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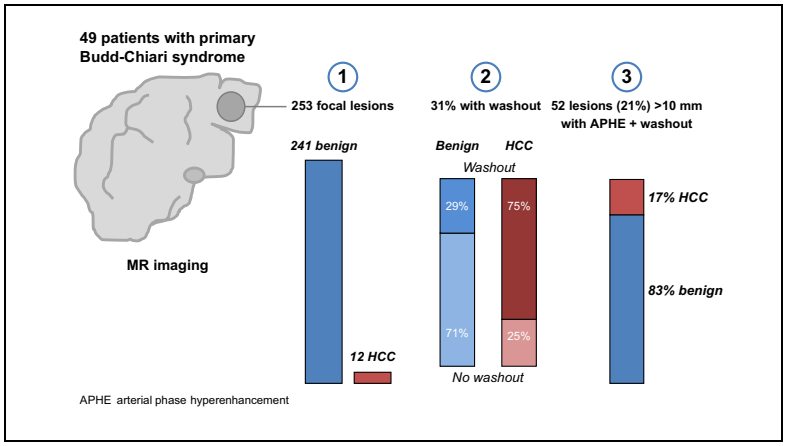
Low specificity of washout to diagnose hepatocellular carcinoma in nodules showing arterial hyperenhancement in patients with Budd-Chiari syndrome

Graphical abstract



Highlights

- Washout depicted in close to 30% of benign nodules in patients with Budd-Chiari syndrome.
- Non-invasive diagnosis of HCC cannot be applied to patients with Budd-Chiari syndrome.
- Ancillary imaging findings help differentiate benign nodules and HCC.
- Alpha-fetoprotein serum rate remains low in patients with benign nodules.

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Lay summary

Washout on MRI is depicted in a significant proportion of benign nodules in patients with Budd-Chiari syndrome (BCS), limiting its value for the differentiation between benign and malignant lesions. Criteria proposed for the non-invasive diagnosis of hepatocellular carcinoma in patients with cirrhosis cannot be extrapolated to patients with BCS. Additional imaging findings and patient characteristics, including alpha-fetoprotein serum level, can help determine the probability of a nodule being HCC in patients with BCS.

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Low specificity of washout to diagnose hepatocellular carcinoma in nodules showing arterial hyperenhancement in patients with Budd-Chiari syndrome

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Background & Aims: It remains unclear whether the classic imaging criteria for the non-invasive diagnosis of hepatocellular carcinoma (HCC) can be applied to chronic vascular liver diseases, such as Budd-Chiari syndrome (BCS). Herein, we aimed to evaluate the diagnostic value of washout for the discrimination between benign and malignant lesions in patients with BCS.
Methods: This retrospective study included all patients admitted to our institution with a diagnosis of BCS and focal lesions on MRI from 2000 to 2016. MRI images were reviewed by 2 radiologists blinded to the nature of the lesions. Patient and lesion characteristics were recorded, with a focus on washout on portal venous and/or delayed phases. Lesions were compared using Chi-square, Fisher's, Student's *t* or Mann-Whitney *U* tests.
Results: A total of 49 patients (mean age 35 ± 12 years; 34 women [69%] and 15 men [31%]) with 241 benign lesions and 12 HCC lesions were analyzed. Patients with HCC were significantly older (mean age 44 ± 16 *vs.* 33 ± 9 years, $p = 0.005$), with higher alpha-fetoprotein (AFP) levels (median 16 *vs.* 3 ng/ml, $p = 0.007$). Washout was depicted in 9/12 (75%) HCC, and 69/241 (29%) benign lesions ($p < 0.001$). A total of 52/143 (36%) lesions ≥1 cm with arterial hyperenhancement showed washout (9 HCC and 43 benign lesions). In this subgroup, the specificity of washout for the diagnosis of HCC was 67%. Adding T1-w hypointensity raised the specificity to 100%. A serum AFP >15 ng/ml was associated with 95% specificity.
Conclusion: Washout was observed in close to one-third of benign lesions, leading to an unacceptably low specificity for the diagnosis of HCC. The non-invasive diagnostic criteria proposed for cirrhotic patients cannot be extrapolated to patients with BCS.

Lay summary: Washout on MRI is depicted in a significant proportion of benign nodules in patients with Budd-Chiari syndrome (BCS), limiting its value for the differentiation between benign and malignant lesions. Criteria proposed for the non-invasive diagnosis of hepatocellular carcinoma in patients with cirrhosis cannot be extrapolated to patients with BCS. Additional imaging findings and patient characteristics, including alpha-fetoprotein serum level, can help determine the probability of a nodule being HCC in patients with BCS.

Introduction

Primary Budd-Chiari Syndrome (BCS) is a rare vascular disorder involving hepatic venous outflow impairment at any level between the small hepatic veins and the right atrium.[1–4] In Western countries, primary BCS is commonly associated with prothrombotic conditions such as myeloproliferative neoplasms, coagulation disorders of various causes, paroxysmal nocturnal hemoglobinuria, antiphospholipid syndrome and Behçet's disease. The use of oral contraceptives is frequently associated with BCS, but it seems to act as a co-factor.[3,5–7]

One of the consequences of chronic BCS is the development of focal liver lesions. The vast majority are benign and correspond to large regenerative lesions called focal nodular hyperplasia-like (FNH-like) lesions.[8] They develop as a consequence of chronic portal blood deprivation and the compensatory increase in the arterial blood supply to the liver parenchyma.[8–10] BCS is also a recognized risk factor for hepatocellular carcinoma (HCC) with an incidence varying from country to country: 6% to 41% of patients with BCS in Japan; 48% of patients in South Africa; and 25% in the US.[3,11–13] Thus, it is important to accurately differentiate benign lesions from HCC, as patient management will greatly differ. From this perspective, imaging, especially MRI, plays an important role as a first non-invasive step in the diagnostic process.

Few studies have reported imaging findings of focal liver lesions in patients with BCS.[9,10,14] All have shown that both

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benign and malignant lesions appear markedly hyperenhanced on contrast-enhanced CT or MRI during the arterial phase. They have also shown that lesion size, number and serum alpha-fetoprotein (AFP) level are useful for further characterization.[9,10,11,15]

In patients with cirrhosis, the classic imaging hallmarks of HCC (*i.e.* combination of hyperenhancement on arterial phase and washout for lesions greater than 1 cm) on either CT or MRI are sufficient to allow for a non-invasive diagnosis.[16,17] The question of whether these imaging criteria might be applied in chronic vascular liver diseases at risk of benign lesions and HCC, such as BCS, remains open. Indeed, cirrhosis and chronic BCS both share decreased liver perfusion and increased arterial inflow, but liver congestion is a peculiar finding observed in liver venous outflow obstruction and not in cirrhosis. As liver congestion is seen as persistent and heterogeneous enhancement on contrast-enhanced CT or MRI during portal venous and delayed phases, washout observed in liver lesions may be due to a different mechanism and could therefore be less specific for HCC in that setting.

The aim of this study was to evaluate the diagnostic value of washout for the discrimination between benign and malignant lesions in patients with primary Budd-Chiari syndrome, in order to assess whether the non-invasive imaging criteria for HCC validated in patients with cirrhosis can be applied in this setting.

Materials and methods

Patient population

This single-center retrospective study, including chart review, was approved by our institutional review board and the requirement for written informed consent was waived. All patients admitted to our tertiary center for vascular liver disorders (Beaujon University Hospital, Clichy, France) between 2000 and 2016 with a diagnosis of primary BCS were retrieved from our prospective electronic database. Inclusion criteria were i) the diagnosis of acute, subacute or chronic BCS, and ii) initial diagnosis and follow-up including contrast-enhanced MRI. BCS was defined as hepatic venous outflow impairment at any level between the small hepatic veins and the right atrium.[4] The date of the diagnosis of BCS was that of the first imaging examination demonstrating obstructed venous outflow.

For all patients, all available MRI examinations were screened by 2 abdominal radiologists (MVW and MR) and only those showing at least 1 focal liver lesion (defined as a round, well-circumscribed lesion greater than 5 mm in diameter seen on unenhanced or contrast-enhanced sequences) were retained. Patients who had no focal liver lesion on initial or follow-up MRI were excluded. Patients who only had benign lesions with less than 12 months of follow-up were also excluded (Fig. 1). Demographic, clinical, laboratory, and outcome data were retrieved from patient medical records. Patients were tested for prothrombotic factors such as myeloproliferative neoplasm associated with the JAK-2 mutation, paroxysmal nocturnal hemoglobinuria, coagulation disorders, antiphospholipid syndrome, and Behçet's disease. Oral contraception and pregnancy were considered thrombotic risk factors. A history of endovascular treatment (stenting of hepatic veins or transjugular intrahepatic portosystemic shunt [TIPS]) was also recorded.

The final study group included 49 patients with a mean age of 35 ± 12 years [range 13–70] (34 women (69%) 34 ± 12 years old [13–70]; 15 men (31%) 38 ± 11 years old [18–59]).

MRI protocol

Patients were explored using various MRI scanners because some were referred to our center with their own MR examinations. Thirty-six patients had at least 1 MRI performed in our institution. In our institution, MRI was performed on a 1.5 T clinical MR system until December 2012 and on a 3 T clinical MR system thereafter (Intera, Philips Medical System, Best, The Netherlands) using a phased-array body coil. All patients included in the study population had a standard liver MR exam, including the following sequences acquired in the axial plane: a respiratory-triggered fat-suppressed fast spin-echo T2-weighted sequence, an in- and opposed-phase gradient-echo T1-weighted sequence, a free breathing diffusion-weighted sequence with a b value of >400 s/mm,[2] a fat-suppressed 3D gradient-echo T1 weighted sequence, before and after intravenous injection of extracellular gadolinium chelates (blinded for review) at a dose of 0.1 mmol per kilogram of body weight followed by a 20 ml bolus of saline, obtained at the arterial (bolus triggering), portal (50 s), and delayed (3 min) phases. Contrast agent and saline were injected with a power injector (Medrad; Pittsburgh, PA).

Image analysis

MRI examinations with focal liver lesions were retrospectively reviewed in consensus by 2 abdominal radiologists (with 4 years and 10 years of expertise) on a picture archive and communication system workstation (Carestream Health, Rochester, NY). Readers were aware of the diagnosis of BCS but blinded to the nature of the liver lesions, and patient clinical and biological data.

Readers recorded the following items: i) number of liver lesions; ii) lesion location according to the Couinaud classification; iii) largest diameter of the lesion (in mm); iv) signal intensity on T1-weighted images; v) signal intensity on T2-weighted images; vi) signal intensity on high b-value diffusion-weighted images, vii) signal intensity on arterial phase, portal venous, and delayed phase images (for items 4 to 7, each lesion was compared to the surrounding liver parenchyma and categorized as hypo, iso, or hyperintense when they respectively showed lower, similar, or higher signal intensity than the liver); viii) peripheral rim enhancement (present or absent) defined as peripheral marked enhancement with relative central lower enhancement; ix) fat component (present or absent) defined as signal drop in the lesion on opposed-phase T1-weighted gradient recalled echo (GRE) when compared to in-phase T1-weighted GRE images; x) hepatic steatosis (present or absent) defined as signal drop of the liver on opposed-phase T1-weighted GRE when compared to in-phase T1-weighted GRE images. In patients with more than 10 liver lesions, only the largest 10 were included in the analysis. Lesions showing signal hyperintensity on arterial phase images were considered as having arterial phase hyperenhancement (APHE). For lesions showing signal hyperintensity on precontrast T1-weighted sequences, APHE was assessed on subtracted images. A "washout appearance" was considered to be present if a lesion showed hypointensity, in part or in the totality of the lesion, on the portal venous and/or delayed phase compared to the surrounding liver parenchyma according to recent guidelines.[16,17] A third

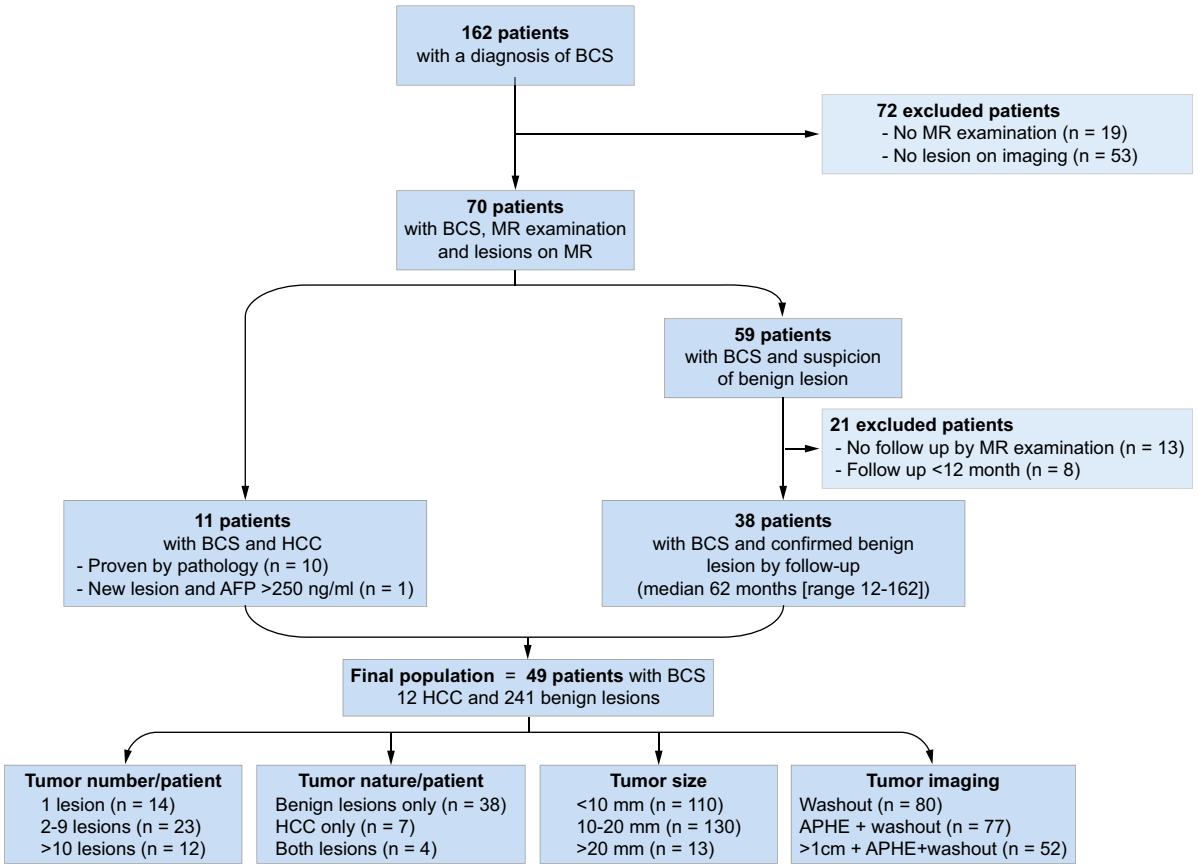

Fig. 1. Flow chart of the study population. AFP, alpha-fetoprotein; APHE, arterial phase hyperenhancement; BCS, Budd-Chiari syndrome; HCC, hepatocellular carcinoma.

reader performed an independent read to assess inter-reader agreement for washout.

Final diagnosis

Lesions were diagnosed on the basis of histopathologic analysis of specimens obtained by surgical resection or percutaneous biopsy, or on the basis of clinical and biologic data combined with a minimum of 12 months follow-up. Malignant cells at histologic examination, serum AFP level greater than 250 ng/ml, or both, enabled the diagnosis of HCC. Indications for focal liver lesion biopsy were as i) focal lesion associated with an AFP serum level >15 ng/ml; ii) lesion modification, *i.e.* appearance of previously absent washout, or ≥50% size increase in ≤6 months; iii) lesion >10 mm showing arterial phase hyperenhancement and washout and ancillary imaging features, especially mild-moderate signal hyperintensity on T2-weighted images or signal hyperintensity on high b-value diffusion-weighted images. The absence of malignant cells with findings suggestive of regenerative lesions at histologic examination, or no change or disappearance of the lesions with serum AFP levels lower than 15 ng/ml during follow-up,[11] were the criteria used for the diagnosis of a benign lesion.

Statistical analysis

Categorical data were expressed as frequencies and percentages, and continuous variables were expressed as means and standard deviations, or medians and ranges, as suitable. A Fisher's exact test or a Chi-square test was used for comparison of frequencies. The Student's *t* test or Mann-Whitney *U* test were used to compare continuous variables according to the distribution of data. Inter-reader agreement for washout identification was assessed with kappa coefficients (0.00–0.20 indicated slight agreement; 0.21–0.40, fair agreement; 0.41–0.60, moderate agreement; 0.61–0.80, substantial agreement; and 0.81–1.00, almost perfect agreement). A p value of 0.05 was considered to be statistically significant and all tests were 2-sided. All analyses were performed using the Statistical Package for the Social Sciences (SPSS) software (version 23.0. SPSS Inc., Chicago, IL).

Results

Patient population and lesions

Characteristics of the 49 patients included in the study are presented in Table 1. We included 15 men (31%) and 34 women (69%), with a mean age of 35 ± 12 years (range 13–70).

The etiology of BCS was identified in 34 patients (69%) with a predominance of myeloproliferative neoplasms (n = 22, 45%) and coagulation disorders (n = 12, 24%). Five patients (10%) had several causes of BCS. Fourteen (41%) female patients used oral contraception and 18 had a history of at least 1 pregnancy. Nine patients (18%) had associated inferior vena cava thrombosis and 3 (6%) had associated portal vein thrombosis. Three patients (6%) had a history of hepatic vein stenting and 21 patients (43%) had undergone TIPS placement.

A total of 253 focal liver lesions were analyzed, with a mean diameter of 12 ± 7 mm (range 5–55). Fourteen patients (29%)

Table 1. Baseline characteristics of the 49 patients with primary Budd-Chiari syndrome and focal liver lesions.

Characteristics	Values
Women, n (%)	34 (69)
Mean age ± SD (range)	
Overall	35 ± 12 (13–70)
Women	34 ± 12 (13–70)
Men	38 ± 11 (18–59)
Prothrombotic risk factors*, n (%)	
Myeloproliferative neoplasm (Jak 2 +)	22 (45)
Hemoglobinuria	2 (4)
Behçet's disease	1 (2)
Coagulation disorder	12 (24)
Antiphospholipid syndrome	5 (10)
Unknown	15 (31)
Oral contraception	14 (41)
Pregnancy	18 (53)
Involved vessels, n (%)	
Inferior veina cava thrombosis	9 (18)
Associated portal vein thrombosis	3 (6)
Median alpha-fetoprotein serum level (range) ng/L	3 (2–9,000)
Previous treatment, n (%)	
TIPS	21 (43)
Hepatic vein stenting	3 (6)
Liver steatosis, n (%)	1 (2)

Numbers in parentheses are percentages.
* The total exceeds the number of patients because some patients had multiple causes TIPS, transjugular intrahepatic portosystemic shunt.

had a solitary lesion, 23/49 patients (47%) had 2–9 lesions, and 12/49 patients (24%) had 10 lesions or more. Thirty-eight patients had only benign lesions, 7 had only HCC lesions and 4 had both types of lesion. Focal lesions were located in all liver segments but were most frequent in the right liver (n = 170, 67%).

A total of 15 patients underwent liver biopsy, 13 for the characterization of a focal liver lesion suspected of being an HCC, and 2 as part of the diagnostic work-up for BCS. Details are provided in Table 2. Briefly, 3 patients had liver cirrhosis, and others had various degrees of fibrosis deposition. Diagnosis of HCC was confirmed in 10/13 patients (77%). In the 3 remaining patients, the biopsied lesion corresponded to regenerative nodules (n = 2), or atypical focal nodular hyperplasia (n = 1). One patient with an AFP serum level >15 ng/ml did not undergo biopsy (AFP = 25 ng/ml) because focal lesions were all <10 mm in size and did not harbor washout. No lesion initially considered as benign was diagnosed as being an HCC.

Imaging features of focal liver lesions

The median time delay between initial diagnosis and depiction of liver lesions was 10 months [range 0–120] in the entire population (median 9.5 months [0–103] *vs.* 40 [0–120] in patients with only benign lesions, and with HCC, respectively, $p = 0.126$).

Imaging features of focal liver lesions are provided (Table 3). Briefly, most lesions showed signal hyperintensity on T1-weighted MR images (n = 203, 80%). The signal on T2-weighted MRI was more variable, with a predominance of signal hypointensity (n = 144, 57%). All but 5 lesions showed APHE (97%). Washout appearance was noted in 33 (13%) and 68 (31%) lesions on portal venous and delayed phase images, respectively. Readers agreed in 236/253 nodules (93.4%) regarding the presence or absence of washout. The inter-reader agreement for washout was almost perfect, with a kappa value of 0.85 ± 0.04. Authors always agreed regarding the washout of HCC, and discrepancies all belonged to the group of benign lesions. Patients were followed up for a median period of 62 months [range 12–162] during which 77 benign lesions (32%) disappeared.

Features of benign regenerative lesions

Characteristics of benign lesions are provided (Table 3B). Overall, 38 patients (78%) developed 241 benign regenerative lesions. The diagnosis of benign lesions was established by biopsy in 3 patients (Table 2). These patients were biopsied because lesions were suspected of being HCC (significant size growth and washout). The diagnosis of benignity was based on imaging follow-up in the remaining patients. No patients initially diagnosed as having only benign lesions were finally diagnosed as having HCC. The mean diameter of lesions was 11 ± 5 mm [5–39]. Most patients (n = 21/38, 55%) had between 2 and 9 lesions. Lesions

Table 2. Characteristics of patients who underwent liver biopsy.

					Focal lesion		Biopsy		
Patient	Gender	Age (yr)	Cause of BCS	AFP (ng/ml)	Size (mm)	Location (segment)	Indication of liver biopsy	Liver fibrosis	Pathology of focal lesion
#1	F	36	Myeloproliferative neoplasm	4	16	VII	Suspicion of HCC	F3	Atypical FNH
#2	M	46	Myeloproliferative neoplasm	6	15	V	Suspicion of HCC	F3	Regenerative nodule
#3	F	55	PNH	2	39	V	Suspicion of HCC	F1	Regenerative nodule
#4	F	26	Unknown	2	–	–	Diagnosis of BCS	F0	–
#5	M	46	Unknown	4	–	–	Diagnosis of BCS	F0	–
#6	M	44	Unknown	402	22	VII	Suspicion of HCC	F4	MD-HCC
#7	F	42	Inherited coagulation disorder	7	45	V	Suspicion of HCC	F4	MD-HCC
#8	F	26	Inherited coagulation disorder	3.7	15	II	Suspicion of HCC	F4	MD-HCC
					15	V			WD-HCC
#9	M	59	Unknown	23	53	II	Suspicion of HCC	F3	WD-HCC
#10	M	18	Antiphospholipid syndrome	3	48	IV	Suspicion of HCC	F3	WD-HCC
#11	F	26	Inherited coagulation disorder	39	14	V	Suspicion of HCC	F3	WD-HCC
#12	M	48	Myeloproliferative neoplasm	2	53	VI	Suspicion of HCC	F2	WD-HCC
#13	F	42	Unknown	12	42	V	Suspicion of HCC	F2	MD HCC
#14	F	61	Unknown	389	20	IV	Suspicion of HCC	F2	MD-HCC
#15	M	44	Inherited coagulation disorder	637	19	VII	Suspicion of HCC	F2	WD-HCC

AFP, alpha-fetoprotein; BCS, Budd-Chiari Syndrome; HCC, Hepatocellular carcinoma; MD, moderately differentiated; WD, well-differentiated; F/M, female/male; PNH, paroxystic nocturnal hemoglobinuria. Fibrosis was scored on a 4-point scale (0, no fibrosis; 1, venocentric fibrosis without bridging; 2, extensive venocentric fibrosis with bridging; 3, Numerous venoportal bridging; 4, "venoportal cirrhosis").

Table 3. Comparison of patients with benign lesions and HCC, and imaging findings of benign lesions and HCC.

A) Patients	All (n = 49)	With benign lesions and no HCC (n = 38)	With HCC (n = 11)	*p* value
Mean age (range)	35 (13–70)	33 (13–55)	44 (18–70)	0.005
Women, n (%)	34 (69)	10 (26)	5 (45)	0.143
Prothrombotic risk factors* n (%)				
Myeloproliferative neoplasm	22 (45)	20 (53)	2 (18)	0.083
Hemoglobinunria	2 (4)	2 (5)	0 (0)	1.000
Behçet's disease	1 (2)	1 (3)	0 (0)	1.000
Coagulation disorders	12 (24)	8 (21)	4 (36)	0.427
Antiphospholipid syndrome	5 (10)	4 (11)	1 (9)	1.000
Unknown	15 (31)	11 (29)	4 (36)	0.061
Oral contraception[1]	14 (41)	13 (45)	1 (13)	0.123
Pregnancy[1]	18 (53)	16 (55)	2 (25)	0.232
Involved vessels, n (%)				
Inferior vena cava thrombosis	9 (18)	5 (13)	4 (36)	0.179
Associated portal vein thrombosis	3 (6)	2 (5)	1 (9)	0.542
Median AFP serum level, ng/ml				
Median (range)	3 (2–9,000)	3 (2–25)	16 (2–9,000)	0.007
>15	4 (8)	1 (3)	6 (55)	<0.001
Previous treatment, n (%)				
TIPS	21 (43)	17 (45)	4 (36)	0.737
Hepatic vein stenting	3 (6)	2 (5)	1 (9)	0.542
Liver steatosis, n (%)	1 (2)	1 (3)	0 (0)	1.000
Number of focal lesions, n (%)				
Solitary	14 (29)	7 (18)	7 (64)	
Between 2 and 9	23 (47)	21 (55)	2 (18)	0.167
10 and more	12 (24)	10 (26)	2 (18)	
B) Focal lesions	**All (n = 253)**	**Benign lesions (n = 241)**	**HCC (n = 12)**	***p* value**
Mean size, mm (range)	12 (5–55)	11 (5–39)	32 (14–55)	<0.001
<10	110 (43)	110 (45)	0 (0)	
10–20	130 (51)	125 (52)	5 (42)	<0.001
>20	13 (6)	6 (3)	7 (58)	
Location, n (%)				
Right liver	167 (66)	158 (66)	8 (67)	
Left liver	79 (31)	75 (31)	4 (33)	0.832
Caudate lobe	7 (3)	7 (3)	0 (0)	
Signal intensity, n (%)				
T1-weighted				
Hypo-intense	17 (7)	10 (4)	7 (58)	
Iso-intense	33 (13)	31(13)	2 (17)	0.001
Hyperintense	203 (80)	200 (83)	3 (25)	
T2-weighted				
Hypo-intense	144 (57)	141 (58)	3 (25)	
Iso-intense	59 (23)	57 (24)	2 (17)	0.003
Hyperintense	50 (20)	43 (18)	7 (58)	
Diffusion-weighted on high b value[2]				
Hyperintense	21 (12)	14 (6)	7 (58)	0.001
Arterial phase[3]				
Hypo-intense	2 (1)	0 (0)	2 (25)	
Iso-intense	3 (1)	3 (1)	0 (0)	0.001
Hyper-intense	245 (97)	238 (98)	10 (75)	
Portal venous phase				
Hypo-intense	33 (13)	26 (11)	7 (58)	
Iso-intense	78 (31)	78 (32)	0 (0)	<0.001
Hyperintense	142 (56)	137 (57)	5 (42)	
Delayed phase[4]				
Hypo-intense	68 (31)	57 (28)	11 (92)	
Iso-intense	123 (56)	122 (59)	1 (8)	<0.001
Hyperintense	28 (13)	28 (13)	0 (0)	
Washout, n (%)				
Overall	80 (32)	69 (29)	11 (92)	<0.001
Hyperenhancement and washout, n (%)				
Overall	77 (30)	68 (28)	9 (75)	<0.001
>1 cm	52 (21)	43 (18)	9 (75)	<0.001

Table 3 (*continued*)

B) Focal lesions	All (n = 253)	Benign lesions (n = 241)	HCC (n = 12)	*p* value
Disappearance, n (%)	77 (31)	77 (32)	0 (0)	<0.001
Other, n (%)				
Fat content[5]	5 (2)	2 (1)	3 (25)	0.001
Capsule	6 (2)	3 (1)	3 (25)	0.002

AFP, alpha-fetoprotein; HCC, hepatocellular carcinoma; TIPS, transjugular intrahepatic portosystemic shunt.
Statistical tests: categorical variables compared with Chi-square and Fisher's exact test. Means compared with the Student's *t* test and medians with the Mann-Whitney *U* test.
(A) Comparison of patients with only benign lesions and those with at least one HCC. (B) Imaging findings of benign lesions and HCC. Numbers in parentheses are percentages.
* The total exceeds the number of patients because some patients have multiple causes. 1. In women. 2. Data available for 172 lesions (161 benign lesions and 11 HCC). 3. Hyperenhancement was assessed on subtracted images for lesions showing signal hyperintensity on precontrast T1-weighted sequences). 4. Data available for 219 lesions (207 benign lesions and 12 HCC). 5. Data available for 246 lesions (234 benign lesions and 12 HCC).

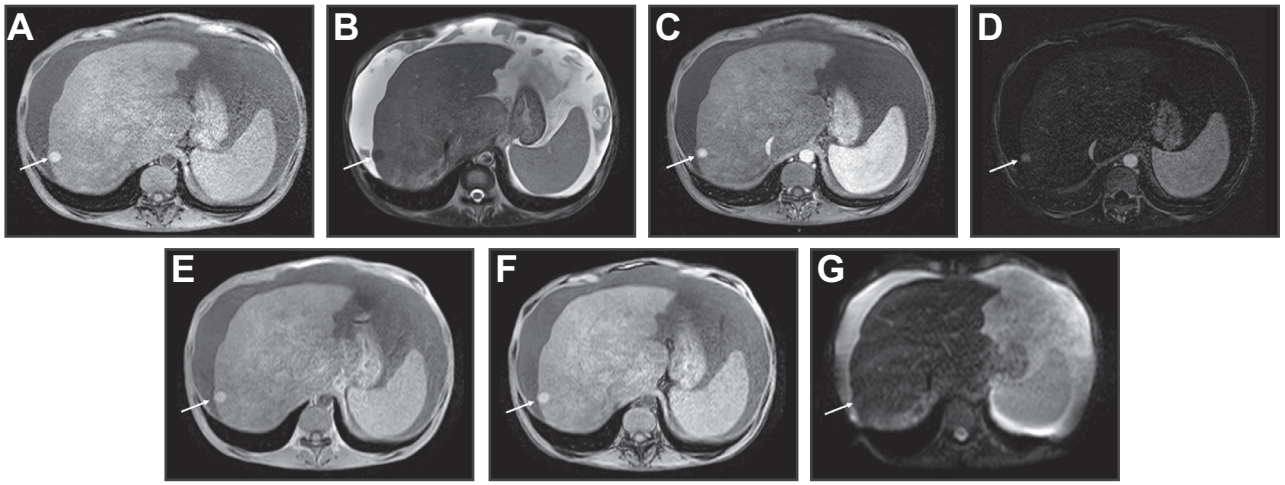

Fig. 2. Benign lesion without washout appearance in 36-year-old woman with primary Budd-Chiari syndrome due to myeloproliferative neoplasm and anti-phospholipid syndrome. (A) Precontrast T1-w images showed a 15 mm hyperintense lesion in the right liver. (B) This lesion was hypointense on T2-w images. (C-F) Extracellular gadolinium-based enhanced fat-suppressed T1-weighted GE MR images showed arterial phase hyperenhancement (C), confirmed by image subtraction (D), hyperintensity on portal venous phase (E) and hyperintensity on delayed phase (F). (G) The lesion was not seen on diffusion-weighted images. Serum alpha-fetoprotein was 5 ng/L. The patient was followed up for 12 months and remained hepatocellular carcinoma-free.

were solitary in 7 patients (18%). The majority of benign regenerative lesions showed signal hyperintensity (n = 200, 83%) on fat-suppressed T1-weighted images, and signal hypointensity on T2-weighted images (n = 141, 58%) (Fig. 2). APHE was seen in almost all lesions (n = 238/241, 99%). Twenty-six lesions (11%) showed washout on portal venous phase images, and 57 lesions showed washout on delayed phase images (28% of 207 lesions with acquired delayed phase) (Fig. 3). Overall, 43/241 benign lesions (18%) were greater than 1 cm in size and showed both APHE and washout. During follow-up, 77/241 lesions (32%) disappeared in 21/38 patients and 28/38 patients (74%) developed new lesions.

HCC imaging features

A diagnosis of HCC was established for 12 lesions in 11 patients (23%). Most patients (n = 7/12, 64%) had a solitary lesion, 2 (18%) had between 2 and 9 lesions, and 2 (18%) had 10 lesions or more (including HCC and benign lesions). HCC was confirmed by means of histopathologic examination in 10/11 (91%) patients. In 1 patient the diagnosis of HCC was based on the development of a new lesion together with an elevated serum AFP level greater than 250 ng/ml.

Lesion characteristics are summarized in Table 3B. Mean lesion diameter was 32 ± 16 mm [14–55]. Signal intensity on T1-weighted and T2-weighted MR images was variable, with a predominance of signal hypointensity on T1-weighted MR (n = 7/12, 58%) and signal hyperintensity on T2-weighted MR images (n = 7/12, 58%). Ten HCCs (83%) showed APHE, and washout was observed in 7 (58%) and 11 (92%) HCCs on portal venous and delayed phase images, respectively (Fig. 4). Overall, 9/12 (75%) HCC were greater than 1 cm in size and showed both APHE and washout.

Focus on lesions greater than 1 cm showing both APHE and washout

A total of 52/143 lesions greater than 1 cm in size with APHE showed washout, including 9 HCC (17%) and 43 benign lesions (83%). Therefore the specificity of washout for the diagnosis of HCC was 67% (95% CI 59–75%) in this subgroup. After exclusion of the 3 cirrhotic patients from the analysis, the specificity remained unchanged (data not shown). Characteristics of lesions (and corresponding patients) are provided (Table 4).

In this subgroup of 52 lesions, signal hypointensity on T1-weighted images was observed significantly more frequently in HCC (n = 6/9, 67%) than benign lesions (n = 0, 0%, p <0.001). Signal hyperintensity on T2-weighted images was more frequent in HCC (77% *vs.* 11% in benign lesions, p <0.001) and on high b-value diffusion-weighted images (88% *vs.* 15%, p <0.001). Among the 21 patients with at least 1 lesion greater than 1 cm showing both APHE and washout, the serum AFP level was >15 ng/ml in 1/12 (8%) patients with benign lesions and 6/9 (67%) patients with HCC (p <0.001).

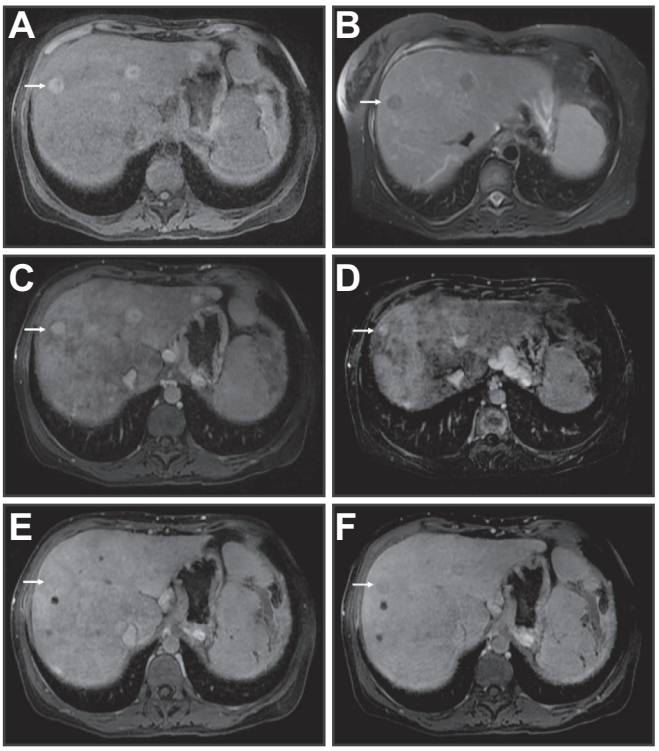

Fig. 3. Multiple benign lesions with washout appearance in a 38-year-old woman with primary Budd-Chiari syndrome due to myeloproliferative neoplasm. The lesions appeared hyperintense on (A) precontrast T1-w images and hypointense on (B) T2-weighted images. (C-F) Extracellular gadolinium-based enhanced fat-suppressed T1-weighted GE MR images showed a 13 mm lesion in the right liver with arterial phase hyperenhancement (C), confirmed by image subtraction (D), mild signal hypointensity on portal venous phase (E) and signal hypointensity on delayed phase (F). Serum alpha-fetoprotein was 4 ng/L. The patient was followed up for 57 months and remained hepatocellular carcinoma-free.

The diagnostic performance of adding several ancillary features for the diagnosis of HCC in lesions greater than 1 cm in size is provided (Table 5). The best specificity (100% [95% CI 92–100%]) was reached by adding hypointensity on T1-w images to the classic imaging hallmarks of HCC, and the highest sensitivity was obtained with hyperintensity on high b-value DWI (88% [95% CI 76–94%]).

Discussion

Our study confirms on a large scale (250 lesions in 49 patients with primary BCS) that MRI is helpful for the differentiation between HCC and benign regenerative lesions. Indeed, if both showed APHE in the vast majority of cases, several features significantly differed between them, particularly the rate of washout appearance. Yet, if washout was seen in most HCC as expected, it was also observed in 29% of benign lesions, and up to 18% of benign lesions were greater than 1 cm and showed both APHE and washout. This meant that the classic imaging hallmarks of HCC had an unacceptably low specificity for the non-invasive diagnosis of HCC in patients with BSC. Nevertheless, ancillary imaging features – such as signal intensity on T1 weighted images – or tumor markers resulted in an improved diagnostic performance in lesions greater than 1 cm.

BCS is a rare hepatic disorder characterized by obstruction of the hepatic venous system by primary hepatic vein thrombosis or by primary thrombosis of the inferior vena cava at its hepatic portion. Cazal-Hatem *et al.* have shown that a marked increase in hepatic arterial perfusion is observed in patients with long-standing BCS,[8] similar to the effect of "hepatic arterial buffer response" described by Lautt *et al.* in animals.[18] This triggers the development of chronic nodular regenerative hyperplasia,[1,8] further leading to large regenerative lesions showing predominantly arterial uptake. This is in accordance with the pathogenesis of unique focal nodular hyperplasia historically proposed by Wanless *et al.*,[19] and explains why the vast majority of the

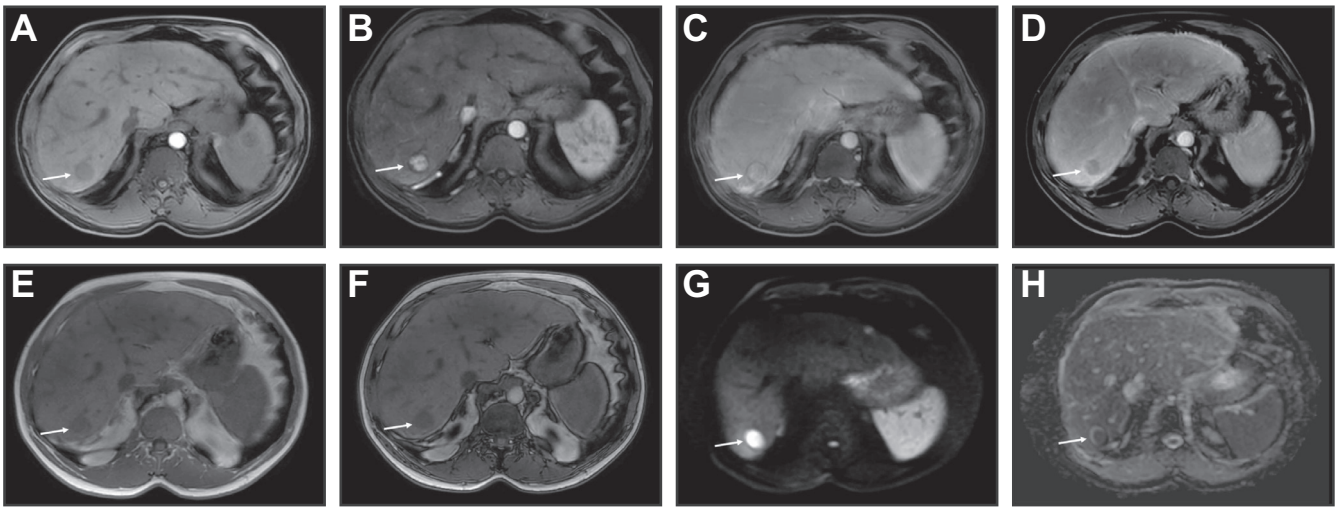

Fig. 4. HCC in a 47-year-old man with primary Budd-Chiari syndrome of unknown cause. (A-C) Extracellular contrast-enhanced fat-suppressed T1-weighted GE MR images showed a hypointense lesion on precontrast T1-weighted images located in the right liver (A). The lesion showed (B) arterial phase hyperenhancement (arrow), (C) mild hyperintensity on portal venous phase and (D) washout appearance on delayed phase. (E) In- and (F) opposed-phase T1-weighted GE MR images show that the lesion did not contain fat. The lesion appears markedly hyperintense on (G) high b-value diffusion-weighted images with (H) low apparent diffusion coefficient values. The serum alpha-fetoprotein level was 402 ng/L. The patient underwent liver biopsy confirming the diagnosis of moderately differentiated HCC, which was treated by percutaneous radiofrequency ablation. HCC, hepatocellular carcinoma.

Table 4. Characteristics of patients with and without HCC and comparison of HCC and benign lesions.

A) Patients	All (n = 21)	With benign lesions and no HCC (n = 12)	With HCC (n = 9)	*p* value
Mean age (SD)	37 ± 13	31 ± 7	46 ± 15	0.006
Men (%)	4 (19)	1 (8)	3 (33)	0.272
Prothrombotic risk factors*, n (%)				
Myeloproliferative neoplasms	8 (38)	7 (58)	1 (11)	0.067
Hemoglobinuria	1 (5)	1 (8)	0 (-)	1.000
Behcet disease	1 (5)	1 (8)	0 (-)	1.000
Coagulation disorder	6 (29)	2 (17)	4 (44)	0.331
Anti-phospholipid syndrome	2 (10)	2 (17)	0 (-)	0.486
Oral contraception[1]	8 (47)	7 (58)	1 (11)	0.067
Pregnancy[1]	8 (47)	6 (50)	2 (22)	0.367
Involved vessels, n (%)				
Inferior vena cava thrombosis	6 (29)	2 (17)	4 (44)	0.331
Portal vein thrombosis	2 (10)	1 (8)	1 (11)	1.000
AFP serum level[a], ng/ml	3 (2–9,000)	3 (2–4)	31 (2.5–9,000)	<0.001
>15	7 (33)	1 (8)	6 (67)	<0.001
Previous treatment, n (%)				
TIPS	7 (33)	5 (42)	2 (22)	0.642
Hepatic vein Stenting	1 (5)	0 (–)	1 (11)	0.429
Steatosis, n (%)	0 (–)	0 (–)	0 (–)	–
Number of focal lesions, n (%)				
One	6 (29)	0 (–)	6 (67)	
Between 2 and 9	10 (48)	8 (67)	2 (22)	0.004
More than 10	5 (24)	4 (33)	1 (11)	
B) Lesions	**All (n = 52)**	**Benign lesions (n = 43)**	**HCC (n = 9)**	***p* value**
Size, mm	18 ± 9	15 ± 5	29 ± 14	<0.001
10–19	44 (85)	40 (93)	4 (44)	0.002
>20	8 (15)	3 (7)	5 (66)	
Localisation, n (%)				
Right liver	40 (77)	32 (74)	8 (89)	
Left liver	12 (23)	11 (26)	1 (11)	0.191
Segment I and IX	0 (–)	0 (–)	0 (–)	
Signal intensity n (%)				
T1-weighted				
Hypo-intense	6 (12)	0 (–)	6 (67)	
Iso-intense	4 (8)	3 (7)	1 (11)	<0.001
Hyper-intense	42 (81)	40 (93)	2 (22)	
T2-weighted				
Hypo-intense	36 (69)	35 (81)	1 (11)	
Iso-intense	4 (8)	3 (7)	1 (11)	<0.001
Hyper-intense	12 (23)	5 (11)	7 (78)	
Diffusion-weighted[2,3,4]				
Hyper-intense	11 (32)	4 (15)	7 (88)	<0.001
Disappearance, n (%)	6 (12)	6 (14)	0 (–)	0.572
Other, n (%)				
Fat	3 (6)	1 (7)	2 (22)	0.074
Capsule	6 (12)	3 (2)	3 (33)	0.057

Numbers in parentheses are percentages. 1. In the female population. 2. Data available for 34 lesions (26 benign lesions and 8 HCC). a. Expressed as median (range). AFP alpha-fetoprotein, HCC, hepatocellular carcinoma; TIPS, transjugular intrahepatic portosystemic shunt.
Statistical tests: categorical variables compared with Chi-square and Fisher's exact test. Means compared with the Student's *t* test and medians with the Mann-Whitney *U* test. (A) Characteristics of patients with and without HCC among those with at least one lesion greater than 1 cm showing arterial phase hyperenhancement and washout. (B) Comparison of HCC and benign lesions greater than 1 cm showing arterial phase hyperenhancement and washout.

Table 5. Performance of imaging findings and biological features for the diagnosis of HCC *vs.* benign lesions in lesions greater than 1 cm showing APHE and washout.

	Benign (n = 43)	HCC (n = 9)	Sensitivity (95% CI)	Specificity (95% CI)	LR+ (95% CI)	LR– (95% CI)
APHE + washout + hypointensity on T1-w	0 (0%)	6 (67%)	67% (35–87)	100% (92–100)	–	0.33 (0.13–0.84)
APHE + washout + hyperintensity on T2-w	5 (11%)	7 (77%)	78% (45–93)	88% (76–94)	6.69 (2.73–16.37)	0.25 (0.07–0.86)
APHE + washout + fat content	1 (7%)	2 (22%)	22% (6–54)	97% (87–100)	8.67 (0.88–85.45)	0.80 (0.56–1.14)
APHE + washout + capsule	3 (2%)	3 (33%)	33% (12–65)	93% (81–98)	4.78 (1.14–19.96)	0.72 (0.45–1.15)
APHE + washout + hyperintensity on DWI*	4 (15%)	7 (88%)	88% (53–98)	85% (66–94)	5.68 (2.23–14.54)	0.15 (0.02–0.93)
APHE + washout + AFP >15 ng/ml	2 (5%)	6 (67%)	67% (35–88)	95% (84–99)	14.33 (3.43–59.89)	0.35 (0.14–0.88)

* Among the 34 lesions with available data. AFP, alpha-fetoprotein; APHE, arterial phase hyperenhancement; DWI, diffusion-weighted imaging; LR+/LR-, positive/negative likelihood ratio; HCC, hepatocellular carcinoma.

lesions analyzed in the present study showed hyperenhancement in the arterial phase, in line with previous reports.[9,10,14,20] According to this hypothesis, the pathogenesis of benign lesions is different from lesion formation in cirrhosis and is directly attributable to chronic liver congestion. Importantly, HCC also shows hyperenhancement in the vast majority of patients.[9,11,12] Therefore, differentiation between malignant and benign lesions requires the use of other features.

From a clinical and biological point of view, patients with benign lesions significantly differed from those with HCC regarding serum AFP levels and age. The negative predictive value of the cut-off of 15 ng/ml for AFP proposed by Moucari *et al.* was efficient since only 1 patient with a benign lesion had a higher value. Male gender and inferior vena cava obstruction, also reported by Moucari *et al.* as risk factors for HCC, were not associated with this diagnosis in the current population, even though the frequency of the latter was higher in patients with HCC.[11] Yet, and as stressed by Moucari *et al.*, inferior vena cava obstruction may be more a marker of long-standing BCS than a risk factor for HCC *per se*.[11] As a consequence, patient characteristics are insufficient, and imaging is required for the differential diagnosis.

Imaging features of regenerative lesions that develop in BCS have been well documented:[9,10,14] as in the present study, most appear hyperintense on T1-weighted MR images, and hypointense on T2-weighted MR images. Classically, the washout appearance is associated with the diagnosis of HCC, and regenerative lesions are expected to present with contrast fading (hyperenhancement and progressive disappearance), or marked and persistent contrast uptake.[9,10,14] This is derived from the European Association for the Study of the Liver (EASL) and the American Association for the Study of Liver Diseases (AASLD) guidelines for the diagnosis of HCC that recommend that every lesion greater than 1 cm with arterial hyperenhancement and washout on dynamic contrast-enhanced imaging should be considered as HCC.[16,17] Yet, these recommendations are only validated in patients with cirrhosis.[15,17] Whether or not they can be transposed to other clinical contexts, and especially to patients with vascular disorders of the liver, remains unclear. Our results show that these recommendations cannot be followed in this setting. First, 25% of HCC did not show this feature. The limited sensitivity of washout on the portal venous phase was reported by Moucari *et al.*[11] Yet, sensitivity is not the aim of imaging as a non-invasive diagnostic tool. As a matter of fact, such low sensitivity is also observed in patients with small HCC in the setting of cirrhosis.[21–23] More important is the specificity offered by the non-invasive criteria. Since close to 20% of benign lesions were greater than 1 cm and showed arterial hyperenhancement and washout appearance on portal venous and/or delayed phase images, the resulting specificity of the classic hallmarks for the non-invasive diagnosis of HCC was unacceptably low. Few patients were pathologically diagnosed with cirrhosis in our series. Yet, and noticeably, this was rare, and analyses performed after exclusion of these patients showed that results remained unchanged. Moucari *et al.* have suggested that washout in HCC in the context of BCS might also be explained by the venous congestion within the liver parenchyma.[11] We hypothesize that liver congestion might also, and more importantly, explain the high prevalence of washout in benign lesions.

Interestingly, other imaging features were shown to be helpful in the differentiation of malignant and benign lesions. HCC more frequently showed signal hypointensity on T1-w images, hyperintensity on T2-w and diffusion-weighted images, capsule and fat content, and were larger than benign lesions. This is in line with previous reports by Vilgrain *et al.*[9] and Brancatelli *et al.*[10] Associating these features helped improve the diagnostic performance of imaging. Therefore, carefully assessing the presence of these features is of the utmost importance.

Aside from its retrospective design, this study suffers from several limitations. First, the population was not large. This is explained by our inclusion criteria, since we focused on patients with primary BCS with focal liver lesions, and with baseline and follow-up MR imaging. Yet, the population is consecutive, well characterized, and includes a large number of lesions. Moreover, it is representative of a Western BCS cohort, with a preponderance of women, and a high frequency of myeloproliferative neoplasms.[11] Second, we did not use MR hepatospecific contrast agent. Most patients were diagnosed before the large dissemination of hepatospecific contrast agents. We also felt it was important to analyze these patients with extracellular MR contrast agents. We acknowledge that the choice of the contrast agent in vascular liver diseases is an important question since few case reports have been published thus far.[24–26] This question is currently under investigation in our department. Third, the imaging ancillary features we used favoring the diagnosis of HCC were derived from those included in the LI-RADS system.[27] Yet, they would need to be validated prospectively in patients with BCS. Finally, the definition of washout was purely qualitative, which may result in subjectivity and inter-reader variability. This variability has been acknowledged in previous publications.[28] Yet, this definition follows the recommendations of international guidelines.[16,17] Moreover, if one could hypothesize that a quantitative definition, in line with that proposed by Chang *et al.*,[29] would result in more reproducible identification of washout, an article by Liu *et al.* showed that a purely quantitative definition of washout correlated well with radiologists' assessments of enhancement pattern of lesions but resulted in a lower positive predictive value than visual assessment.[30] Moreover, the quantitative approach may miss a partial washout due to averaging of the signal intensity in the lesion. This suggests that, at present, a quantitative method cannot replace qualitative analysis.

In conclusion, MR imaging is helpful for the differentiation between HCC and benign liver lesions in patients with BCS. The value of washout appearance is limited since it was observed in a significant proportion of benign lesions greater than 1 cm, leading to an unacceptably low specificity for the diagnosis of HCC. Therefore, the non-invasive diagnostic criteria proposed by the AASLD and EASL for cirrhotic patients cannot be applied in this clinical setting. Other imaging features and patient characteristics should be carefully analyzed, especially lesion signal intensity on precontrast sequences and serum AFP levels, because their combination with classical imaging features increases the diagnostic confidence.

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Conflict of interest

The authors declare no conflicts of interest that pertain to this work.

Please refer to the accompanying ICMJE disclosure forms for further details.

Authors' contributions

Study design: M van Wettere, M Ronot, V Vilgrain. *Data collection:* M van Wettere, M Ronot, A Plessier, A Payancé, PE Rautou, D Cazal-Hatem. *Data analysis:* M van Wettere, M Ronot, O Bruno, D Cazal-Hatem. *Study coordination:* M Ronot. *Logistic support:* M Ronot V Vilgrain. *Manuscript drafting:* M van Wettere, Y Purcell, M Ronot. *Manuscript revision:* All authors. *Manuscript final approval:* All authors.

Supplementary data

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