Fibronodular hepatocellular carcinoma—a new variant of liver cancer: clinical, pathological and radiological correlation

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ABSTRACT

Aims To establish and define a new, not previously reported hepatocellular carcinoma (HCC) variant, termed fibronodular HCC (FN-HCC).

Methods We retrospectively reviewed 290 HCC cases and identified 29 FN-HCC and 24 scirrhous HCC (SCHCC). Clinical, pathological and radiological features of FN-HCC were reviewed and compared with 30 conventional HCCs (CV-HCC) and SC-HCC.

Results FN-HCCs were more likely to arise in non-advanced fibrotic livers with lower advanced Barcelona Clinic Liver Cancer (BCLC) stage, had lower rates of progression and longer time to progression and were more likely to be surgically resected compared with CV-HCCs and SC-HCCs. Imaging analysis of FN-HCCs demonstrated higher rates of non-peripheral washout and a new distinct pattern of enhancement which is characterised by the presence of multiple rounded nodules within a lesion embedded in fibrotic-appearing parenchyma.

Conclusions FN-HCC may represent a specific variant of HCC with distinct pathological, radiological and clinical features with potential ramifications for outcome.

INTRODUCTION

The incidence of hepatocellular carcinoma (HCC)-related deaths has risen in the last two decades making HCC the second most common cause of cancer-related deaths.[1–3] Various types of HCC have been recognised including solid/compact, trabecular, pseudoglandular/acinar, scirrhous, fibrolamellar, clear cell, steatohepatitic, chromophobe and recently described macrotrabecular subtypes.[4 5] The remaining group of HCCs that do not fit into a specific type are variably designated as conventional (CV) or classical (CL) HCC.[5] Studies have shown that HCC types may present with distinct clinical and radiological imaging characteristics that may warrant consideration in diagnosis, affect patient prognosis and influence clinical management.[6–8] In addition to the existing HCC types, we observed a pathologically distinct group of HCC and we designated it as a variant of HCC—'fibronodular HCC (FN-HCC)' due to its morphological appearance. The FN-HCC is defined by extensive fibrosis that divides tumour cells into multiple, well-circumscribed tumour nodules in a single HCC lesion. The presence of significant amounts of fibrotic tissue within the tumour resembles the well-described scirrhous HCC (SC-HCC). However, SC-HCC differs from FN-HCC in the presence of dispersed tumour cells in a background of fibrosis creating a relatively homogeneous appearance of the tumour,[9] whereas in the newly designated FN-HCC the fibrosis encircles the intratumorous tumour cell nodules with an absence of fibrosis between the individual tumour cells. This results in a histological appearance that mimics hepatic cirrhosis with fibrosis encircling tumour nodules in a single HCC lesion.

The purpose of this study was to investigate a new histopathological variant of HCC termed FN-HCC and compare it with already existing SC-HCC and CV-HCC based on its pathological appearance, clinical presentation and radiological MRI findings.

MATERIALS AND METHODS

Case selection and HCC pathological evaluation

This HIPAA (Health Insurance Portability and Accountability Act) compliant, single centre, retrospective study was approved by our institutional review board and the requirement for patient consent was waived. A total of 290 HCC cases were identified from the Yale New Haven Hospital pathology database between 2010 and 2018. The inclusion criteria for FN-HCC were as follows: the entire lesion is composed of multiple, varying sized, distinct 'cirrhosis-like' tumour nodules encircled by fibrous septa. The 'cirrhosis-like' nodularity of the lesion was easily visible on gross and low magnification microscopic examination. The gross appearance is often very distinct from the background liver, even in the presence of cirrhosis. These tumour nodules are seen within a well-defined single mass lesion, unlike the 'cirrhotomimetic pattern' of HCC where the tumour nodules are scattered throughout the liver parenchyma. The inclusion criteria of SC-HCC have been described previously.[4 5] HCC lesions with previous treatment by locoregional treatment modalities such as chemoembolisation, radiofrequency ablation or microwave ablation were excluded from the study. In addition, patients younger than 18 years or presenting with liver metastases were also excluded. Electronic medical records of the identified cases were reviewed and the following data were collected: disease characteristics including aetiology of cirrhosis, Child-Pugh score, Barcelona Clinic Liver Cancer (BCLC) stage, stage of liver fibrosis, portal hypertension and main portal vein thrombosis. The liver fibrosis staging was based on the Batts-Ludwig staging system.[10] Stages

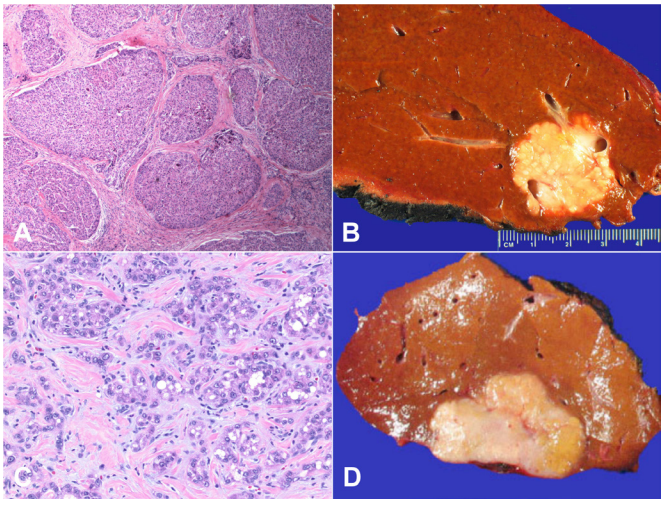

Figure 1 Macroscopic and microscopic features of fibronodular hepatocellular carcinoma (FN-HCC) and scirrhous hepatocellular carcinoma (SC-HCC). (A) Histological picture of FN-HCC demonstrating a fibronodular appearance characterised by extensive fibrosis dividing the tumour cells into multiple, well-circumscribed tumour nodules in a single HCC lesion; (B) gross picture of FN-HCC showing a nodular cut surface; (C) histological picture of SC-HCC demonstrating a diffuse fibrotic appearance characterised by abundant intratumorous fibrous stroma surrounding the tumour islands and/or fine fibre infiltrating between the tumour cells and D) gross picture of SC-HCC showing a fibrotic cut surface.

0–2 were classified as no or early fibrosis and stages 3–4 were classified as advanced fibrosis. In addition, tumour characteristics such as tumour size, multifocality and treatment response after histological diagnosis were assessed. Clinical laboratory values including alpha-fetoprotein (AFP), albumin and bilirubin were also collected. Disease progression was determined based on histological and radiological reports.

HCC imaging evaluation

Dynamic contrast-enhanced MRI using the Liver Imaging Reporting and Data System (LI-RADS) major and ancillary criteria (updated 2018) were used in the assessment of HCC lesions.[11] Patients who underwent MRI less than 4 months prior to histological diagnosis were included in the subsequent image analysis. Lesions smaller than 1.5 cm were excluded from the imaging analysis as their size restricted the identification of specific intratumorous characteristics observed with larger lesions. A number of MRI findings were tabulated and analysed including the bidirectional maximum diameter of the tumour, tumour margins, presence or absence of tumour capsule and signal intensity characteristics of the tumour observed on static and dynamic contrast-enhanced imaging.

Statistical analysis

Statistical analyses were performed on GraphPad Prism (San Diego, California, USA), and statistical significance was assumed when the p value was less than 0.05. Kruskal-Wallis test was used for non-parametric baseline characteristics; analysis of variance was used for parametric baseline characteristics and χ^2 test was used for categorical data. A repeated Mann-Whitney U test was used to compare the clinical laboratory values for different HCC groups. The overall survival outcomes and the time to progression were evaluated with the Kaplan-Meier method. The event in overall survival was defined as death in the observed time period. Similarly, the event in time to progression was defined as extrahepatic or intrahepatic progression in the observed time period (end date: 1 February 2019).

RESULTS

Based on histopathological characteristics, a total of 29 FN-HCCs, 24 SC-HCCs were identified out of a total 290 histologically diagnosed HCC cases. In the FN-HCCs, the tumours were entirely composed of multiple variable sized nodules separated by fibrous septae mimicking cirrhotic liver. The number of tumour cells in each nodule was highly variable and depended on the size of tumour nodule (figure 1A). The number of nodules in each tumour was also variable depending on the tumour size and amount of stroma. The tumour cells in each of the nodules were mostly arranged in trabecular (n=25) or solid growth pattern (n=4) with scattered pseudo-acini. The tumours were invariably well-differentiated to moderately differentiated HCC and showed histological features similar to CV-HCC. Macroscopically, the cut surface of FN-HCCs was distinctly nodular (figure 1B). In comparison, SC-HCCs displayed dispersed single or small cluster of tumour cells in a background of extensive fibrosis (>50% of tumour area) creating a relatively homogeneous appearance of the tumour without distinct intratumorous nodule formation microscopically (figure 1C). Macroscopically, the cut surface of SC-HCCs also appeared more homogeneous, tan to whitish and firm (figure 1D). Additionally, a control group of 30 CV-HCCs were randomly selected from the 290 HCCs. As seen in table 1 that all three HCC groups were predominantly seen in men with 82.76%, 79.17% and 86.67% in the FN-HCC, SC-HCC and CV-HCC groups, respectively. The median age of the cohort was 68.17, 66.10, 68.96 years, respectively. Viral hepatitis, and more specifically hepatitis C, was the predominant aetiological factor of underlying liver disease (FN-HCC: 55.17%, SC-HCC: 62.50%, CV-HCC: 46.67%). Of note, compared with CV-HCCs, hepatitis B infection was more commonly seen in FN-HCCs (p=0.035). There were no significant differences in age (p=0.4749), sex (p=0.7636), Child-Pugh class (p=0.6184), main portal vein tumour thrombosis (p=0.7020), tumour size (p=0.5164) and multifocality (p=0.3828) among all groups. AFP values were recorded for all three groups at the closest time from the date of diagnosis and prior to any form of medical or interventional management. There was no significant difference among the three groups of patients with AFP levels measuring >100 ng/mL.

Based on the BCLC staging system stages, the disease were divided into very early/early (BCLC 0/A) stage and intermediate/advanced (BCLC B/C) stage as following: BCLC 0/A: 82.14% (FN-HCC), 64.70% (SC-HCC) and 80.00% (CV-HCC) and BCLC B/C: 17.36% (FN-HCC), 35.29% (SC-HCC) and 20.00% (CV-HCC). There were no significant differences in overall BCLC staging among the three groups (p=0.4625); however, the percentage of stage C BCLC was relatively lower in FN-HCC (3.57) compared with the other two groups (SC-HCC: 11.76, CV-HCC: 13.33). FN-HCCs were more frequently resected (78.57%) than SC-HCCs (19.05%) (p<0.0001) and CV-HCCs (10.34%) (p<0.0001). The percentage of cases with underlying liver advanced fibrosis (stages 3–4) was significantly lower in FN-HCCs (58.62%) compared with SC-HCCs (91.67%, p=0.0056) and CV-HCCs (86.67%, p=0.0154) (table 1).

Analysis of the MRI studies performed before and after administration of intravenous contrast material demonstrated several distinctive findings between FN-HCC and SC-HCC

Table 1 Baseline characteristics

	FN-HCC, n (%) (N=29)	SC-HCC, n (%) (N=24)	CV-HCC, n (%) (N=30)	P value
Age (years±SD)	68.17±8.98	66.08±8.33	67.62±8.51	0.4749
Sex (male:female)	24:5 (82.76:17.24)	19:5 (79.17:20.83)	26:4 (86.67:13.33)	0.7636
Size (cm)	3.73±2.59	2.49±0.88	3.7±2.39	0.5164
Multifocal	9 (32.14)	8 (40)	15 (50)	0.3828
Liver fibrosis				0.0262
Stages 0–2	12 (41.38)	2 (8.33)	4 (13.33)	
Stages 3–4	17 (58.62)	22 (91.67)	26 (86.67	
Background liver disease				0.1343
Hepatitis C	16 (55.17)	15 (62.50)	14 (46.67)	
Hepatitis C+B	3 (10.34)	0 (0)	6 (20)	
Hepatitis B	4 (13.80)	2 (8.33)	0 (0)	
Alcoholic	1 (3.45)	1 (4.17)	3 (10)	
NAFLD	2 (6.90)	5 (20.83)	2 (6.67)	
Unknown	3 (10.34)	1 (4.17)	5 (16.67)	
Child-Pugh class				0.6184
A	21 (72.41)	16 (80)	24 (82.76)	
B	8 (27.59)	4 (20)	5 (17.24)	
BCLC stage				0.4625
Stage 0	3 (10.71)	1 (5.88)	1 (3.33)	
Stage A	20 (71.43)	10 (58.82)	23 (76.67)	
Stage B	4 (13.79)	4 (23.53)	2 (6.67)	
Stage C	1 (3.57)	2 (11.76)	4 (13.33)	
Main portal vein tumour thrombosis	0 (0)	0 (0)	1 (3.33)	0.7020
Treatment				<0.0001
Embolisation	4 (13.79)	8 (38.10)	13 (44.83)	
DEB-TACE	2 (6.90)	6 (28.57)	11 (37.93)	
Y90-radioembolisation	2 (6.90)	2 (9.52)	1 (3.45)	
Bland embolisation	0 (0)	0 (0)	1 (3.45)	
Ablation	2 (7.14)	9 (42.86)	12 (41.38)	
Resection	22 (78.57)	4 (19.05)	3 (10.34)	
Transplant	3 (10.71)	3 (14.29)	1 (3.45)	
Disease progression				0.0017
Intrahepatic progression	7 (28.00)	6 (30.00)	15 (68.18)	
Extrahepatic progression	0 (0)	1 (5.00)	3 (13.64)	
Local recurrence	2 (8.00)	7 (35.00)	6 (27.27)	
No progression	16 (64.00)	6 (30.00)	2 (9.10)	

BCLC, Barcelona Clinic Liver Cancer; CV-HCC, conventional hepatocellular carcinoma; DEB-TACE, drug-eluting bead transarterial chemoembolisation; FN-HCC, fibronodular hepatocellular carcinoma; NAFLD, non-alcoholic fatty liver disease; SC-HCC, scirrhous hepatocellular carcinoma.

groups. Specifically, when compared with SC-HCC group, the most characteristic distinctive feature of FN-HCC was a characteristic 'popcorn' appearance of the lesions. Thus, on the arterial phase of imaging the FN-HCC showed contrast enhancement of multiple well-defined rounded nodules within a single lesion separated by thin poorly enhancing bands of tissue resulting in a 'popcorn' appearance of the lesion. Similarly, on the delayed phase of imaging the nodules within the lesion showed homogeneous washout with delayed enhancement of the thin bands of tissue surrounding each nodule, again resulting in the 'reverse popcorn' appearance of the lesion (figure 2A). This pattern of enhancement corresponded to the appearance of the lesion seen on histopathology. Another distinctive feature of FN-HCC was non-peripheral washout that was seen more commonly than in SC-HCC (table 2). In addition, FN-HCC more commonly displayed a lobular contour when compared with SC-HCC (p=0.0041). In contrast, compared with FN-HCC, SC-HCC more commonly had satellite lesions (p=0.0043) associated with the main lesion and demonstrated rim arterial peripheral hepatic enhancement (p=0.0313) on the dynamic MRI imaging (table 2 and figure 2B). To evaluate any difference in HCC diagnosis between FN-HCC and SC-HCC by using LI-RADS system, imaging assessment was performed on 13 CL-HCC and 14 SC-HCC lesions based on the reports of prior available MRI or CT images. As seen in table 2, based on the major and ancillary LI-RADS criteria, 92.3% (12/13) of FN-HCC cases were classified as LR-5. SC-HCCs had variable LI-RADS classification with only five cases classified as LR-5 (35.7%). Six cases were classified as LR-4 (42.9%) and three cases as LR-3 (28.6%).

In the current study, median follow-up duration was 54.57 months (range 4.13–94.43 months) in FN-HCC, 38.6 months (range 2.83–108.07 months) in SC-HCC and 43.59 months (range 0.53–97.40 months) in CV-HCC. Of note, the median survival could not be calculated since more than 50% of the patients were still alive by the end of the observation period. There was no significant difference in overall survival among the three groups (p=0.9412) (figure 3A). However, compared with SC-HCC and CV-HCC, FN-HCC showed a lower rate of disease

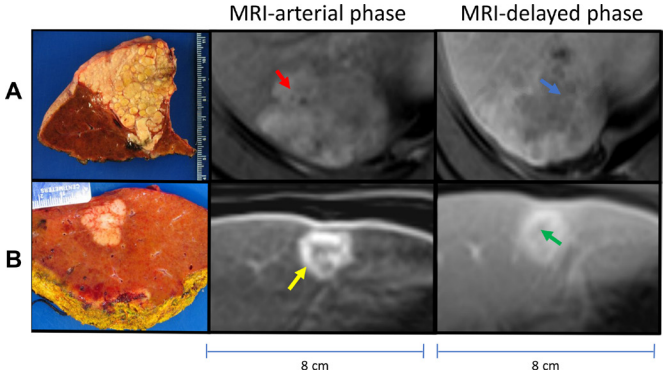

Figure 2 MRI findings of fibronodular hepatocellular carcinoma (FN-HCC) and scirrhous hepatocellular carcinoma (SC-HCC): (A) FN-HCC gross picture with nodular surface (left) and corresponding nodules (red arrow) and septations (blue arrow) seen in the arterial phase. (B) SC-HCC gross picture with fibrotic surface (left) and corresponding rim-like enhancement (yellow arrow) in the arterial phase without washout (green arrow) in the delayed phase.

progression including intrahepatic and extrahepatic progression and local recurrence in the observed time period (p=0.001) (table 1). Specifically, FN-HCC demonstrated lower rate of disease progression when compared with CV-HCC (p=0.0003) and SC-HCC (p=0.0472), but there was no difference between SC-HCC and CV-HCC (p=0.0997). Similarly, there was significant difference in time to progression among these three groups (p=0.0059), and specifically, FN-HCC took a longer time to progress when compared with CV-HCC (p=0.0017) and SC-HCC (p=0.0148) (figure 3B), while there was no significant difference between SC-HCC and CV-HCC (p=0.5899).

DISCUSSION

It is well known that HCC has a wide spectrum of histological appearances and growth patterns. Recognition of these pathological differences is important as these often have significant clinicopathological features.[4] For example, macrotrabecular HCC has been recognised as an aggressive subtype.[7 12] In this study, we identified a group of HCC—FN-HCC which is histologically and radiologically distinct from SC-HCC and CV-HCC.

Table 2 Radiographic feature analysis results

	FN-HCC, n/N (%)	SC-HCC, n/N (%)	P value
Enhancement			
Non-rim APHE	14/14 (100)	11/14 (78.57)	0.2222
Heterogeneous	7/14 (50)	5/14 (35.71)	
Non-peripheral washout	14/15 (93.33)	3/14 (21.43)	0.0001
Rim APHE	3/13 (23.08)	9/14 (64.29)	0.0313
Peripheral washout	0/15 (0)	1/14 (7.14)	0.1032
Enhancing capsule	15/17 (88.24)	9/14 (64.29)	0.1975
Shape			
Lobular contour	12/16 (75)	5/14 (35.71)	0.0041
Nodules embedded in septations (popcorn)	12/16 (75)	0/14 (0)	<0.0001
Other			
T2 hyperintense	14/19 (73.68)	10/14 (71.43)	>0.9999
Blood products in mass	4/18 (22.22)	0/14 (0)	0.1129
Satellite lesions	2/14 (14.29)	7/14 (50)	0.0043

APHE, arterial phase enhancement; FN-HCC, fibronodular hepatocellular carcinoma; SC-HCC, scirrhous hepatocellular carcinoma.

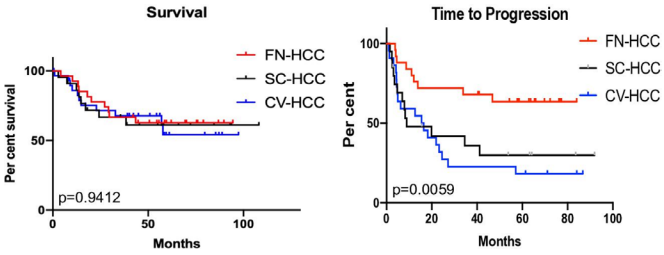

Figure 3 Overall survival and time to progression. CV-HCC, conventional hepatocellular carcinoma; FN-HCC, fibronodular hepatocellular carcinoma; SC-HCC, scirrhous hepatocellular carcinoma.

Different from carcinomas from other organs, HCCs usually lack fibrotic stroma except SC-HCCs. Due to the similarity of SC-HCC and FN-HCC on histopathology with dense fibrosis and the possible misclassification of FN-HCC as SC-HCC, we compared the clinicopathological and radiological features of FN-HCC, SC-HCC and CV-HCC. Most studies have shown no differences in demographics, presence of chronic liver disease, presence of cirrhosis, serum AFP levels or prognosis in SC-HCC compared with CV-HCC,[4 9 13–15] although a few studies show a poorer prognosis in SC-HCC.[16] Similar to prior studies, there were no significant differences in the clinical outcome, demographics, background liver disease, fibrosis, serum AFP levels, tumour size, multifocality and BCLC stages between SC-HCC and CV-HCC. In the current small cohort study, FN-HCCs were more likely to arise in the absence of advanced fibrosis and resection was the most common treatment option for the initial management of these lesions when compared with SC-HCCs and CV-HCCs. FN-HCCs showed fewer cases in advanced BCLC stage (stage C), lower rates of disease progression and longer time to progression in the observed time period compared with SC-HCCs and CV-HCCs. Of note, the limitation of this study is the small sample size of the cohort. More comprehensive studies with more cases are needed to further classify this new histological variant HCC.

Imaging studies are an important modality in the diagnosis of HCC. This study confirmed some of the imaging features identified in previous studies that make the SC-HCC appear atypical on MRI. As result of these atypical features, SC-HCC may be frequently misdiagnosed as cholangiocarcinoma which would impact further treatment choices.[9 17 18] Compared with SC-HCCs, FN-HCCs on MRI demonstrated a distinct characteristic 'popcorn' appearance on arterial and delayed phase of imaging. Additional features of FN-HCC that were associated with this variant included high rate of non-peripheral washout, enhancing capsule, lobular contour and presence of blood products. In contrast, SC-HCCs more commonly demonstrated rim arterial peripheral hepatic enhancement on the dynamic MRI. The findings indicate that MRI, especially the persistent enhancement on the delayed phase and nodules embedded in septations ('popcorn' appearance), can aid in differentiating FN-HCC from SC-HCC.

The incidence and cancer-related death of HCC continue to rise.[2 19] The main risk factors for HCC include chronic liver disease and cirrhosis due to hepatitis B and/or hepatitis C infection, alcoholic liver disease, non-alcoholic fatty liver disease (NAFLD), aflatoxin and others, with hepatitis C infection accounting for most of the cases in western countries. Although more and more HCCs arise in a background of non-cirrhotic liver with hepatitis B, NAFLD or other unknown aetiology, the majority of HCCs develop in a cirrhotic liver or liver with advanced fibrosis.[3 20]

As seen in our present study, most of the HCCs in FN-HCC, SC-HCC and CV-HCC groups developed in a background of advanced fibrosis, and hepatitis C infection was the major aetiology. Of note, HCCs in the FN-HCC group were more likely seen in a liver without advanced fibrosis or cirrhosis, and hepatitis B infection is more commonly seen in FN-HCCs. The treatment of HCC includes curative and non-curative interventions, and the former includes surgical resection, transplantation and ablation.[21] BCLC stages, liver function and adequate hepatic reserve after resection are important factors to be considered if undergoing HCC surgical resection.[21 22] Fibrolamellar HCC, a tumour that arises in a non-cirrhotic liver, is often treated with surgical resection with good overall survival after resection due to the absence of cirrhosis and adequate hepatic reserve after resection.[6 15] In our current study, although BCLC stages were not significantly different, the percentage of stage C BCLC was relatively lower in the FN-HCC compared with SC-HCC and CV-HCC groups. Furthermore, the percentage of cases with advanced fibrosis (stages 3–4) in the background liver was significantly lower in the FN-HCCs compared with SC-HCCs and CV-HCCs. Radiographic imaging plays an important role in HCC diagnosis. In this small FN-HCC cohort, FN-HCCs were more likely to meet the LI-RADS criteria for diagnosing HCCs (LI-RADS 5, 92.3%), thus a definitive imaging diagnosis could be rendered. These findings of definitive radiographic diagnosis, lower BCLC stage and less background liver fibrosis/cirrhosis with good hepatic reserve might have led to resection more frequently in FN-HCCs. These factors may also have led to overall better outcome in FN-HCC with lower rates of disease progression (intrahepatic or extrahepatic progression and local recurrence) and longer time to progression. We did not see any significant difference in overall survival between the three groups. This is likely due to the fact that the sample size was small, follow-up was short and over 50% of the patients were still alive at the time of analysis.

In summary, we described a variant of HCC with fibronodular appearance showing distinct pathological, radiological and clinical features. In this limited cohort, FN-HCCs were more likely to be associated with the absence of advanced fibrosis/cirrhosis, earlier BCLC stage, lower rates of disease progression and longer time to progression in the observed time period compared with SC-HCCs and CV-HCCs. Furthermore, the study demonstrated specific MRI features that clearly differentiate FN-HCC from SC-HCC. Further studies with more cases and a longer follow-up period are needed to validate our findings. In addition, elucidation of the molecular phenotype could further support its designation as a distinct HCC variant and not a mere unique growth pattern.

Take home message

- Fibronodular hepatocellular carcinoma (FN-HCC) is a potential new variant of hepatocellular carcinoma (HCC) with a distinct histological appearance of multiple tumour nodules mimicking 'cirrhosis' in a single HCC lesion.
- FN-HCCs show discrete MRI features that significantly deviated from those observed in the scirrhous HCCs.
- FN-HCCs are more likely to be associated with absence of advanced fibrosis/cirrhosis, earlier BCLC stage, lower rate of disease progression and longer time to progression.

Correction notice This article has been corrected since it was published Online First. Abstract was missing and author middle name has been added.

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