



Imaging findings of hepatic epithelioid hemangioendothelioma and fibrolamellar hepatocellular carcinoma: a critical appraisal of current literature about imaging features of two rare liver cancers

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Abstract: Hepatic epithelioid hemangioendothelioma (HEHE) and fibrolamellar hepatocellular carcinoma (HCC) are rare malignant neoplasms of the liver. Contrarily to HCC, no distinctive imaging criteria based on contrast enhancement pattern are known for these neoplasms, thus they are frequently misdiagnosed as other liver tumors. Due to their infrequency, very few data principally based on reports of few patients are currently available in literature. This results in several issues pending on the application of imaging in the diagnosis of these cancers, which absolutely needs pathological examination. Nevertheless, imaging techniques are fundamental in the diagnostic work-up and in the management of affected patient. This review summarizes the current evidence about imaging systems in the diagnosis of HEHE and fibrolamellar carcinoma (FLC), discussing the significance of the principal iconographic hallmarks and the prospective potentials of the most employed techniques.

Keywords: Hepatic epithelioid hemangioendothelioma (HEHE); fibrolamellar hepatocellular carcinoma (fibrolamellar HCC); liver cancer; imaging

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Introduction

Hepatic epithelioid hemangioendothelioma (HEHE) and fibrolamellar carcinoma (FLC) are two rare primary neoplasm of the liver, usually involving young subjects without underlying chronic liver disease, contrarily to hepatocellular carcinoma (HCC) (1). The paucity of consistent data available in current literature related to the uncommonness of the cases, make the final diagnosis of these cancers difficult with imaging techniques alone. Accordingly, main features of HEHE and FLC may not be familiar to physicians and it is not possible to identify a target population to screen. However, both diseases show harsh prognostic impact when identified in advanced stage. Thus, the current role of imaging in the diagnosis

of these cancers is based on the early identification of their malignant nature, prompting biopsy for pathological definitive examination.

The aim of this review is to separately report and discuss the current state of the art of imaging techniques in the diagnosis of HEHE and FLC, in order to increase awareness about these rare tumors and improve the clinical management of affected patients.

HEHE

HEHE is a rare vascular neoplasm characterized by low to intermediate malignant potential and primary liver involvement (2). Endothelial origin of the tumor cells

together with the epithelial histological appearance account for its name, coined by Weiss and Enzinger in 1982 (1,3). Since then, very few cases are available in literature, testifying the rarity of this disease and inducing a high risk of misdiagnosis in clinical practice.

Peak incidence occurs in young females (almost 60% of the cases) with a median age between 30 and 50 years for both genders. Exposure to vinyl chloride, trauma and subjects using oral contraceptives have been indicated as risk factors for HEHE, albeit with uncertain relationship (1,4). Despite of its usual low malignant potential, the absence of definite risk factors does not allow to outline a solid and cost-effective screening program in target populations. For these reasons, about 30% of patients present diffuse or metastatic disease at the time of diagnosis (5,6).

Extrahepatic spread is common to the lung, peritoneum, lymph nodes, spleen and bone marrow. As a consequence, prognosis of HEHE may extensively vary depending on the promptness to make an accurate early diagnosis, which strongly affects the indication to curative treatments (7,8). The variability of the outcome reflects in part the lack of validated consensus protocols on imaging diagnostic features and treatments. Therefore, HEHE is often misdiagnosed as other liver tumors, as cholangiocarcinoma, atypical hemangioma, hepatocellular adenoma and carcinoma, lymphoma or metastases (9,10). The heterogeneity of this list indicates the variable appearance that HEHE might display, especially with contrast-enhanced techniques, due to the irregular distribution of neoplastic vessels (1).

Histologically, HEHE is composed by epithelioid cells of vascular origin and dendritic cells in variable proportions, affecting the imaging presentation of the tumor (1). Larger neoplasms classically contain intracytoplasmic lumina with erythrocytes (11). The obliteration of sinusoids and the growth along terminal hepatic venules might account for the heterogeneous enhancement of HEHE with contrast agents, whereas the loose mucinous stroma of the core is related to the frequent finding of central unenhanced areas (1,12).

General imaging features

HEHE is generally described with imaging as solitary, multiple or coalescent nodules, possibly following a temporal progression. The tendency to converge might reflect the potential of cancer cells to grow along the sinusoids, particularly in the most aggressive forms. The most frequent scenario reported at the moment of the diagnosis is multinodular, varying from 60% to 90%,

whereas the solitary nodules size may range from 1 up to more than 5 cm (9,10,13). It has been reported that lesions classically involve the whole liver or the right lobe alone, often in the subcapsular region; less frequently they develop in the left lobe (10,14). Especially when multinodular, the typical finding of retraction of liver capsule over the tumor nodules (overall occurring in about 50% of cases) might be useful to distinguish HEHE from similar lesions as cholangiocarcinoma (15-18).

Abdominal ultrasound (US) is the imaging technique which most frequently allows to firstly detect focal liver lesions. Considering HEHE, patients might be asymptomatic at the moment of the diagnosis and US is demanded as first-line technique to clarify alterations of liver enzymes at blood test (9,10). Otherwise, US is performed in order to investigate the occurrence of abdominal pain, portal hypertension-related symptoms, liver failure or Budd-Chiari syndrome. Also, nonspecific signs as mild anemia and weight loss are reported (9,10). Usually US findings in patients with final diagnosis of HEHE lead to confirm the hypothesis of malignancy with computed tomography (CT) or magnetic resonance imaging (MRI) techniques.

Contrarily to HCC, no diagnostic imaging criteria are known for HEHE, possibly due to the rarity of the disease which impairs the size of the sample to study and the involvement of non-cirrhotic liver which extremely increases pre-test probability to face different kind of malignant nodules, especially metastasis. However, imaging techniques play a fundamental role in the diagnostic work-up of HEHE as they can endorse the suspicion of malignancy and identify patients to submit to liver biopsy. If the presence of multiple and coalescent nodules easily leads to perform invasive procedures due to the high suspicion of secondary lesions (regardless of the contrast-enhanced aspect), HEHE might be detected as a single lesion in some patients (10,15). The importance of the awareness about the imaging features of HEHE is particularly relevant in these cases, as the delay in performing liver biopsy might deprive patients from curative therapies, as surgical resection or liver transplantation (19). Moreover, it seems that the typical imaging features of HEHE are less frequent in single nodule type, further complicating the diagnosis (15).

Main imaging features of HEHE are discussed in this section separately for each technique, considering the currently available data in literature. A summary of the radiological features of HEHE is provided in *Table 1*.

Table 1 Key imaging features of HEHE for each imaging technique.

Technique	Features
General imaging aspects	Multiple lesions Prevalent involvement of peripheral region of the liver Prevalent involvement of the right lobe Subcapsular retraction Coalescence of the lesions
Ultrasound	Lesions frequently hypoechoic Possibility of hyperechoic calcific spots
CEUS	Variable pattern in the arterial phase (rim-enhancement or diffuse irregular hyperenhancement) Wash-out of contrast agent in the late phase described in almost all cases
CT	Hypointense nodules Sometimes hyperintense border is evident
Contrast-enhanced CT	Faint enhancement in the arterial phase with or without progression during the late phase Lollipop sign
MRI	Two-layered halo-sign T1WI: usually hypointense core T2WI: usually hyperintense core DWI: restricted diffusion of the periphery
MRI with gadoxetic acid	Enhancement pattern similar to CT
¹⁸ F-FDG PET-CT	Variable uptake of FDG (usually higher than the liver), also in different lesions of the same patient Utility of delayed imaging is still debated

HEHE, hepatic epithelioid hemangioendothelioma; CEUS, contrast-enhanced ultrasound; CT, computed tomography; MRI, magnetic resonance imaging; T1WI, T1-weighted imaging; T2WI, T2-weighted imaging; DWI, diffusion weighted imaging; ¹⁸F-FDG PET, ¹⁸F-fludeoxyglucose positron emission tomography.

US

US features of HEHE must be absolutely known by sonographers, considering the relevance of this technique as first line method to screen subjects who need further imaging investigations or liver biopsy. Moreover, contrast-enhanced US (CEUS) might be an useful tool to improve the diagnostic performance in detecting HEHE, especially considering its potential to reliably depict the real vascularization due to the exclusive intravascular distribution of the contrast agent (9,10). However, no solid criteria are definitely known to identify HEHE with CEUS, since very few data are currently available. Further, the validation of this technique is still ongoing in different countries, differently from Europe where its clinical employment is largely endorsed.

HEHE appears very frequently as a hypoechoic lesion at B-mode US, usually with regular margin. Echotexture can be heterogeneous texture, especially with calcification and when multifocal. The possible presence of capsular retraction might back up the suspicion of malignity. Doppler US might detect the presence of intralesional vessels (9). In addition, hypertrophy of residual liver, splenomegaly and Doppler signs of portal hypertension as deceleration of portal vein flow might be revealed by this technique, indicating liver decompensation and intrahepatic congestion due to the presence of multinodular disease (20). Doppler study of splenic and portal district is mandatory in patient with diffuse liver disease as a basic parameter for the clinical management and the indication to surgical treatments.

CEUS may be very helpful in uninodular cases (of

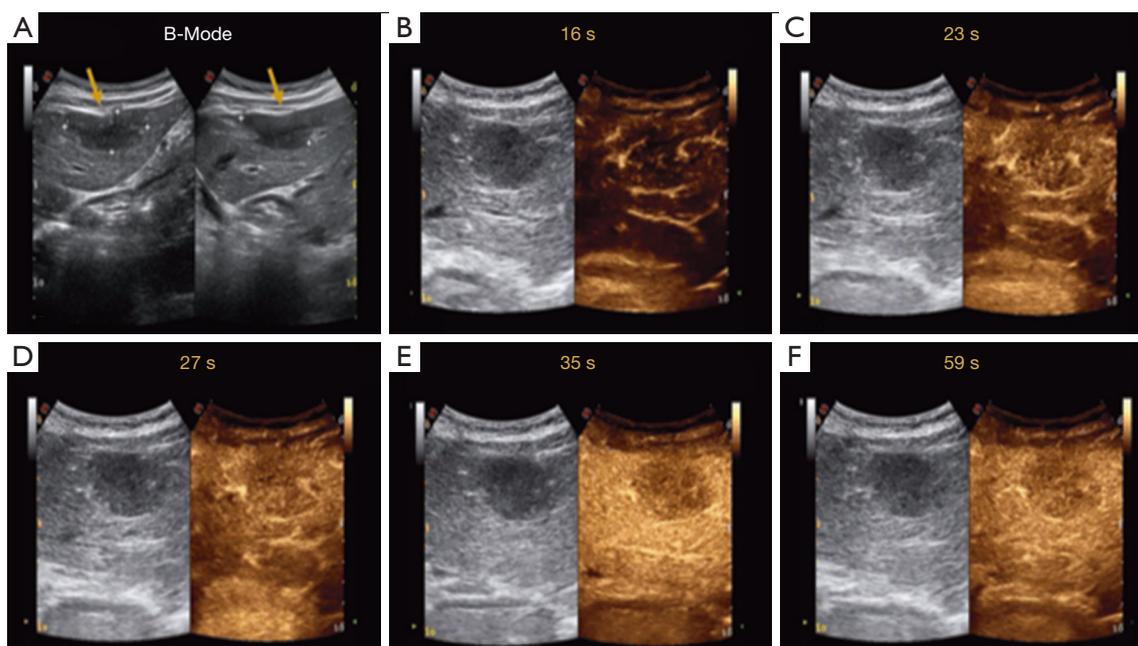


Figure 1 B-mode US and CEUS appearance of a subcapsular hepatic lesion proven to be HEHE with pathological examination. (A) B-mode US showing a hypoechoic lesion of 42 mm × 39 mm × 21 mm (white calipers) at the III segment of the liver. Yellow arrows indicate the presence of capsular retraction, a typical finding of peripheral lesions. (B,C,D,E,F) CEUS appearance after injection of 2.4 mL of SonoVue®. Time from contrast injection is shown in second(s) on the top of the image. The left part of each picture from (B) to (F) represents the B-mode background reference, while on the right side the corresponding contrast-enhanced image is shown. (B) During the very early arterial phase feeding arteries are visible on both sides of the lesion. (C) Inhomogeneous arterial filling during the arterial phase. (D) Globally, the lesion shows moderate hypoenhancement at the end of the arterial phase. (E,F) Marked hypoenhancement with early and marked wash-out of the contrast agent in the portal phase, due to the lack of portal vessel in the lesion. This feature is highly suggestive for the malignant nature of the lesion and should prompt to further examination. US, ultrasound; CEUS, contrast-enhanced US; HEHE, hepatic epithelioid hemangioendothelioma.

more than 1 cm of diameter), considering the importance of the contrast-enhanced appearance in the late phase in determining the indication to biopsy. Nevertheless, accessible data about CEUS appearance of HEHE are very limited (9,21,22). In a recent report of 25 patients with biopsy-proven HEHE, nodules show predominantly a rim-like (18/25) or heterogeneous hyperenhancement (7/25) in the arterial phase with early wash-out in the portal and late phase. The latter was present in all the patients with HEHE included in the study (9). This feature is a precious hint suggesting the indication for further imaging investigations or even directly a liver biopsy, considering its strong relationship to malignancy regardless of the nature of the lesion. The wash-out of contrast agent in the late phase is related to the angiogenetic shift of HEHE, characterized by the lack of portal vessel inside the nodules (23,24). The variation in vessel distribution is typical also of other kind

of cancers, but it does not happen in benign lesions (25). The typical appearance of HEHE at CEUS is resumed in *Figure 1*. Finally, CEUS might help to assist US-guided biopsy, due to its ability to detect more lesions than B-mode exam alone (9).

CT

Contrast-enhanced CT scan is the most diffused technique to stage the disease and establish the response to local and systemic therapies; otherwise it might be employed as a second technique after US exam or eventually alone. However, its diagnostic potential is restricted to the indication to biopsy since no specific diagnostic pattern is known. Nodules are classically hypointense in comparison with the liver parenchyma. Nodular or coarse calcifications with irregular spots can be seen inside the lesions in

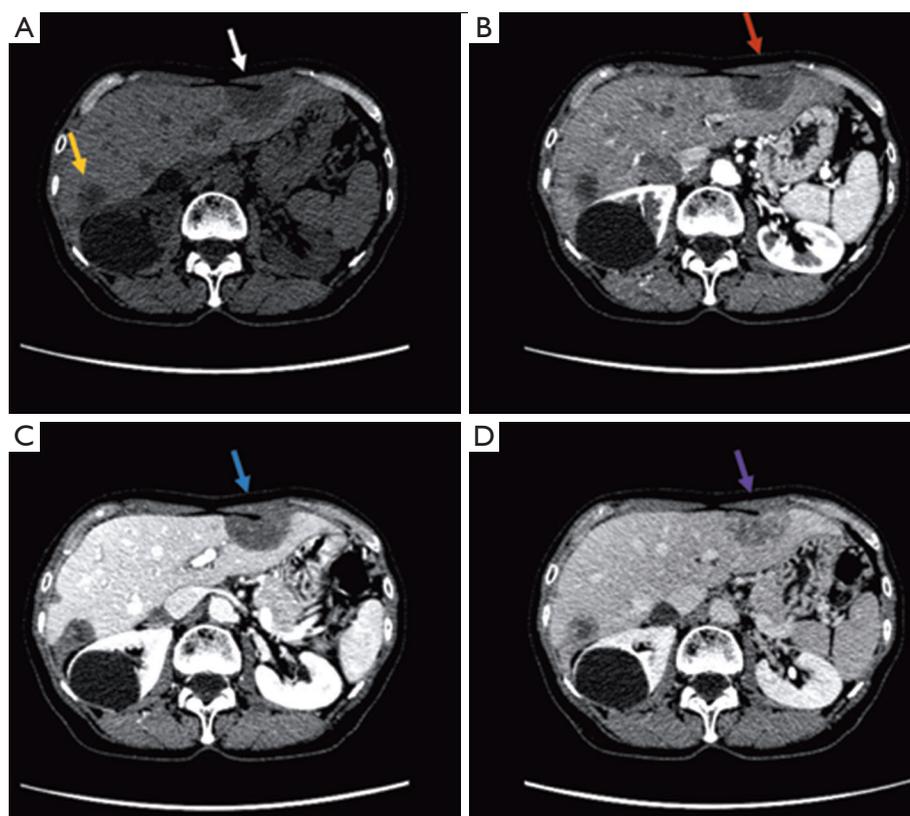


Figure 2 Contrast-enhanced CT scan of a histologically proven HEHE. (A) White arrow indicates a subcapsular hypoattenuating lesion with the typical finding of capsular retraction, visible on the anterior margin of the III segment of the liver (yellow arrow). Another lesion with similar iconographic features is visible at the right lobe. (B) Arterial phase of contrast-enhanced CT showing hypoenhancement of the lesion in comparison with the surrounding parenchyma (red arrow). (C) Persistence of hypoenhancement in the portal phase (blue arrow). (D) During the late phase the lesion is still hypoenhanced in comparison with liver parenchyma, despite an irregular contrast uptake can be appreciated inside the nodule (purple arrow). Overall, this behavior in contrast uptake cannot be related to any known pattern useful to suggest a specific nature of the lesion. CT, computed tomography; HEHE, hepatic epithelioid hemangioendothelioma.

15–25% of the cases (26–28). The thicker cellularity at the periphery of the nodules might determine a mild hyperintensity in this area. Alomari reported in 5 patients with HEHE a key feature called the “lollipop sign”, which consists in a contrast enhanced vessel as the stick ending in a hypointense area representing the candy (29). This hallmark seems to be highly suggestive for HEHE, albeit it might be missing in a percentage of cases variable among the studies (26–29).

Contrast pattern observed with CT agents is classically described as faintly enhancing in the arterial phase, with or without progression of the uptake in the portal and late phase, sometimes with a ring pattern. Otherwise, some lesions can show no uptake of contrast during the

whole examination. A Chinese report of 2015 including 11 patients with 312 nodules tries to define 3 different pattern of contrast enhancement: mild homogeneous stable enhancement without progression up to the portal phase (71.5%), ring-like enhancement and heterogeneous arterial enhancement with progression to the late phase. Curiously, a transition from the first to the third pattern has been related to the dimension of the nodule (6).

The mild and progressive uptake of contrast agent and the absence of washout might mislead the radiologist in determining the malignancy of the lesion and the indication to biopsy, considering its frequency in small nodules, especially when single. *Figure 2* displays a case of multifocal HEHE with typical radiological findings at CT scan.

MRI

MRI has been claimed to be superior to CT in detecting small size lesions, especially when subcapsular (14,16,30,31).

Nodules generally appear hypointense in comparison with surrounding liver at T1-weighted imaging (T1WI). A typical halo appearance has been reported in several studies, consisting in a three-layered pattern with alternating hypo- and hyper-intense rims. The core of this structure can appear both hypo- or hyper-intense, depending on the singular case and evidently on T1 or T2-weighted imaging (T2WI). Hyperintense rim with hypointense halo is typical in T1WI (32). On the contrary, the signal is heterogeneous and usually higher than the liver with T2WI. The two layered halo sign appears also in T2WI with hyperintense center with percentage up to almost 80% reported in literature (16). Diffusion weighted imaging (DWI) can reveal the two-layered target sign with high intensity core and external rim in about 60% of cases (16,28). On low b-value DWI signal is similar to T2WI, which is reversed as b-value increase (28). In this condition peripheral areas markedly increase their signal, indicating a restricted diffusion in contrast to the core which is characterized by a low signal. This behavior nicely depicts the higher cellularity of the outer areas and the presence of myxoid and fibrous stroma. Comprehensively, the halo sign has been reported in a range variable from 20% to 80% of nodules. Likewise, lamellar architecture can be seen in different percentages (9,21,30,33-35).

After gadolinium-based contrast agents injection the enhancement seen is similar to CT, with a progressive and mild hyperenhancement often persistent up to the late phase (9,21,33-35). Usually the enhancement starts from the center whereas in a minority of cases it involves firstly the periphery (16,28). This feature can mimic the behavior of benign hemangioma during the arterial phase. However, the combination of the halo sign with progressive and persistent enhancement after gadolinium injection might potentially be helpful to differentiate HEHE from other similar cancers as metastasis and hepatic angiosarcoma. As a further typical HEHE hallmark, Bruegel reported the apparent diffusion coefficients (ADCs) showing particularly high values (mean $1.86 \times 10^{-3} \text{ mm}^2/\text{s}$) on 30 nodules of HEHE. This variable might be useful to differential diagnosis with other malignancies, rarely showing such high values (28). Notably the values are lower at the periphery, according to the higher cellularity in this area. This might

explain also the presence of halo sign and the pattern of contrast enhancement.

Positron emission tomography (PET)

18-F-fludeoxyglucose PET-CT (18FDG PET-CT) is generally employed in the assessment of response to systemic and radiation therapies or staging of HEHE in unclear cases (36). The employment of ^{18}F FDG PET-CT in liver tumors bases its rationale on the relatively high activity of glucose-6-phosphatase in hepatocytes, provoking a rapid clearance of FDG from liver tissue in comparison to several malignant liver lesions (37).

Conversely, the high uptake of FDG by healthy hepatocytes may impair the possibility to identify neoplastic lesions in the early phase due to their unpredictable timing of uptake and dismissal of FDG. The possible irregularity of FDG pattern, provided by a variable degree of activity of glucose-6-phosphatase of malignant lesions, has led to suggest dual-time-point analysis in order to improve diagnostic performance of 18FDG PET-CT with delayed imaging acquisitions (37-42).

Nevertheless, different kinds of pattern of FDG uptake are described in literature for HEHE, predominantly more intense than the surrounding liver. Lesions with different behavior are reported, even with low standardized uptake values (SUVs), and nodules might show themselves up at different timing after FDG injection. Sometimes a hypermetabolic rim can be observed at the periphery of the lesion of high size, reflecting the higher cellularity of this area. A report of 6 patients concludes that the uptake might vary on the cellularity rather than the size of the nodules (6,43).

This observation might point out of the variability of FDG uptake shown by HEHE and further observations are needed to precisely clarify the most common kinetic of FDG in HEHE nodules.

Conclusions

Albeit the paucity of available knowledge that currently prevents the possibility to perform a certain diagnosis with imaging techniques, some typical hallmarks of HEHE can be recognized in literature. Capsular retraction, lollipop sign, coalescence of the nodules, the prevalence of right liver involvement and subcapsular localization are among

the most reported signs of HEHE and their presence in an adequate setting should always arise suspicion of this neoplasm. Contrast-enhanced techniques might enforce the diagnostic hypothesis, even if attention must be paid to the cases where the pattern can mimic benignant lesion. MRI seems to have promising performance in identifying different key features of HEHE as the halo appearance, especially considering nodules of inferior size. Further, the possibility to perform multiparametric studies as DWI and ADCs analysis increases the potential of this technique in uncovering further features typical of HEHE.

CEUS might be a relatively safe and cost-effective tool in the diagnostic work-up of HEHE, especially in accomplished centers with experienced operators. The hypoenhancement in the late phase might play a relevant role in early directing patients to liver biopsy since its strong relation with malignity. Actually, CEUS is the unique technique displaying wash-out of contrast agent in the late phase in biopsy-proven HEHE.

¹⁸F-FDG PET-CT might add suitable elements helpful to formulate diagnosis of HEHE, even if a defined pattern of FDG uptake and SUV still need to be identified.

Nevertheless, no defined diagnostic criteria of HEHE with imaging techniques are validated to date, reflecting both the difficulty to enroll a sufficient sample to study and the natural heterogeneity of the histologic architecture of this tumor. Thus, more evidences are absolutely needed about HEHE, possibly with comparison of different imaging techniques in a multicentric background in order to get a relevant sample to study.

FLC

FLC is a rare form of primary HCC, firstly described by Edmondson in 1956 (44), accounting from 1% to 5% of all liver malignancies (45,46). Recently, a translocation generating a fusion transcript of the *DNAJ7B1* and *PRKACA* genes was discovered as molecular peculiarity of this cancer (47,48).

FLC seems to affect equally male and female, while conventional HCC usually prefers male individuals. Patients affected are generally young: about 65–85% of cases involve subjects younger than 40 years old. Contrariwise, only around 2–4% of traditional HCC occurs in this population. The mean age at diagnosis of FLC is around 25 years, compared with 65 years of HCC (49). Furthermore, a second peak of incidence is reported between 60 and 69 years (50).

Unlike conventional HCC, FLC usually occurs in patients

without underlying liver disease. Since there are no known risk factors for FLC, surveillance programs for this neoplasm are not feasible. Thus, the resulting delayed diagnosis is clearly associated with a poorer outcome. Indeed, FLC is usually remarkably large at diagnosis, with an average diameter of 13 cm (from 7 to 20 cm) (51). Besides, around 70% of cases of FLC is associated with metastatic lymph nodes at the diagnosis (52). Peritoneal spread is the most common extra-nodal pattern of advanced disease, whereas lung and adrenal metastases rarely occur. The clinical presentation of FLC is generally nonspecific and, when symptoms are present, they include nausea, abdominal discomfort or fullness, weight loss, and/or night sweats, commonly related to the mass-effect caused by the lesion. Alfa-fetoprotein levels typically within the range can help for the differential diagnosis with common HCC: only 7–11% of FLC is associated with increased alfa-fetoprotein (52–55).

The milestone of the treatment is classically surgical resection with adequate lymphadenectomy (54). Liver transplantation can also be considered if partial resection is not feasible. Systemic chemotherapy has been studied for inoperable patients, resulted in a worse response compared with HCC. Hepatic artery embolization could be another therapeutic option for non-responder individuals (52).

Prognosis of FLC seems to be better than conventional HCC. It accounts an overall 5-year survival of about 30%, in contrast with 6–7% reported for HCC (56). Nevertheless, disease recurrence is unfortunately high even after curative-intent surgery (reported to be from 33% to 100%) and it mostly appears in the first 4 years after surgery. The better overall survival of FLC in spite of its high recurrence rate might be explained considering that prognosis of HCC is often worsened by the underlying liver disease. Hence, prolonged follow-up is necessary because recurrence can even occur years after diagnosis (57).

The suspicion of FLC is commonly based on the association of clinical scenario and imaging findings, which play a large role in the differentiation among primary malignant liver tumors. Nevertheless, the pathological examination on surgical or biopsy specimens represents the gold standard to confirm the diagnosis. The pathological diagnosis of FLC can be simplified into the following triad: large neoplastic cells with strongly eosinophilic cytoplasm; the presence of macronucleoli; abundant fibrous stroma organized in thin parallel lamellae around tumour cells (58).

The differentiation of FLC from both conventional HCC and benign FNH might be troublesome for the radiologist. At imaging techniques FLC usually appears as

a solitary, large, well-defined, lobulated mass sometimes with a fibrotic central scar. This suggestive hallmark is detectable in a variable range of cases depending on the considered imaging technique. Calcification is often present. On contrast-enhanced imaging, conventional HCC presents hyperenhancement in the arterial phase and shows washout in the late phases. Differently, the enhancement of FLC tends to be heterogeneous in the arterial phase, whereas wash-out might be not present (59). Nevertheless, when conventional HCC involves non-cirrhotic liver, the differentiation between FLC and HCC on the basis of imaging characteristics alone may be challenging (60). While US mostly represents the initial diagnostic approach for evaluating the liver, CT-scan is optimal for the preoperative study of nodal and thoracic metastases, and MRI plays a central role in the characterisation of FLC as a focal liver mass (61). Main characteristics helpful in differential diagnosis of FLC from other common neoplasms are separately discussed below and summarized in *Table 2* for each imaging technique.

US

FLC is often firstly detected with US imaging.

FLC shows a variable echo-pattern at B-mode examination. Intrahepatic or extrahepatic ductal dilatation just as portal vein thrombosis can be present (62). Hyperechoic or isoechoic elements are often visible within the lesion. B-mode US seems to be only partially successful in detecting the central fibrous scar, with a sensitivity of 33–60% when compared with pathological examination (25,63,64). The central scar, when present, may be visualized as a central area of hyperechogenicity. Furthermore, US is less accurate in demonstrating tumor necrosis, which appears as cystic areas in less than 5% of the cases. Although regional lymphadenopathy can be visible, US is less appropriate than CT and MR for the tumor staging. However, US seems to be useful to reveal calcification, usually localized within the scar (63,65,66). Besides, Doppler imaging commonly shows increased vascularization within the tumor (62).

CEUS has not been exhaustively evaluated for the diagnosis of FLC. The reported enhancing features of this malignancy mostly consist in heterogeneous enhancement in the arterial phase and relative washout respect to the adjacent liver parenchyma in the portal venous phase (67,68).

Despite its currently rare employ and the paucity of studies about the use of this technique for the diagnosis of FLC, CEUS is notoriously endowed with relative safety,

favorable cost-benefit ratio and might have the potential to provide helpful diagnostic hints.

CT

Iodinate contrast-enhanced multiphasic CT is the most commonly used tool for detection and characterization of liver lesions.

On CT scans FLC generally appears as a heterogeneously enhancing mass in a context of a non-cirrhotic liver. Occasionally, FLC may present as multiple intrahepatic lesions with cystic aspect (69). In the unenhanced scans, it predominantly appears hypoattenuating compared with the normal liver parenchyma. Central stellate scar is present in 65–70% of patients with FLC at CT scan (64). However, this sign is not pathognomonic of FLC and it has been reported in many benign and malignant liver lesions, such as FNH (in which was firstly described), large hemangioma, and rarely in conventional non-fibrolamellar HCC, cholangiocarcinoma, and some hepatic metastases (64). However, the finding of a wide scar (larger than 2 cm) with the presence of radiating fibrotic bands or septa are more distinctive for FLC and might help to differentiate it from other neoplasms (59). Calcifications within the lesion are present in 68% of cases and can be useful to distinguish this malignancy from conventional HCC (52) and from FNH, where are rarely seen (59). Necrotic areas may be visible, but intralesional bleeding is infrequent (51). Portal vein thrombosis is associated with FLC in only 5–10% of cases (59). Furthermore, biliary obstruction is also rare. FLC presents nodal metastasis at the diagnosis in up to 50–60% of imaging studies, predominantly localized at the hepatic hilum and hepatoduodenal ligament. Distant metastasis has been reported in about in 20–30% of cases, mostly in peritoneum, lungs and adrenal glands (57).

After contrast injection, more than 90% of FLC show heterogeneous hyperenhancement during the arterial phase images (59). This heterogeneity could be caused by the characteristic hypovascular fibrotic bands embracing hypervascular neoplastic cells. This behaviour is often present also in FNH, complicating the differential diagnosis between these two focal liver lesions.

The features of FLC in the portal venous and delayed phases are variable. On the portal venous phase, approximately 50% of FLC become iso-intense in comparison with liver. However, they may also be hyper- (36%) or hypo-intense (16%), as well as in the delayed phase (51). Central scar might show a variable enhancement, present in 25–65% of

Table 2 Key imaging features of FLC for each imaging technique

Technique	Features
General imaging aspects	Solitary nodule in a context of noncirrhotic liver Large, well-defined, lobulated mass Central scar Calcifications
Ultrasound	Variable echogenicity Limited sensitivity in detecting central scar, usually hyperechoic Demonstrates calcifications, mainly within the scar
CEUS	Not largely employed Heterogeneous enhancement in the arterial phase Relative washout in the portal venous phase
CT	Mainly hypoattenuating Calcifications and central scar (not pathognomonic) Nodal involvement discovered as abnormal lymphadenopathy Distant metastases in peritoneum, lung and adrenal glands Portal vein thrombosis and biliary obstruction extremely rare
Contrast-enhanced CT	Heterogeneous hyperenhancement on arterial phase Variable enhancing in portal venous and delayed phases, mostly hyperenhancing Absent or delayed enhancement of the scar
MRI	T1WI: usually hypointense T2WI: usually hyperintense DWI: usually hyperintense Central scar generally hypointense on T1WI and T2WI No calcifications and no fat components reported
MRI with gadoteric acid	Enhancement pattern similar to CT Heterogeneous hyperenhancement on the arterial phase Isointensity or washout on the portal venous and delayed phase HBPI: usually hypointense, rarely hyperintense
¹⁸ F-FDG PET-CT	Lower FDG uptake in FLC compared with conventional HCC Best sensitivity compared with conventional HCC

FLC, fibrolamellar carcinoma; CEUS, contrast-enhanced ultrasound; CT, computed tomography; MRI, magnetic resonance imaging; T1WI, T1-weighted imaging; T2WI, T2-weighted imaging; DWI, diffusion weighted imaging; ¹⁸F-FDG PET, ¹⁸F-fluorodeoxyglucose positron emission tomography; HCC, hepatocellular carcinoma.

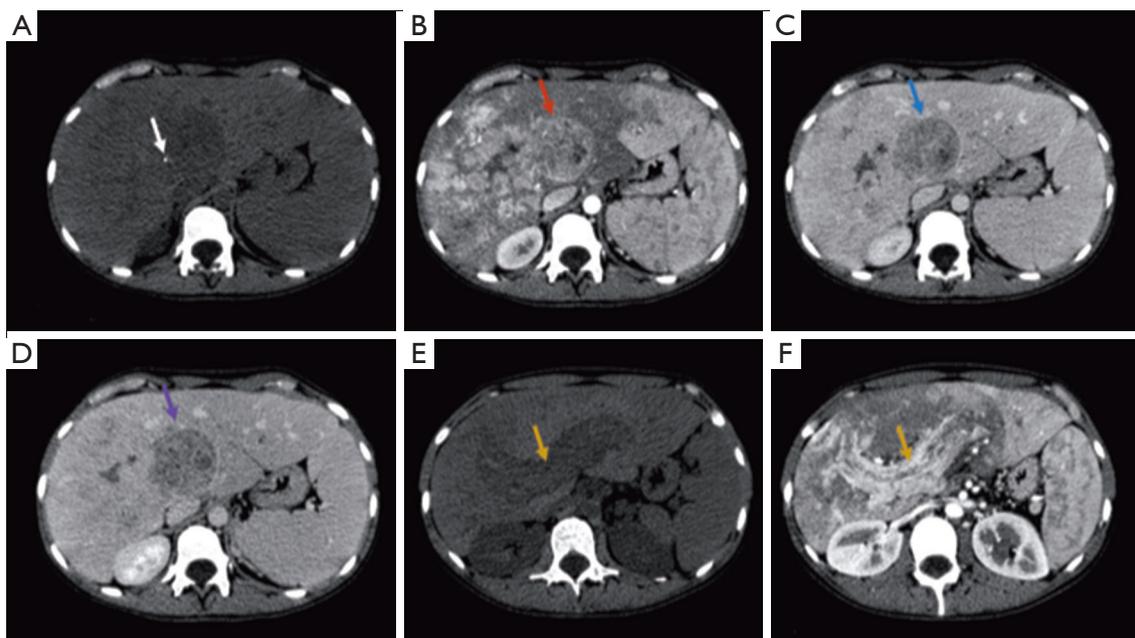


Figure 3 Contrast-enhanced CT scan of a case of FLC in a 20-year-old patient. (A) Non-enhanced scan showing a non-cirrhotic liver with a 55 mm parahilar inhomogeneous mass infiltrating VIII, IV and VII segments. A typical millimetric calcifications is visible adjacent to the lesion (white arrow). (B) During the arterial phase the lesion appears heterogeneously hyperenhancing (red arrow). (C,D) Portal venous (C) and delayed (D) phases displaying a delayed wash-out of the mass (blue and purple arrow). (E,F) CT scan of the patient reveals also wide thrombosis (indicated by yellow arrows) of the main portal branches (E), which shows rich contrast uptake during the arterial phase (F), thus confirming the neoplastic nature. CT, computed tomography; FLC, fibrolamellar carcinoma.

cases (59). Considering the presence of this feature also in FNH, it should not be used for differential diagnosis between these neoplasms. *Figure 3* displays the CT appearance of a histology proven FLC.

MRI

FLC is usually hypointense on T1WI and hyperintense on T2WI at unenhanced MRI (51,61,65). Contrast enhancement relative to the adjacent liver parenchyma is more variable on MRI in comparison with CT. Hallmarks of FLC at gadolinium contrast enhanced MRI mimic the patterns seen on CT, showing predominantly marked heterogeneous hyperenhancement during the arterial phase with isointensity or wash-out on the portal venous and delayed phase. With DWI it usually appears hyperintense (46,59).

MRI can also be more accurate than CT in detecting the central scar, which is generally hypointense on both T1WI and T2WI as a result of its fibrous composition. This feature can be useful to distinguish FLC from FNH, which shows a predominantly hyperintense central scar in

T2WI. Nevertheless, in some cases central scar may appear hyperintense in T2WI, similar to FNH (70).

Like HCC, FLC appears hypointense in the majority of cases if hepatobiliary phase (HBP) specific contrast material is used (i.e., gadoxetate disodium and gadobenate dimeglumine). Conversely, FNH typically shows hyperenhancement in HBP. Hence, this feature can help to differentiate between FLC and FNH (46).

The presence of intratumoral fat has not been reported in FLC, whereas it may be seen in 10–40% of conventional HCC (71). Calcifications within the lesion are not easy to detect with MRI (65).

PET

The role of nuclear medicine imaging in the diagnostic process of FLC has not been fully evaluated yet, in spite of its potential to combine the study of metabolic activity with cross sectional imaging provided by CT.

PET-CT with FDG might be useful to staging and re-staging as well, due to its ability to detect distant

metastases (59,72).

Concerning differential diagnosis, FNH usually displays low metabolic activity, in contrast with FLC. Furthermore, ¹⁸F-DG uptake is generally lower in FLC compared with conventional HCC, generally showing a more indolent behaviour.

The recently developed ¹⁸F-choline and ¹¹C-acetate based PET-CT techniques have a potential application in the diagnosis of FLC, but evidence is needed to validate this hypothesis (72).

Conclusions

FLC is a rare variant of HCC, affecting younger patients without known risk factors and serum markers useful to back up the diagnosis. FLC singular features on imaging techniques, that therefore represent the most important part of its diagnostic workup. FLC commonly appears as a singular, large and well-defined mass. The central fibrous scar is a frequent hallmark, although it is not pathognomonic. Calcifications, in particular within the scar, are more peculiar.

US is generally the primary available imaging technique in the diagnostic workup of FLC, but CEUS has not been largely studied and only few case reports describe the sonographic features of FLC after contrast administration. However, the presence of wash-out, due to its relationship with malignant nature of the lesion plays a basic role in prompting patients to diagnostic liver biopsy. Further, considering the relative high recurrence rate of FLC after surgery (even after 5 years), long lasting surveillance must be maintained and CEUS might candidate to represent a standard of care to detect local recurrence.

FLC resulted to have a similar behaviour at CT and MRI after contrast injection, thus these techniques can be considered competitive rather than complementary (although in uncertain cases the clinician might decide to perform both). CT-scan is generally the most employed technique for the preoperative staging of the disease, due to its ability to identify regional and distant metastases. Moreover, CT demonstrates calcifications in FLC better than MRI and it could be useful to differentiate this neoplasm. On the other hand, MRI may be more sensitive than CT in detecting small hepatic lesions and the fibrous central scar.

¹⁸F-DG PET-CT can detect hypermetabolic activity in several cases helping to figure out the malignant nature of the lesions, despite the uptake of radioactive glucose is

inconstant.

In conclusion, FLC can be currently suspected combining features from different imaging techniques with good sensitivity, which however absolutely need to be endorsed by pathological examination to confirm the diagnosis.

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