

# Imaging Features of Fibrolamellar Hepatocellular Carcinoma with Contrast-Enhanced Ultrasound

## Bildgebungsmerkmale des fibrolamellären hepatozellulären Karzinoms im kontrastverstärkten Ultraschall

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### ABSTRACT

**Purpose** Fibrolamellar hepatocellular carcinoma (f-HCC) is a rare primary liver tumor. Imaging plays an important role in diagnosis. The aim of this retrospective study was to analyze

contrast-enhanced ultrasound (CEUS) features of histologically proven f-HCC in comparison to benign focal nodular hyperplasia (FNH).

**Materials & Methods** 16 patients with histologically proven f-HCC lesions and 30 patients with FNH lesions were retrospectively reviewed regarding CEUS features to determine the malignant or benign nature of the focal liver lesions (FLL). Five radiologists assessed the CEUS enhancement pattern and came to a consensus using the EFSUMB (European Federation of Societies for Ultrasound in Medicine and Biology) guideline criteria.

**Results** Fibrolamellar hepatocellular carcinoma manifested as a single and huge FLL. On CEUS, f-HCC showed heterogeneous hyperenhancement in the arterial phase and hypoenhancement (16/16, 100%) in the portal venous and late phases (PVLP) as a sign of malignancy. In contrast to the hypoenhancement of f-HCC in the PVLP, all patients with FNH showed hyperenhancement as the most distinctive feature ( $P < 0.01$ ). 8 f-HCC lesions showed a central scar as an unenhanced area (8/16, 50.0%), which could also be detected in 53.3% (16/30) of FNH lesions ( $P > 0.05$ ).

**Conclusion** By analyzing the hypoenhancement in the PVLP, CEUS imaging reliably diagnosed f-HCC as a malignant FLL. CEUS also showed differentiation between f-HCC and FNH lesions, showing similar non-enhanced central scars, whereas f-HCC lesions showed peripheral hyperenhancement in the arterial phase and early washout in the PVLP.

### ZUSAMMENFASSUNG

**Ziel** Das fibrolamelläre hepatozelluläre Karzinom (f-HCC) ist ein seltener primärer Lebertumor. Die Bildgebung spielt bei der Diagnose eine wichtige Rolle. Ziel dieser retrospektiven Studie war es, die Merkmale im kontrastverstärkten Ultraschall (CEUS) bei histologisch nachgewiesenem f-HCC im Vergleich zur benignen fokalen nodulären Hyperplasie (FNH) zu analysieren.

**Material und Methoden** 16 Patienten mit histologisch nachgewiesenen f-HCC-Läsionen und 30 Patienten mit FNH-Läsionen wurden retrospektiv auf CEUS-Merkmale untersucht, um die maligne oder benigne Natur der fokalen Leberläsionen (FLL) zu bestimmen. 5 Radiologen bewerteten das CEUS-Enhancement-Muster und kamen zu einem Konsens unter

Verwendung der Kriterien der EFSUMB (European Federation of Societies for Ultrasound in Medicine and Biology) -Richtlinien.

**Ergebnisse** Das fibrolamelläre Leberzellkarzinom manifestierte sich als eine einzige und große FLL. Im CEUS zeigte das f-HCC ein heterogenes Hyperenhancement in der arteriellen Phase und ein Hypoenhancement (16/16, 100%) in der portalvenösen und späten Phase (PVLP) als Marker für Malignität. Im Gegensatz zum Hypoenhancement des f-HCC in der PVLP zeigten alle Patienten mit FNH ein Hyperenhancement als auffälligstes Merkmal ( $p < 0,01$ ). 8 f-HCC-Läsionen zeigten eine

zentrale Narbe als Bereich ohne Anreicherung (8/16; 50,0%), welche auch bei 53,3% (16/30) der FNH-Läsionen nachgewiesen werden konnte ( $p > 0,05$ ).

**Schlussfolgerung** Durch die Untersuchung des Hypoenhancements in der PVLP konnte die CEUS-Bildgebung f-HCC zuverlässig als maligne FLL diagnostizieren. Außerdem konnte CEUS zwischen f-HCC und FNH-Läsionen differenzieren und zeigte ähnliche zentrale Narben ohne Anreicherung, wobei f-HCC-Läsionen ein peripheres Hyperenhancement in der arteriellen Phase und ein frühes Wash-out in der PVLP zeigten.

## Introduction

Fibrolamellar hepatocellular carcinoma (f-HCC) is a rare primary liver tumor. In 1956, Edmondson first reported f-HCC as a unique subtype of hepatocellular carcinoma (HCC) [1]. In 1980, it was named f-HCC by Craig [2]. Until the 2010 edition of the World Health Organization (WHO) Classification of Tumors, f-HCC was assigned its own WHO classification code [3].

Fibrolamellar hepatocellular carcinoma significantly differs from conventional HCC based on its unique clinical, epidemiologic, histopathologic and cytogenetic features [4]. The etiology of f-HCC remains unclear, and serum  $\alpha$ -fetoproteins (AFP) are not elevated in most cases [5]. In contrast to HCC, 95% of f-HCC occur in patients without any evidence of hepatitis, cirrhosis, metabolic dysfunction or liver inflammation [5]. The diagnosis of f-HCC is often difficult and careful assessment of the clinical findings and complementary imaging modalities before surgical operation plays an important role in the diagnosis, staging and surveillance of f-HCC [6].

Conventional B-mode ultrasound (BMUS) is the most commonly used imaging method for preoperative diagnosis of focal liver lesions (FLLs) and contrast-enhanced ultrasound (CEUS) is most specific for differential diagnosis [7–11]. However, due to the rarity of the disease, there is limited data on the ultrasound imaging features of f-HCC. It has been reported that f-HCC can appear as a solid, heterogeneous and encapsulated FLL on BMUS. The lesion was mainly isoechogenic with hyperechogenic areas, and there were no signs of chronic hepatopathy or portal or biliary permeability alterations [6].

Histopathologically, f-HCC are composed of well-differentiated neoplastic hepatocytes surrounded by sheets of fibrous tissue in lamellar distribution. The fibrolamellae may coalesce and form a central scar, which help to distinguish this rare tumor from other liver tumors [12]. A similar central scar on imaging has also been described in focal nodular hyperplasia (FNH) and was considered to be characteristic of this benign FLL [13]. Because of their clinical and imaging similarities, FNH is often confused with f-HCC [14]. According to the EFSUMB (European Federation of Societies for Ultrasound in Medicine and Biology) guidelines and recommendations for the use of CEUS in liver [15], CEUS allows differentiation of most benign and malignant FLLs in the portal venous

and late phases (PVLP) [16]. Until now, CEUS features of f-HCCs have been rarely reported.

The aim of our current retrospective study is to investigate the value of CEUS features of histologically proven f-HCC, in comparison to benign FNH.

## Patients and Methods

### Patients

Between January 2003 and October 2018, 16 consecutive patients (10 males, 6 females, mean age:  $21 \pm 8$  years; range: 16–35 years) diagnosed with f-HCC were retrospectively analyzed. All lesions were histopathologically proven following hepatic surgery ( $n = 14$ ) or real-time ultrasound-guided 18-gauge core needle biopsy ( $n = 2$ ). All patients had a single lesion in the f-HCC group (► **Table 1**).

30 patients (19 males, 11 females, mean age:  $35 \pm 12$  years; range: 24–47 years) with FNH lesions with CEUS images were also retrospectively analyzed. Four patients in the FNH group had multiple FLLs. We evaluated the one that was histopathologically proven. All lesions were histopathologically proven, following hepatic surgery in 25 cases and by 18-gauge core needle biopsy in 5 cases. Biopsy/surgery was mainly performed in patients who had unclear findings on CT or MRI or inconclusive cross-sectional imaging findings and/or malignant underlying diseases, such as a history of malignant tumor.

### 2D CEUS

Conventional BMUS and CEUS examinations were performed by five experienced radiologists (more than 10 years of CEUS of the liver), who were aware of the patients' clinical histories.

All ultrasound examinations were performed using five ultrasound systems: S2000 HELX OXANA unit (Siemens Medical Solutions, Germany, 6C1 convex array probes, 3.5 MHz), LOGIQ E9 (GE Healthcare, Milwaukee, WI, United States; C1–5 convex array probes, 1–5 MHz), Philips EPIQ7 unit (Philips Bothell, WA, United States; C5–1 convex array probes, 1–5 MHz), Samsung RS80 A unit (Samsung Healthcare, C1–7 convex array probe, 1–7 MHz) and Aloka Prosound F75 unit (Hitachi Healthcare, UST 9115 convex array probe, 8–3 MHz).

► **Table 1** Baseline characteristics of patients included in our study.

characteristic	f-HCC (n = 16 patients)	FNH (n = 30 patients)	p-value
age (year)			
▪ mean ± SD	21 ± 8	35 ± 12	n.s.
▪ range	16–35	24–47	n.s.
male/female	10/6	19/11	n.s.
number of FLLs (single/multiple)	16/0	26/4	n.s.
histological results			
▪ hepatic surgery	14	25	n.s.
▪ core needle biopsy	2	5	n.s.

## CEUS Procedure

CEUS was performed using contrast harmonic real-time imaging at a low MI, 0.05–0.30. Each examination lasted about 5 minutes after the bolus injection. SonoVue® (Bracco Imaging Spa, Milan, Italy) was used as the contrast agent. For each CEUS examination, a dose of 1.5–2.4 mL of SonoVue® was injected as a quick bolus via a 20-gauge intravenous catheter placed in the cubital vein, and followed by 5–10 mL of a 0.9% normal saline flush. Repeated injection of SonoVue® was performed when necessary.

To characterize the lesion, SonoVue® enhancement during the arterial phase (10–30 s), portal venous phase (20–120 s) and late vascular phase (120–300 s) was evaluated. All examinations were digitally recorded in a PC-based workstation connected to the ultrasound systems.

## Image analysis

All CEUS images were read by five independent radiologists (17, 18, 19, 20 and 22 years of abdominal ultrasound imaging experience) blinded to clinical and pathologic data who agreed on a consensus report. The evaluated ultrasound criteria included number of lesions, maximum diameter, echogenicity compared with the surrounding liver parenchyma (hyperechoic, hypoechoic or isoechoic; homogeneous or heterogeneous), margin (ill- or well-defined appearance), shape (regular or lobulated) and color Doppler imaging (CDI) features. On CEUS, the pattern of contrast enhancement of the lesion in comparison to the surrounding liver parenchyma (hypoenhancing, hyperenhancing, iso-enhancing), homogeneity of enhancement (homogeneous, heterogeneous) and additional features of enhancement during the arterial, portal venous and late phases were noted as well, e. g., central hypoechoic scar, centripetal ‘wheel-shaped’ enhancement.

## Statistical analysis

Data were expressed as mean ± SD. All statistical analyses were performed with SPSS 17.0 software package (SPSS, Chicago, IL, United States). The  $\chi^2$  test was used to compare f-HCC lesions with FNH lesions in terms of enhancement pattern. For the features that played a statistically significant role in the differentia-

tion diagnosis, the sensitivity and specificity were calculated. A difference was considered statistically significant in the case of  $P < 0.05$ .

## Institutional Board Approval

This retrospective study was approved by the institutional review board of our institution. The procedure that was followed was in accordance with the Declaration of Helsinki.

## Results

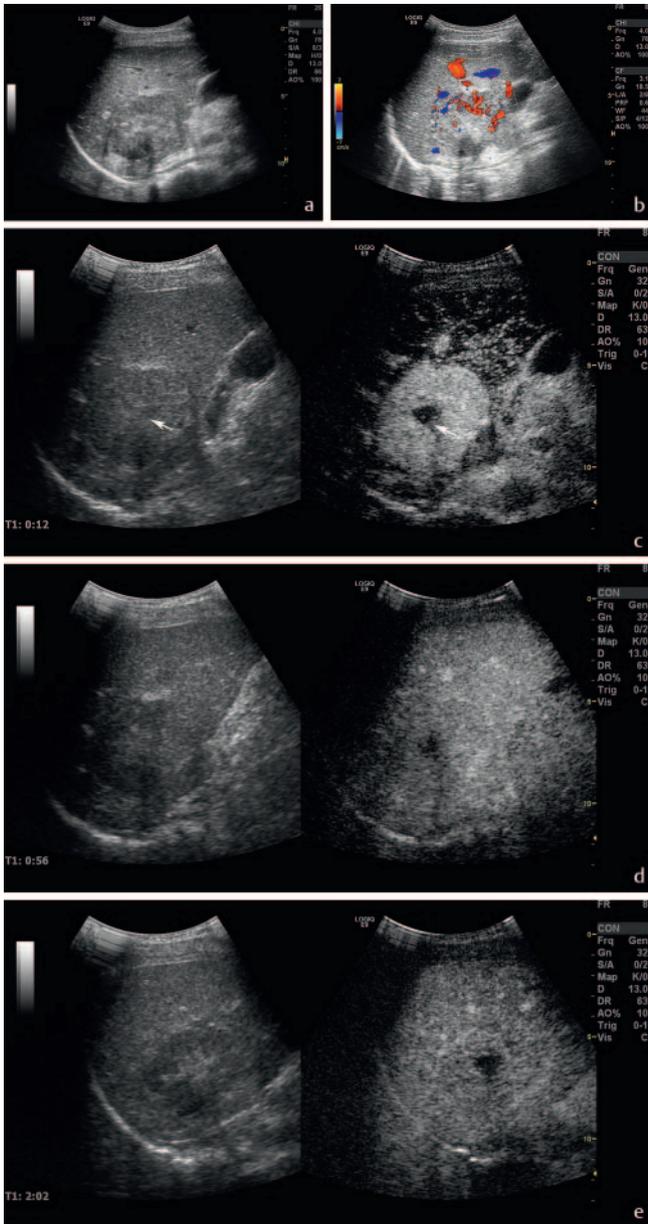
### Clinical and general pathologic features

FLLs were incidentally detected on conventional ultrasound in all patients. Laboratory tests (including transaminases, bilirubin, gamma-glutamyl transpeptidase (gGT)) were within normal limits in all patients. AFP (alpha-fetoprotein), carcinoembryonic antigen (CEA), cancer antigen 19–9 (CA-199), as well as HBV and HCV were negative in all patients.

Final pathologic diagnosis of f-HCC lesions showed typical well-differentiated neoplastic hepatocytes surrounded by fibrous bands arranged in lamellar distribution. On immunohistochemical staining, overexpression of anterior gradient-2 was seen in most f-HCC cases (n = 12). Also, moderate to intense expression of CD133 (n = 14), CD44 (n = 11) and CK7 (n = 12) was found in the f-HCC patients.

### Features with conventional ultrasound in f-HCC lesions

On conventional BMUS, f-HCC lesions manifested as a huge solitary, heterogeneous and encapsulated FLL. The mean size of f-HCC lesions was 13.5 cm (range: 6.4–21 cm). The tumors were large and three or more hepatic segments were involved in 12/16 (75%) patients in our cases. The f-HCC lesions were mainly well-defined hypo- or isoechogenic lesions with hyperechogenic areas (81.2%, 13/16). Hyperechogenic central scars were seen in 8/16 (50.0%) of the f-HCC cases. None of the patients had BMUS features of cirrhosis or steatosis, and there was no sign of chronic hepatopathy or portal or biliary permeability alterations (► **Fig. 1**).



► **Fig. 1** Fibrolamellar carcinoma. **a** B-mode ultrasound image showed a solid, heterogeneous and encapsulated isoechoic lesion located in the left lobe of the liver. **b** Branched color flow signals could be detected within the lesion. **c** Arterial phase, the lesion showed hyperenhancement with a nonenhanced central scar (arrow). **d** Portal venous phase, the lesion showed progressive washout. **e** Late phase, the lesion was hypoenhanced with a central scar.

Color Doppler imaging detected branched intralesional vessels in all f-HCC lesions. The Doppler spectrum was measured in 12 patients. The mean value of the resistive index (RI) was  $0.66 \pm 0.09$  (► **Fig. 2**).

### CEUS features

On CEUS, f-HCC lesions presented heterogeneous hyperenhancement (13/16, 81.2%) or peripheral hyperenhancement (3/16, 18.8%) during the arterial phase (► **Fig. 2**). Irregular, tortuous

intratumor vessels could be clearly demonstrated during the early arterial phase of CEUS (► **Fig. 1**). During the portal venous phase, all f-HCC lesions (100%, 16/16) showed progressive washout beginning at 1 minute or later. The mean washout time of f-HCC lesions was  $72 \pm 11$  seconds (range: 62–94 seconds). In the late phase, all f-HCC lesions became hypoenhanced (100%, 16/16) (► **Fig. 2, 3**). A central unenhanced area was observed in 50.0% (8/16) of f-HCC lesions during all CEUS enhancement phases (► **Fig. 1, 2**).

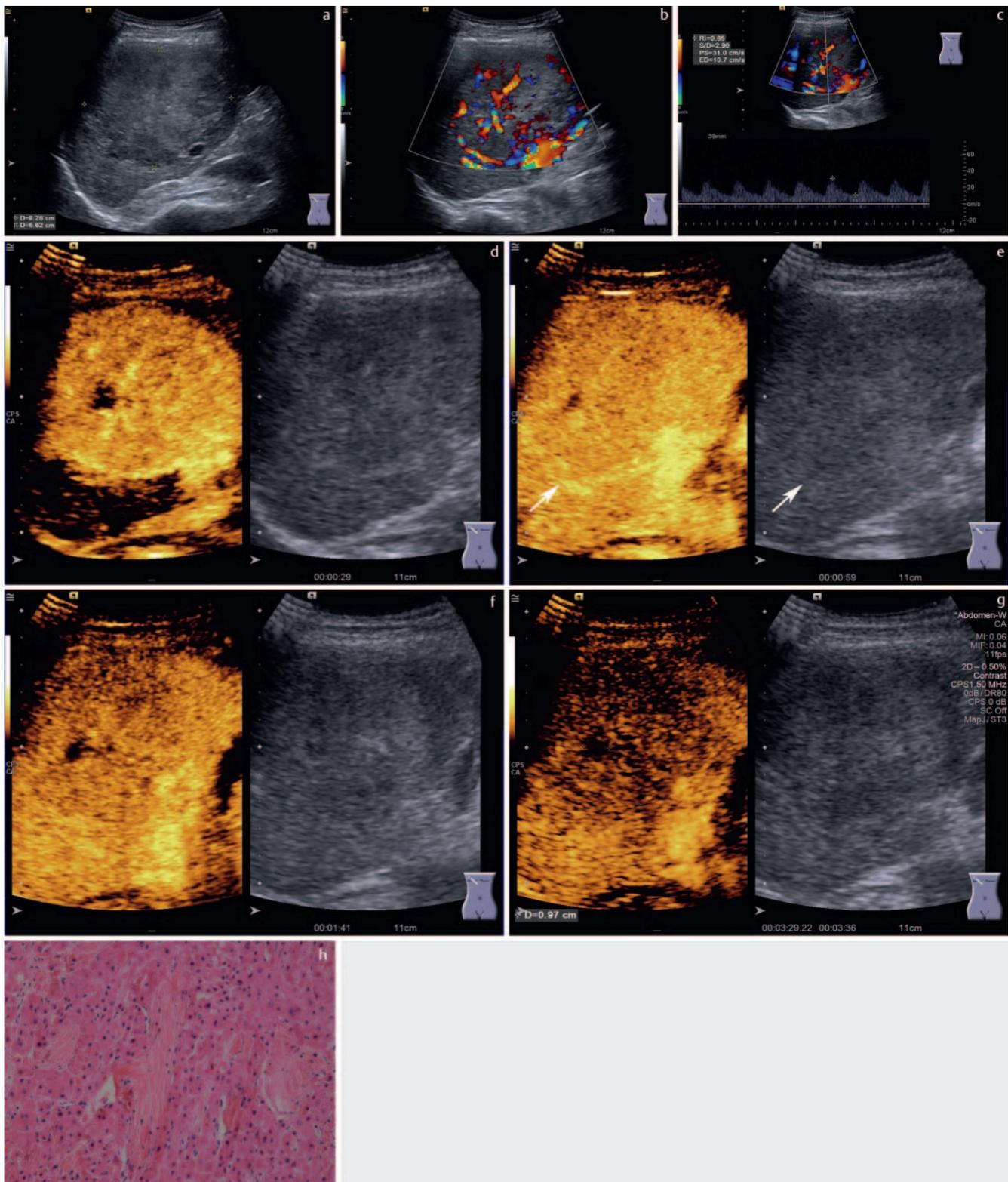
During the arterial phase of CEUS, FNH lesions mostly demonstrated centripetal ‘wheel-shaped’ hyperenhancement (80%, 24/30). They showed pronounced homogeneous enhancement when compared to f-HCC lesions. Also, all FNH lesions showed hyperenhancement in the PVLV as a sign of the benign nature of the lesion. An unenhanced central scar was detected in 53.3% (16/30) FNH lesions.

Compared to FNH lesions, heterogeneous hyperenhancement in the arterial phase and early washout with an unenhanced central scar in the late phase were characteristic CEUS features of f-HCC lesions ( $P < 0.01$ ) (► **Table 2**). The sensitivity was 78.5% for heterogeneous hyperenhancement in the arterial phase; 57.1% for washout with a central scar in the late phase and 90.5% for the combination of both.

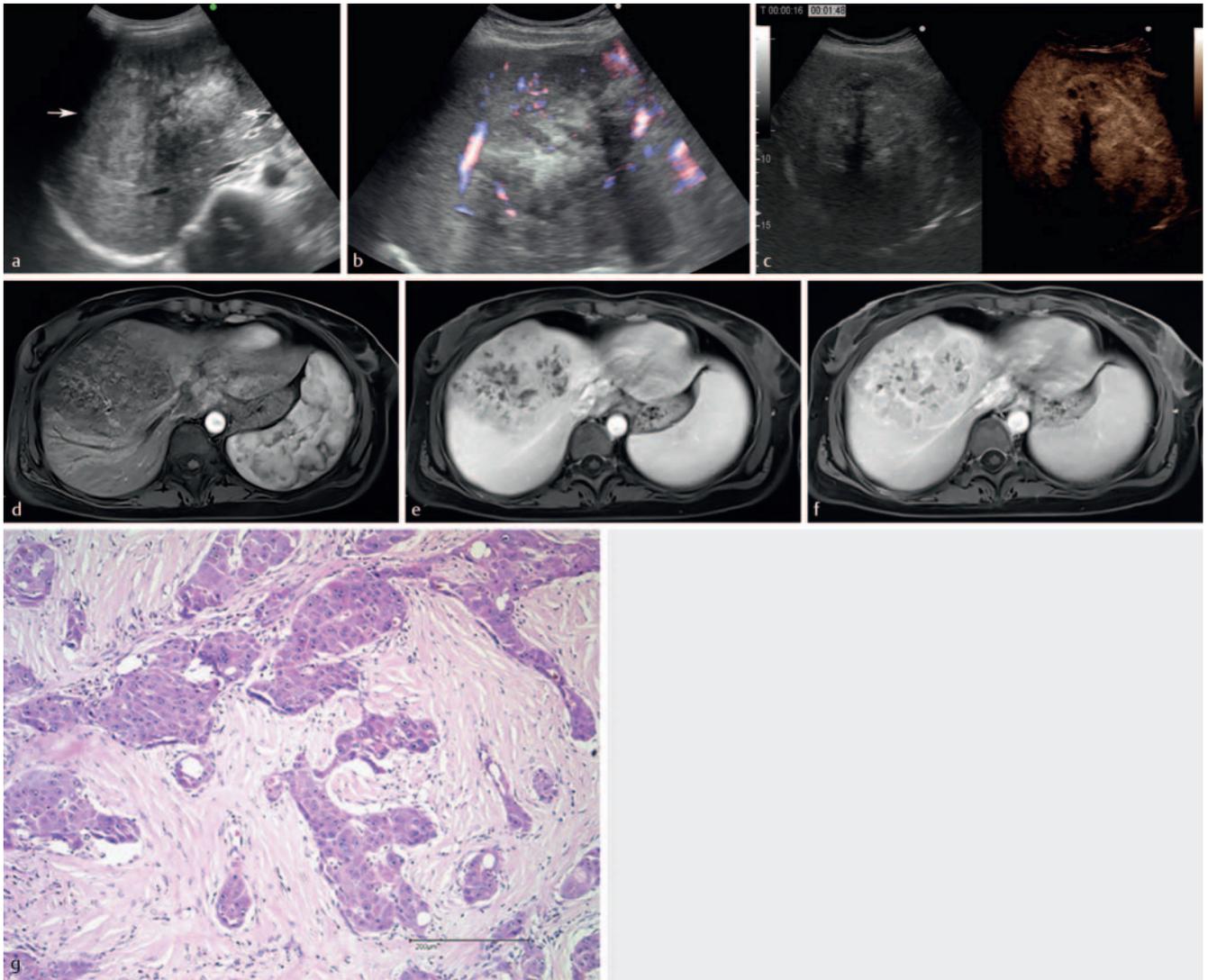
## Discussion

The epidemiology, etiology, and prognosis as well as the molecular portrait of f-HCC are unique and suggest that this tumor type is a distinct entity and not a subset of HCC [3–5, 17, 18]. In comparison with HCC, f-HCC usually has substantially different clinical, laboratory, pathologic, and radiologic features [3, 5]. Previously, many investigators have speculated that f-HCC might closely resemble benign focal liver lesions, such as FNH or hepatic adenoma. Since all those focal liver lesions occur predominantly in younger individuals without underlying cirrhosis, making an accurate noninvasive diagnosis is crucial for appropriate clinical decision-making and management [19, 20].

The diagnosis of f-HCC is often difficult. Imaging features of f-HCC on both computed tomography (CT) and magnetic resonance imaging (MRI) have previously been reported [19, 21]. Both CT and MRI images demonstrated characteristic features that correlated well with the pathologic features of f-HCC [19, 22]. While CT is adequate for initial preoperative imaging of f-HCC, especially for evaluation of the thorax for nodal and pulmonary metastases, MRI may be helpful for initial workup when f-HCC is first discovered as an incidental liver lesion [22, 23]. However, CT and MRI have disadvantages such as being expensive and time-consuming. They are relatively complicated imaging processes. Several prior studies have described the conventional ultrasound characteristics of f-HCC. Most of these were case reports [12, 24, 25]. Current experience with liver ultrasound imaging for f-HCC imaging is still limited. In this study, we have a relatively large series of cases of histopathologically proven f-HCC lesions with features of large, single, well-demarcated, lobulated, non-encapsulated intrahepatic masses on BMUS. The mean size of the f-HCC lesions in our study was 13.5 cm (range: 6.4–21 cm), which



► **Fig. 2** Fibrolamellar carcinoma. **a** B-mode ultrasound image showed a large solid, heterogeneous and encapsulated hypoechoic focal liver lesion in the right lobe of the liver. **b** Branched color flow signals could be detected within the lesion. **c** A relatively high RI value (0.65) was measured by Doppler spectrum. **d** The lesion showed hyperenhancement during the arterial phase. **e** The lesion showed progressive washout during the portal venous phase. **f** A nonenhanced central scar was obvious during all contrast-enhanced phases. **g** The lesion showed more clear washout in the late phase. **h** The final pathological image showed the lesion composed of well-differentiated neoplastic hepatocytes surrounded by fibrous bands in lamellar distribution. The surrounding liver had no underlying cirrhosis.



► **Fig. 3** Biopsy and histopathologically proven fibrolamellar carcinoma. **a** B-mode ultrasound showed a large hypoechoic lesion in the right lobe of the liver. **b** Color flow signals showed no blood flow within the lesion. **c** The lesion showed progressive washout during the late phase of contrast-enhanced ultrasound. **d** Gadolinium contrast-enhanced MRI showed marked heterogeneous contrast enhancement in the arterial phase. **e** The lesion was hypoenhanced in the portal venous. **f** The lesion was hypoenhanced in the delayed phase. **g**) The final pathological results indicated the lesion was composed of well-differentiated neoplastic hepatocytes surrounded by fibrous bands arranged in lamellar distribution. The surrounding liver had no underlying cirrhosis.

is similar to the average tumor size of 13 cm (range: 3–27 cm) as reported in other studies [14, 22]. The tumors were large and usually three or more hepatic segments are involved in more than 50% of the cases. In our study, color Doppler imaging depicted increased branched vascularization within the tumor in all f-HCC lesions. The mean RI value of the Doppler spectrum was relatively higher ( $0.66 \pm 0.09$ ), which could also be considered an ultrasound feature of liver malignancy [26].

On CEUS, the dynamic enhancement patterns demonstrated in the present cases were of associated hypervascularity during arterial phases with heterogeneous hyperenhancement. Irregular, tortuous intratumoral vessels could be clearly demonstrated by CEUS. Early washout after 1 minute with an unenhanced central scar in the portal venous and late phase was also a characteristic CEUS feature of f-HCC. This CEUS feature might also be helpful for

the differential diagnosis of hepatocellular adenoma and FNH versus f-HCC. For most FNH lesions, CEUS demonstrates distinguished centrifugal hyperenhancement during the arterial phase. This pattern was not observed in f-HCC and, therefore, allows differentiation. In f-HCC enhancement was centripetal, without any central artery or feeding radiating branches corresponding to the spoke-wheel sign [27]. Fibrolamellar hepatocellular carcinoma is different from HCC with respect to epidemiology, etiology, and prognosis. When compared to typical HCC, f-HCC also showed relatively early washout in the portal venous phase.

Pathologically, the fibrotic tissue may coalesce to form a scar with radiating fibrous bundles in 20–60% of cases [14, 25]. Fibrosis has also been described as involving the adjacent liver on CT, infrequently resulting in capsular retraction [14]. The differential diagnosis of f-HCC includes all hepatic tumors which contain a

► **Table 2** Comparison of CEUS features between f-HCC and FNH patients

CEUS features	f-HCC (n = 16 patients)	FNH (n = 30 patients)
arterial phase		
▪ heterogeneously hyperenhancement	13 (81.2%)	0
▪ homogeneously hyperenhancement	0	6 (20%)
▪ peripheral hyperenhancement	3 (18.8%)	0
▪ eccentric hyperenhancement	0	24 (80%)
portal venous phase		
▪ hyperenhancement	0	27 (90%)
▪ isoenhancement	0	3 (10%)
▪ hypoenhancement	16 (100%)	0
late phase		
▪ hyperenhancement	0	24 (80%)
▪ isoenhancement	0	6 (20%)
▪ hypoenhancement	16 (100%)	0
unenhanced central scar	8 (50.0%)	16 (53.3%)

Contrast-enhanced ultrasound: CEUS; fibrolamellar hepatocellular carcinoma: f-HCC; focal nodular hyperplasia: FNH.

scar, including FNH, hepatocellular adenoma, hepatocellular carcinoma, intrahepatic cholangiocarcinoma, giant hemangioma, hypervascular metastasis in adults, and hepatoblastoma in children [14]. FNH, in particular, may simulate fibrolamellar carcinoma, since both have similar demographic and clinical characteristics, and 8% of FNH are seen in patients younger than 15 years old [13, 14]. In f-HCC, the contrast scar is typically large and may be broad or stellate, eccentric or central [28]. Conventional BMUS was reported to be only partially successful in demonstrating central scars, with 33–60% of scars detected on BMUS compared with CT and pathologic analysis results [14, 19]. In our results, CEUS could clearly demonstrate an unenhanced central scar in 50.0% f-HCC lesions, as well as in 53.5% FNH lesions. The central scar of f-HCC showed hypoenhancement with respect to the surrounding liver parenchyma in the arterial, portal venous and late phase of CEUS. This could subsequently be correlated with the central scar shown on CT and MRI.

The present study has several limitations. First, the possibility of a selection bias in the FNH subgroup cannot be excluded due to the retrospective nature of our present study. Second, five different ultrasound devices were used in our multicenter study.

## Conclusion

In summary, CEUS is a useful diagnostic tool for the noninvasive characterization and evaluation of f-HCC. Compared to FNH, peripheral hyperenhancement in the arterial phase and early washout with a central unenhanced area in the late phase were characteristic CEUS features of f-HCC.

## Conflict of Interest

The authors declare that they have no conflict of interest.

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