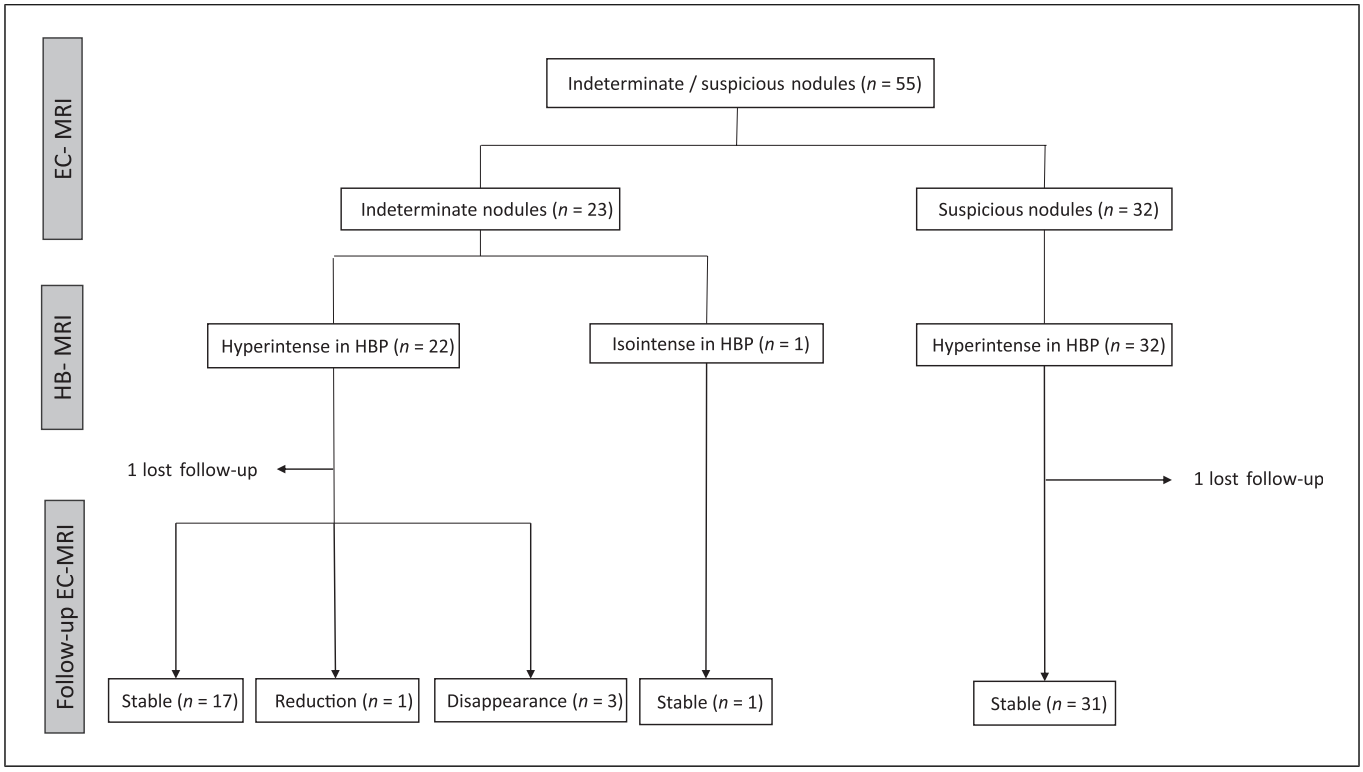

Fig. 2. Flow chart of indeterminate and suspicious nodules. EC-MRI, MRI with extracellular contrast; HB-MRI, MRI with hepatobiliary contrast; HBP, hepatobiliary phase.

follow-up MRI studies were performed for a period of 2 additional years demonstrating stability of size, and washout disappeared on the last MRI. In the second patient, the MRI performed 1 year later demonstrated stability of size of the nodule and no conclusive washout.

Clinical Follow-Up

Clinical, analytical, and sonographic follow-up was performed every 6 months in all patients (with and without nodules) except 1 patient, for a median period of 122 months (IQR: 85–127). There was only one lost follow-up. In addition, all 37 patients with follow-up EC-MRI, also have one or more additional CT or MRI throughout the follow-up for different reasons for a median period of 75 months (IQR: 30–113) after the initial EC-MRI. None of the patients demonstrated evidence of HCC in the follow-up.

A follow-up AFP level was assessed 12.9 (IQR: 11.9–15.1) months after the first EC-MRI in all patients but 5 cases (only one of them had suspicious/indeterminated nodules). The median AFP value was 3 ng/mL (IQR 2–5). None of the patients showed an increase of AFP values.

Two patients underwent liver transplant 1 and 9 years after the inclusion in the study, respectively. The pathologic study of the explanted liver did not show any HCC foci.

Discussion

We report the first prospective long-term follow-up study evaluating the potential malignancy of hepatic nodules associated to BCS in Western countries. At the same time, we have evaluated the usefulness of HB-MRI in the work-up of liver nodules that can be highly suspicious of HCC by imaging. In this sense, it is worth stressing that 17% of our patients had some small benign nodules, showing an enhancing dynamic pattern by MRI that overlaps with that specific vascular pattern of HCC if the patient would have had underlying cirrhosis.

Several studies including series from Asian and African countries have reported a high prevalence of HCC in patients with BCS, most ranging from 5 to 30% [4–6, 23–26]. However, the true incidence in Western countries is unknown. The scarce publications, basically based on

Table 2. Characteristics of the non-conclusively benign nodules detected by MRI with extracellular contrast (EC-MRI)

	Total (APHE)	Suspicious (w washout)	Indeterminated (wo washout)
Nodules, *n* (%)	55	32 (58.2)	23 (41.8)
Size, mm, median [IQR]	12 [10–15]	12 [11–13.5]	12 [10–15]
T1, *n* (%)			
Hyperintense	35 (63.6)	25 (78.1)	10 (43.5)
Hypointense	0 (0)	0 (0)	0 (0)
Isointense	20 (36.4)	7 (21.9)	13 (56.5)
T2, *n* (%)			
Hyperintense	0 (0)	0 (0)	0 (0)
Hypointense	36 (65.5)	27 (84.4)	9 (39.1)
Isointense	19 (34.5)	5 (15.6)	14 (60.9)
Enhancing "capsule," *n* (%)	0 (0)	0 (0)	0 (0)
Fat in mass, *n* (%)	0 (0)	0 (0)	0 (0)
Hyperintensity on diffusion-weighted on high b value	0 (0)	0 (0)	0 (0)
HBP, *n* (%)			
Hyperintense	54 (98.2)	32 (100)	22 (95.7)
Hypointense	0 (0)	0 (0)	0 (0)
Isointense	1 (1.8)	0 (0)	1 (4.3)
Central scar in HBP (no/yes), *n* (%)	43 (78.2)/12 (21.8)	26 (81.3)/6 (18.8)	17 (73.9)/6 (26.1)

HBP, hepatobiliary phase.

isolated cases, makes the incidence and evolution of nodules associated to BCS in Western countries poorly known. A single French study [7] described a prevalence of HCC of 11.3% and a 5-year cumulative incidence of 4%, similar to that reported for other chronic liver diseases. However, the study has some issues that reduce its strength. It was retrospective and, in addition, a high percentage of patients included were non-Caucasian with a potential risk of occult HBV infection. Moreover, almost all the patients included in that study had the venous outflow obstruction level at the inferior cava vein. This fact makes it difficult to establish the true prevalence of HCC in European and American countries where the disease is usually due to thrombosis at the level of the hepatic veins. In the recent Swedish national cohort study [27], <1% of death in BCS were related to fatal HCC events and all occurred in patients with a co-existent liver disease. Authors concluded that further studies are needed to define the risk of HCC and the need for HCC screening in these patients. In our prospective study in which all the included patients had the characteristics of Western BCS form (young Caucasians with thrombosis of the hepatic veins and with predominance of myeloproliferative disorders without other risk factor for liver disease), not a single HCC has been detected. Thus, it appears that the incidence of HCC in these patients is lower than what is thought up to now, or just marginal and likely confounded by several other factors such as occult HBV infection. This is not usually investigated and sure may be an issue in patients from high-risk communities for this infection.

One relevant finding of this study is that up to 60% of patients included in the cohort had benign liver nodules detected by MRI. This prevalence is higher than previously reported [9], probably attributable to the improvement of the imaging techniques in the last years. The nodules are developed as a result of the liver vascular changes related to outflow blockade, decrease of portal flow, and compensatory arterial flow changes, but the specific mechanism has not been elucidated [28]. In some instances, it may be that the placement of a TIPS has primed their development [17, 29].The results of this study support the potential contribution of TIPS placement to the development of the nodules, but it is not the sole determining factor. As shown, 72% of patients with nodules in our series had a TIPS, while only 31% of the patients without nodules had it on. In most cases, the stent had been placed more than 2 years ago. These data

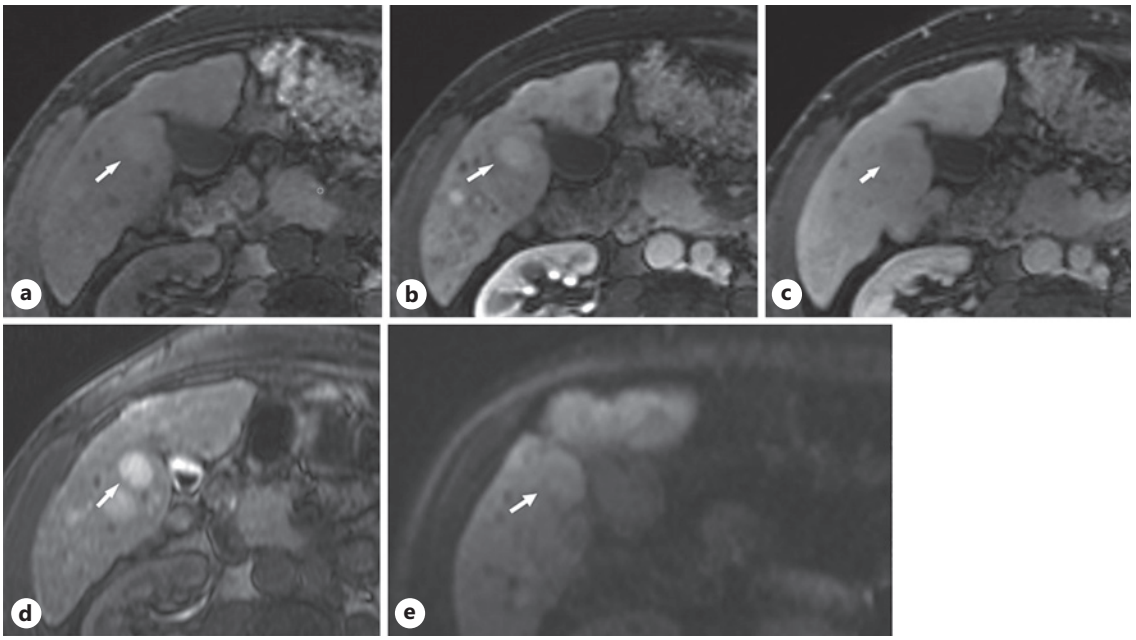

Fig. 3. Suspicious nodule in a patient with BCS. 18 mm nodule in segment 5 (arrows). EC-MRI baseline (**a**), arterial (**b**), and portal phase (**c**). **d** HB-MRI HBP. **e** DWI with high b value. The nodule shows non-rim APHE (**b**) and washout in the portal phase (**c**) and it is homogeneously hyperintense in the HBP (**d**) and there is no diffusion restriction (**e**).

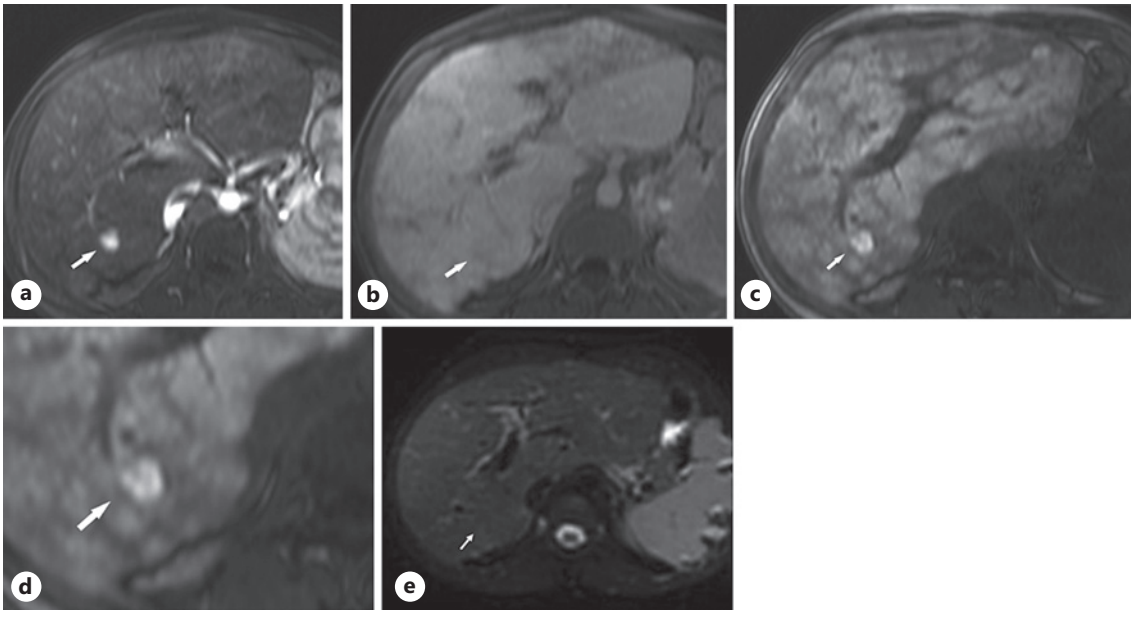

Fig. 4. Indeterminate nodule in a patient with BCS. 15 mm nodule in segment 6 (arrows). EC-MRI arterial (**a**) and delayed venous phase (**b**). **c**, **d** HB-MRI HBP. **e** DWI with high b value. The nodule shows non-rim APHE (**a**) and is isointense in the delayed venous phase (**b**). In the HBP the nodule is hyperintense (**c**) with a central hypointensity corresponding to a central scar (**d**). **e** There is no restriction in DWI sequences.

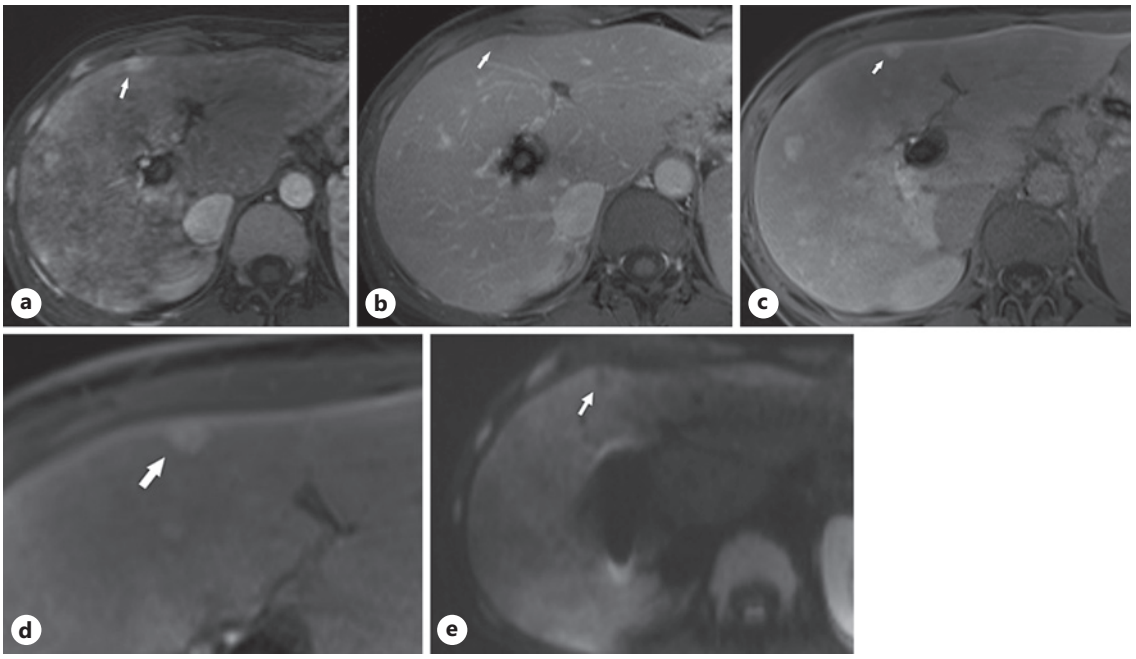

Fig. 5. Detection of central scar in the HBP in a nodule that was suspicious on MRI with extracellular contrast (arrows). EC-MRI arterial (**a**) and delayed venous phase (**b**). **c**, **d** HB-MRI HBP. **e** DWI with high b value. APHE (**a**) and subtle washout in the venous phase (**b**). **c** Contrast uptake in the HBP. **d** Detail of the HBP showing the central hypointense linear scar (characteristic of focal nodular hyperplasia). This linear scar was not detected in the EC-MRI. **e** The nodule is hypointense in high b DWI sequences.

suggest that TIPS probably exerts a priming role in further expanding the niches of benign hepatocytes that have proliferated as a result of the vascular abnormalities related to the outflow blockade. The potential role of TIPS in inducing the development of nodules that may resemble an HCC at imaging is an issue to retain when a potential diagnosis of HCC is raised in patients in whom a TIPS had been placed.

Another factor that seems to contribute to the benign hepatic nodules formation is the age at which the disease was established. According to our results, there seems to be a non-significant trend for the nodules to appear more frequently when the BCS has been developed in young patients. Nevertheless, no relationship has been found between the development of nodules and the duration of the disease.

Despite the low risk of HCC in BCS in Western countries, where liver nodules are mostly benign, we cannot declare a complete absence of risk, especially in long-term disease in which advanced liver fibrosis may have been developed. However, it is likely that the risk is not of enough magnitude to firmly recommend a screening program for patients with BCS. Thus, in our opinion, the current AASLD recommendation to establish surveillance with ultrasound and alpha-fetoprotein level every 6 months to achieve early HCC detection should be revisited [30, 31]. Furthermore, such surveillance plan should also recommend when to engage a diagnostic work-up when a nodule is detected, what kind of contrast-enhanced cross-sectional imaging should be performed, and when should a biopsy be considered. According to our data, the criteria for indicating biopsy should therefore not be based on the appearance on the EC-MRI, neither on the usual criteria of growth nor changes in MRI signal since both are frequent in benign nodules associated with the BCS [32]. These recommendations for practice should also incorporate the potential concern of harm because of the risk of overdiagnosis and overtreatment [33, 34]. Our data provide useful information for this purpose.

Most of the nodules associated with BCS show typical characteristics of focal nodular hyperplasia by MRI allowing the diagnosis of benignity. However, up to 24% of patients included in the present study (corresponding to 40% of patients with liver nodules) had nodules with APHE larger than 1 cm with an MRI behaviour that did not allow to

establish the diagnosis of benignity. This inconclusive benign behaviour was present mainly in small nodules (IQR 10–15 mm). As noted, more than half of these nodules showed non-rim APHE and wash-out in venous phases, making them indistinguishable from HCC. As has already been postulated, the typical congestion associated to the BCS might contribute to the high prevalence of washout in these benign nodules [24]. It is remarkable that all patients who had nodules with APHE and wash-out in our study had a TIPS placed more than 2 years ago. Probably, the absence of portal supply in these patients contributes to the washout appearance. Nevertheless, not all nodules in patients with TIPS showed wash-out.

Our findings support the fact that the typical APHE and wash-out pattern used as non-invasive criteria to diagnose HCC in cirrhotic patients cannot be applied in patients with BCS. Thus, we have prospectively corroborated what was reported by van Wattere et al. [10] in their retrospective study. This false-positive diagnosis would occur using EASL [35], AASLD [36], or LIRADS [30] criteria if their adequate application is not in place. According to LI-RADS, the hyperintensity on DWI is considered an ancillary feature favouring malignancy. In our series, none of the nodules under study was hyperintense on DWI which could support its benign nature. However, as known, imaging criteria for non-invasive diagnosis of HCC, including LI-RADS, should be applied only in patients at high risk of such cancer. In that regard, the results of our study support that fact that BCS does not represent a risk factor to develop HCC. Moreover, due to its inconsistent image quality and to artifact/image degradation, in particular in the left hepatic lobe due to cardiac movement or in the hepatic dome, it could be premature to endorse DWI as part of the main workup in BCS nodules.

Prior studies from our group and others [37–39] have shown that MRI liver-specific contrast agents are not superior to conventional MRI in the diagnosis of HCC in cirrhotic patients. Although other studies have shown good results [40–42], there is not enough evidence currently about the use of HB-MRI for the diagnosis of HCC in cirrhotic patients [43]. However, in the current study, we have found that liver-specific MRI could be a highly useful tool to discard malignancy in patients with BCS. Up to 98% of nodules with APHE larger than 1 cm without conclusive signs of benignity on EC-MRI showed strong up-take in the HBP of the organ-specific contrast. This behaviour is in clear contrast with that of HCC, which is usually hypointense, or if not, isointense on the HBP [44]. It should be noted that none of the liver nodules in our study were hypointense on the HBP. In addition, a small percent of HCC may show some degree of contrast enhancement on the HBP [37]. On the other hand, it is well known that the detection of a central scar on the MRI allows to establish the diagnosis of FNH-like [10, 25]. However, sometimes, especially in the case of small nodules, the scar is not visible. In our study, HB-MRI allowed to demonstrate a central scar in 21% of the inconclusive nodules on EC-MRI and this was instrumental to increase diagnostic confidence.

The sample size, the monocentre cohort, and the absence of malignant lesions during the follow-up could be seen as limitation. However, the BCS is an infrequent disease in Western countries, making it difficult to recruit a large cohort. In this regard, multicentric prospective studies in the future are needed. However, this is a prospective cohort with long-term follow-up with a well-characterized group of patients that are representative of Western clinical profile of the disease. The study has been conducted in only one referral centre but it was a need to develop a proof-of-concept. Patients with BCS are already evaluated and followed in expert centres and hence, imaging expertise should be the same anywhere. Besides, the absence of HCC in our cohort prevents comparison of the behaviour of HCC in BCS with that of the benign nodules associated to this disease. Finally, the absence of pathology verification of all nodules and the follow-up limited to 10 years are other limitations of the study. A longer follow-up could have led to an increased incidence of HCC.

In conclusion, HCC is infrequent in Western patients with BCS when other liver diseases are excluded. EC-MRI suffers from serious limitations in the evaluation of liver nodules in patients with such condition. It may display the APHE and wash-out pattern at dynamic imaging that may wrongly establish an HCC diagnosis. Thus, characterization of suspicious and indeterminated hepatic lesions should include HB-MRI. According to our results, detection of strong enhancement during the HB phase helps rule out an HCC diagnosis.

Statement of Ethics

This study protocol was reviewed and approved by Institutional Ethics Committee for Clinical Research of the Hospital Clinic of Barcelona (HCB 2010/6155). Written informed consent was obtained from participants (or their parent/legal guardian) to participate in the study.

Conflict of Interest Statement

Á.G.-C.: speaker fees from BTG and Terumo. J.R.: consulting fees from Roche, UniversalDx; Travel grants from Bayer. A.D.: speaker fees and travel grants from Bayer. V.S.: travel grants from

Bayer. Consultancy fees from LEO-Pharma. C.A.: reports lectures fee from Bayer; consultancy from Roche.

M.R. has consulted for Bayer-Shering Pharma, BMS, Roche, Ipsen, AstraZeneca, Lilly, BTG, and UniversalDX; lecture fees from Bayer-Shering Pharma, BMS, Gilead, Lilly, ROCHE, and UniversalDX; and received research/educational grants (from the institution), Bayer-Shering Pharma, ROCHE, BTG-Biocompatibles, Eisai, Terumo, Sirtex, Ipsen. J.C.G.-P.: speaker fees from advisory for GORE and consultory fees from Cook. J.B.: has consulted for ArQule, Bayer-Shering Pharma, Novartis, BMS, BTG-Biocompatibles, Eisai, Kowa, Terumo, Gilead, Bio-Alliance, Roche, AbbVie, MSD, Sirtex, Ipsen, Astra-Medimmune, Incyte, Quirem, Adaptimmune, Lilly, Basilea, Nerviano, Sanofi; and received research/educational grants from Bayer, and lecture fees from Bayer-Shering Pharma, BTG-Biocompatibles, Eisai, Terumo, Sirtex, Ipsen.

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Author Contributions

Ángeles García-Criado, Jordi Rimola, Virginia Hernández-Gea, María Reig, Juan Carlos García-Pagán, Jordi Bruix: conceptualization, supervision, design of methodology, validation, writing, review and final approval. Ángeles García-Criado, Jordi Rimola, Anna Darnell, Ernest Belmonte, Carmen Ayuso: interpretation of imaging studies, validation, writing, review and final approval. Susana Seijo, Julián Moreno, Valeria Pérez: collected data, writing, review and final approval. Víctor Sapena: design of methodology, statistic analysis, writing, and review and final approval.

Data Availability Statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

References

1 Tanaka M, Wanless IR. Pathology of the liver in Budd-Chiari syndrome: portal vein thrombosis and the histogenesis of veno-centric cirrhosis, veno-portal cirrhosis, and large regenerative nodules. Hepatology. 1998;27(2):488–96.
2 Oliveira EC, Duarte AGE, Boin IFSF, Almeida JRS, Escanhoela CAF. Large benign hepatocellular nodules in cirrhosis due to chronic venous outflow obstruction: diagnostic confusion with hepatocellular carcinoma. Transplant Proc. 2010;42(10):4116–8.
3 Brancatelli G, Federle MP, Grazioli L, Golfieri R, Lencioni R. Benign regenerative nodules in Budd-Chiari syndrome and other vascular disorders of the liver: radiologic-pathologic and clinical correlation. Radiographics. 2002;22(4):847–62.
4 Kew MC, Hodkinson HJ. Membranous obstruction of the inferior vena cava and its causal relation to hepatocellular carcinoma. Liver Int. 2006;26(1):1–7.
5 Simson IW. Membranous obstruction of the inferior vena cava and hepatocellular carcinoma in South Africa. Gastroenterology. 1982;82(2):171–8.
6 Gwon DI, Ko GY, Yoon HK, Sung KB, Kim JH, Lee SS, et al. Hepatocellular carcinoma associated with membranous obstruction of the inferior vena cava: incidence, characteristics, and risk factors and clinical efficacy of TACE. Radiology. 2010;254(2):617–26.
7 Moucari R, Rautou PE, Cazals-Hatem D, Geara A, Bureau C, Consigny Y, et al. Hepatocellular carcinoma in Budd-Chiari syndrome: characteristics and risk factors. Gut. 2008;57(6):828–35.
8 Brancatelli G, Vilgrain V, Federle MP, Hakime A, Lagalla R, Iannaccone R, et al. Budd-Chiari syndrome: spectrum of imaging findings. AJR Am J Roentgenol. 2007;188(2):168–76.
9 Vilgrain V, Lewin M, Vons C, Denys A, Valla D, Flejou JF, et al. Hepatic nodules in Budd-Chiari syndrome: imaging features. Radiology. 1999;210(2):443–50.
10 Van Wettere M, Purcell Y, Bruno O, Payancé A, Plessier A, Rautou PE, et al. Low specificity of washout to diagnose hepatocellular carcinoma in nodules showing arterial hyperenhancement in patients with Budd-Chiari syndrome. J Hepatol. 2019;70(6):1123–32.
11 Hadi M, Walker C, Desborough M, Basile A, Tsetis D, Hunt B, et al. CIRSE standards of practice on peri-operative anticoagulation management during interventional radiology procedures. Cardiovasc Intervent Radiol. 2021 Apr 1;44(4):523–36.
12 Silva MA, Hegab B, Hyde C, Guo B, Buckels JAC, Mirza DF. Needle track seeding following biopsy of liver lesions in the diagnosis of hepatocellular cancer: a systematic review and meta-analysis. Gut. 2008 Nov;57(11):1592–6.
13 Van Beers BE, Pastor CM, Hussain HK. Primovist, eovist: what to expect? J Hepatol. 2012;57(2):421–9.
14 Yoneda N, Matsui O, Kitao A, Kita R, Kozaka K, Koda W, et al. Hepatocyte transporter expression in FNH and FNH-like nodule: correlation with signal intensity on gadoxetic acid enhanced magnetic resonance images. Jpn J Radiol. 2012;30(6):499–508.
15 Grazioli L, Morana G, Kirchin M, Schneider G. Accurate differentiation of focal nodular hyperplasia from hepatic adenoma at gadobenate dimeglumine-enhanced MR imaging: prospective study. Radiology. 2005;236(1):166–77.
16 Kitao A, Matsui O, Yoneda N, Kita R, Kozaka K, Kobayashi S, et al. Differentiation between hepatocellular carcinoma showing hyperintensity on the hepatobiliary phase of gadoxetic acid-enhanced MRI and focal nodular hyperplasia by CT and MRI. AJR Am J Roentgenol. 2018;211(2):347–57.
17 Renzulli M, Lucidi V, Mosconi C, Quarneti C, Giampalma E, Golfieri R. Large regenerative nodules in a patient with budd-chiari syndrome after TIPS positioning while on the liver transplantation list diagnosed by Gd-EOB-DTPA MRI. Hepatobiliary Pancreat Dis Int. 2011;10(4):439–42.

18 Newerla C, Schaeffer F, Terracciano L, Hohmann J. Multiple FNH-like lesions in a patient with chronic budd-chiari syndrome: Gd-EOB-Enhanced MRI and BR1 CEUS findings. Case Rep Radiol. 2012;2012:1–5.
19 Van Wettere M, Paulatto L, Raynaud L, Bruno O, Payancé A, Plessier A, et al. Hepatobiliary MR contrast agents are useful to diagnose hepatocellular carcinoma in patients with Budd-Chiari syndrome. JHEP Reports. 2020:100097.
20 Maetani Y, Itoh K, Egawa H, Haga H, Sakurai T, Nishida N, et al. Benign hepatic nodules in Budd-Chiari syndrome: radiologic-pathologic correlation with emphasis on the central scar. AJR Am J Roentgenol. 2002;178(4):869–75.
21 Shankar V, Bangdiwala SI. Observer agreement paradoxes in 2x2 tables: comparison of agreement measures. BMC Med Res Methodol. 2014;14(1):100–9.
22 Bangdiwala SI, Shankar V. The agreement chart. BMC Med Res Methodol. 2013;13(1):97.
23 Sakr M, Abdelhakam SM, Dabbous H, Hamed A, Hefny Z, Abdelmoaty W, et al. Characteristics of hepatocellular carcinoma in Egyptian patients with primary Budd-Chiari syndrome. Liver Int. 2017;37(3):415–22.
24 Ren W, Qi X, Jia J, Yang M, Han G. Prevalence of hepatocellular carcinoma in Chinese Budd-Chiari syndrome patients: an extended systematic review using Chinese-language databases. Eur J Gastroenterol Hepatol. 2013;25(10):1241–3.
25 Nakamura S, Takezawa Y. Obstruction of the inferior vena cava in the hepatic portion and hepatocellular carcinoma. Tohoku J Exp Med. 1982;138(1):119–20.
26 Cheng D, Xu H, Lu ZJ, Hua R, Qiu H, Du H, et al. Clinical features and etiology of Budd-Chiari syndrome in Chinese patients: a single-center study. J Gastroenterol Hepatol. 2013;28(6):1061–7.
27 Aberg F, Rajani R, Wester A, Widman L, Hagström H. Three-fold increased risk of death in budd-chiari syndrome compared to matched controls: a population-based cohort study. Clin Gastroenterol Hepatol. 2023;21(4):995–1004.e9.
28 Cazals-Hatem D, Vilgrain V, Genin P, Denninger MH, Durand F, Belghiti J, et al. Arterial and portal circulation and parenchymal changes in Budd-Chiari syndrome: a study in 17 explanted livers. Hepatology. 2003;37(3):510–9.
29 Tanju S, Erden A, Ceyhan K, Soygür IT, Bozkaya HEI, Erden I. Contrast-enhanced MR angiography of benign regenerative nodules following TIPS shunt procedure in Budd-Chiari syndrome. Turk J Gastroenterol. 2004;15(3):173–7.
30 American College of Radiology. LiRADS 2018 [Internet]. 2018. Available from: https://www.acr.org/Clinical-Resources/Reporting-and-Data-Systems/LI-RADS/CT-MRI-LI-RADS-v2018.
31 Northup PG, Garcia-Pagan JC, Garcia-Tsao G, Intagliata NM, Superina RA, Roberts LN, et al. Vascular liver disorders, portal vein thrombosis, and procedural bleeding in patients with liver disease: 2020 practice guidance by the American association for the study of liver diseases. Hepatology. 2021;73(1):366–413.
32 Panvini N, Dioguardi Burgio M, Sartoris R, Maino C, Van Wettere M, Plessier A, et al. MR imaging features and long-term evolution of benign focal liver lesions in Budd-Chiari syndrome and Fontan-associated liver disease. Diagn Interv Imaging. 2022;103(2):111–20.
33 Welch HG, Black WC. Overdiagnosis in cancer. J Natl Cancer Inst. 2010;102(9):605–13.
34 Kramer BS, Croswell JM. Cancer screening: the clash of science and intuition. Annu Rev Med. 2009;60(December 2008):125–37.
35 Llovet JM, Mazzaferro V, Piscaglia F, Raoul JL, European Association for the Study of the Liver Electronic address easloffice@easloffi-ceeu, European Association for the Study of the Liv, er. EASL clinical practice guidelines: management of hepatocellular carcinoma. J Hepatol. 2018;69(1):182–236.
36 Marrero JA, Kulik LM, Sirlin CB, Zhu AX, Finn RS, Abecassis MM, et al. Diagnosis, staging, and management of hepatocellular carcinoma: 2018 practice guidance by the American association for the study of liver diseases. Hepatology. 2018;68(2):723–50.
37 Ayuso C, Forner A, Darnell A, Rimola J, García-Criado Á, Bianchi L, et al. Prospective evaluation of gadoxetic acid magnetic resonance for the diagnosis of hepatocellular carcinoma in newly detected nodules ≤2 cm in cirrhosis. Liver Int. 2019;39(7):1281–91.
38 Paisant A, Vilgrain V, Riou J, Oberti F, Sutter O, Laurent V, et al. Comparison of extracellular and hepatobiliary MR contrast agents for the diagnosis of small HCCs. J Hepatol. 2020;72(5):937–45.
39 Feng Z, Zhao H, Guan S, Wang W, Rong P. Diagnostic performance of MRI using extracellular contrast agents versus gadoxetic acid for hepatocellular carcinoma: a systematic review and meta-analysis. Liver Int. 2021 May 1;41(5):1117–28.
40 Duncan JK, Ma N, Vreugdenburg TD, Cameron AL, Maddern G. Gadoxetic acid-enhanced MRI for the characterization of hepatocellular carcinoma: a systematic review and meta-analysis. J Magn Reson Imaging. 2017 Jan 1;45(1):281–90.
41 Joo I, Kim SY, Kang TW, Kim YK, Park BJ, Lee YJ, et al. Radiologic-pathologic correlation of hepatobiliary phase hypointense nodules without arterial phase hyperenhancement at gadoxetic acid–enhanced MRI: a multicenter study. Radiology. 2020 Aug 1;296(2):335–45.
42 Yoon JH, Lee JM, Lee YJ, Lee KB, Han JK. Added Value of sequentially performed gadoxetic acid-enhanced liver MRI for the diagnosis of small (10–19 mm) or atypical hepatic observations at contrast-enhanced CT: a prospective comparison. J Magn Reson Imaging. 2019 Feb;49(2):574–87.
43 Zech CJ, Ba-Ssalamah A, Berg T, Chandarana H, Chau GY, Grazioli L, et al. Consensus report from the 8th international forum for liver magnetic resonance imaging. Eur Radiol. 2020;30(1):370–82.
44 Choi JW, Lee JM, Kim SJ, Yoon JH, Baek JH, Han JK, et al. Hepatocellular carcinoma: imaging patterns on gadoxetic acid-enhanced MR images and their value as an imaging biomarker. Radiology. 2013;267(3):776–86.