



# Problematic lesions in cirrhotic liver mimicking hepatocellular carcinoma

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## Abstract

Hepatocellular carcinoma (HCC) is a unique malignancy that can be diagnosed and treated based on non-invasive imaging criteria without histological confirmation in cirrhotic patients, which opens the possibility, although rare, of false-positive diagnosis of the tumor. This brief review illustrates benign and non-HCC malignant lesions arising in cirrhotic liver that could have been erroneously diagnosed as HCC based on imaging criteria: focal nodular hyperplasia-like nodules, serum amyloid A-positive nodules, dysplastic nodules, spontaneously regressing lesions, combined hepatocellular-cholangiocarcinoma, cholangiocarcinoma, sarcomatoid carcinoma, lymphoepithelioma-like carcinoma, hepatoblastoma, and metastatic adenocarcinoma. To determine the potential differences in clinical courses and post-treatment outcome of HCC diagnosed by imaging alone and those histologically, we suggest the terms HCCi and HCCp to distinguish between lesions that are diagnosed as HCC based on imaging alone from those diagnosed based on pathological examination, respectively.

## Key Points

- Benign lesions, such as focal nodular hyperplasia-like nodules, serum amyloid A-positive nodules, dysplastic nodules, and spontaneously regressing lesions, may show imaging findings that mislead to the diagnosis of HCC.
- Non-hepatocellular malignant lesions, such as sarcomatoid carcinoma, lymphoepithelioma-like carcinoma, hepatoblastoma, and metastatic adenocarcinomas, can be erroneously diagnosed as HCC based on imaging findings alone, even in cirrhotic liver.

**Keywords** Diagnosis, differential · Liver cirrhosis · Liver neoplasms · Magnetic resonance imaging · Computed tomography, X-ray

## Abbreviations

APHE	Arterial phase hyperenhancement
cHCC-CCA	Combined hepatocellular-cholangiocarcinoma
FNH-LNs	Focal nodular hyperplasia-like nodules
HCC	Hepatocellular carcinoma
HCCi	HCC diagnosed by imaging criteria alone
HCCp	HCC diagnosed on pathologic examination
LELC	Lymphoepithelioma-like carcinoma

LI-RADS	Liver reporting and data system
MF-iCCA	Mass-forming intrahepatic cholangiocarcinoma
SAA	Serum amyloid A

Hepatocellular carcinoma (HCC) is the only malignancy that can be diagnosed and treated based on non-invasive imaging criteria without histological confirmation before treatment in cirrhotic patients [1, 2]. The non-invasive imaging diagnosis of HCC requires demonstration of typical imaging features associating arterial phase hyperenhancement (APHE) and a “washout” appearance on later phases of dynamic imaging, as well as capsule appearance and threshold growth that add evidence to the diagnosis according to liver reporting and data system (LI-RADS) [3–5].

Although various benign or malignant lesions have been reported to mimic HCC in patients with cirrhosis or chronic liver disease, most of these lesions may be correctly differentiated from HCC if diagnostic imaging criteria are properly applied [6–8]. However, there are still several lesions that

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present imaging features typical of HCC and can be falsely diagnosed as such, if the diagnosis is made based on imaging criteria alone.

Various guidelines for imaging diagnosis proposed by expert bodies differ with regard to applicability and diagnostic criteria with potential differences in sensitivity or specificity [9]. For example, the guidelines of the European Association for the Study of the Liver limits the imaging diagnosis only to cirrhotic liver, of which a diagnosis method (histologically or clinically) is not specified [3]. In contrast, according to the American Association for Study of Liver Disease/Liver Reporting and Data System [10], imaging diagnosis can be applied to patients with cirrhosis or chronic hepatitis B, excluding cirrhosis related to certain vascular diseases [11].

In this review, we present benign and malignant hepatic lesions that have occurred in cirrhotic liver that could have been diagnosed as HCC based on non-invasive diagnostic criteria, but were confirmed otherwise. By doing so, we illustrate several limitations of non-invasive diagnosis of HCC by imaging examination alone, either computed tomography (CT) or magnetic resonance imaging (MRI). We suggest that these “HCC diagnosed by imaging criteria alone (HCCi)” may have the potential to show different clinical courses and post-treatment outcomes to those of “HCC diagnosed on pathologic examination (HCCp).”

## Benign lesions

### Focal nodular hyperplasia–like nodules

Focal nodular hyperplasia–like nodules (FNH-LNs) resemble focal nodular hyperplasia on histological examination, but arise in cirrhotic liver, especially in patients with alcoholic cirrhosis or vascular abnormalities [12, 13]. FNH-LN may mimic HCC by demonstrating either APHE or a “washout” and capsule appearance on CT or MRI, although the presence of both APHE and washout appearances is relatively rare [14, 15] (Fig. 1). In a study on 130 cirrhotic explanted livers, FNH-LNs were found in 15% [16]. Meanwhile, in a study including nine FNH-LNs arising in patients at risk for HCC, three (33.3%) could have been wrongly diagnosed as HCC based on imaging diagnosis criteria [14]. The presence of ancillary features of HCC, such as T2 heterogeneity, signs of diffusion restriction, and heterogeneous uptake of hepatocyte contrast material, may be useful to correctly distinguish HCC from FNH-LN [15]. In contrast, findings that are atypical for HCC, such as homogeneous hyperintensity on T1-weighted images, isointensity on T2-weighted images, and homogeneous hyperintensity with central scar on hepatocyte-specific contrast material–enhanced MRI, are indicative of diagnoses other than HCC and prompt histologic confirmation for the correct diagnosis of FNH-LN [15, 17].

### Serum amyloid A–positive nodules

Serum amyloid A (SAA)–positive nodules are benign nodules that have similar characteristics to those of FNH-LN arising in alcoholic cirrhosis, but also share histologic features with inflammatory hepatocellular adenoma based on SAA expression, sinusoidal dilation, and ductular and inflammatory reactions [18]. The differential diagnosis of SAA-positive nodules from HCC can be more difficult than that for FNH-LN, as they show hypointensity on hepatobiliary phase images of hepatobiliary contrast material–enhanced MRI as well as APHE and washout appearance [19]. However, SAA-positive nodules may be distinguished based on the presence of small (< 2 cm) and multiple lesions. The incidence of presenting both APHE and washout appearance in SAS-positive nodules is not well known, although it has been reported that two-thirds (8/12, 67%) of SAA-positive nodules show hypointensity in the hepatobiliary phase of gadoxetate-enhanced MRI [18]. At our institute, among 400 transplanted livers, we noted two SAA-positive nodules in one patient that were difficult to differentiate from HCC (Suppl. Fig. 1).

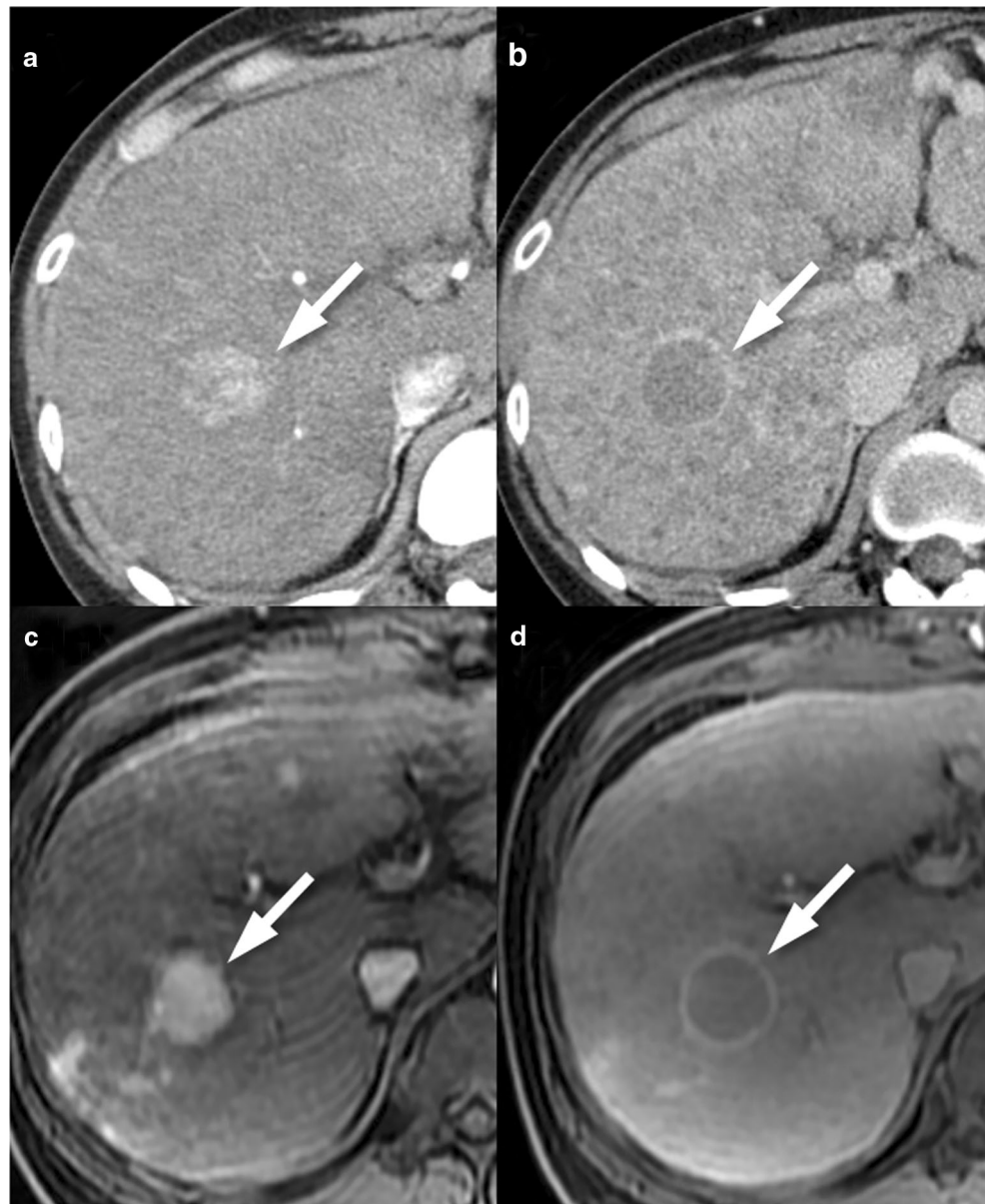
### Dysplastic nodules

Both low- and high-grade dysplastic nodules may demonstrate focal areas of arterial blood supply on CT hepatic arteriography [20]. On dynamic imaging, it may not be uncommon for dysplastic nodules to show APHE or washout appearance [21–23]. Rarely, both APHE and washout appearance can be observed in dysplastic nodules, making differentiation from HCC difficult (Suppl. Fig. 2). In one study, among seven high-grade dysplastic nodules, six showed APHE and five showed “washout” appearance; the specificity of the non-invasive diagnosis was 81% when these nodules were counted as false positive [24]. Therefore, for small lesions (1–1.5 cm) in particular, even though a lesion in cirrhotic liver may show both APHE and washout appearance, the presence of any atypical findings should prompt an alternative diagnostic examination to reduce false diagnosis of HCC [25, 26]. The coexistence of hyperintensity on T2-weighted images or diffusion restriction may favor the diagnosis of HCC, but these findings may also be present in dysplastic nodules [26–28].

### Spontaneously regressing lesions

It is well known that arterially enhancing lesions seen in cirrhotic liver without washout appearance commonly disappear on follow-up examination [29]. However, lesions that show both APHE and washout appearance may also undergo spontaneous regression [30, 31] (Suppl. Fig. 3). The exact incidence of spontaneously regressing hypervascular and washout

**Fig. 1** Focal nodular hyperplasia-like nodule in a 34-year-old woman with alcoholic cirrhosis. Arterial (a) and equilibrium (b) phase images of multiphase dynamic CT examination obtained after administration of 2 mL/kg of 300 mgI/mL of low osmolar non-ionic contrast material show a nodular mass (arrows) with arterial hyperenhancement, washout appearance, and capsule appearance. Gadoxetate-enhanced arterial (c) and venous (d) phase images (0.025 mmol/kg) also show a globally hyperenhancing mass with washout and capsule appearance (arrows)



lesions overall is unknown, although according to a study that included 52 subcentimeter hypervascular and hepatobiliary hypointense lesions, 10 (67%) of 15 lesions showing both APHE and washout appearance turn out to be benign [30]. In such cases, there are two possibilities. One possibility is that the disappearing lesions may actually be benign lesions that undergo regression. Another possibility is that they are actually HCC, but undergo spontaneous necrosis. There have been reports that histologically confirmed HCC showed spontaneous necrosis or regression [32–35]. However, HCC undergoing spontaneous necrosis can also show late recurrence. Therefore, lesions that show spontaneous necrosis should be closely followed, because tumor recurrence may occur from remnant tumors or elsewhere in the liver.

## Non-HCC malignancies

### Combined hepatocellular-cholangiocarcinoma

Combined hepatocellular-cholangiocarcinoma (cHCC-CCA) has been considered a rare hepatic malignancy, but is increasingly recognized in cirrhotic liver [36]. Based on our hospital records and in previous reports [37, 38], cHCC-CCA is the second most common primary liver carcinoma in cirrhotic liver, followed by intrahepatic cholangiocarcinoma excluding perihilar cholangiocarcinoma. Therefore, cHCC-CCA should be the first differential diagnosis of HCC in patients with cirrhosis. There have been reports that 93.5–93.9% of cHCC-CCA may demonstrate at least one ancillary feature indicating

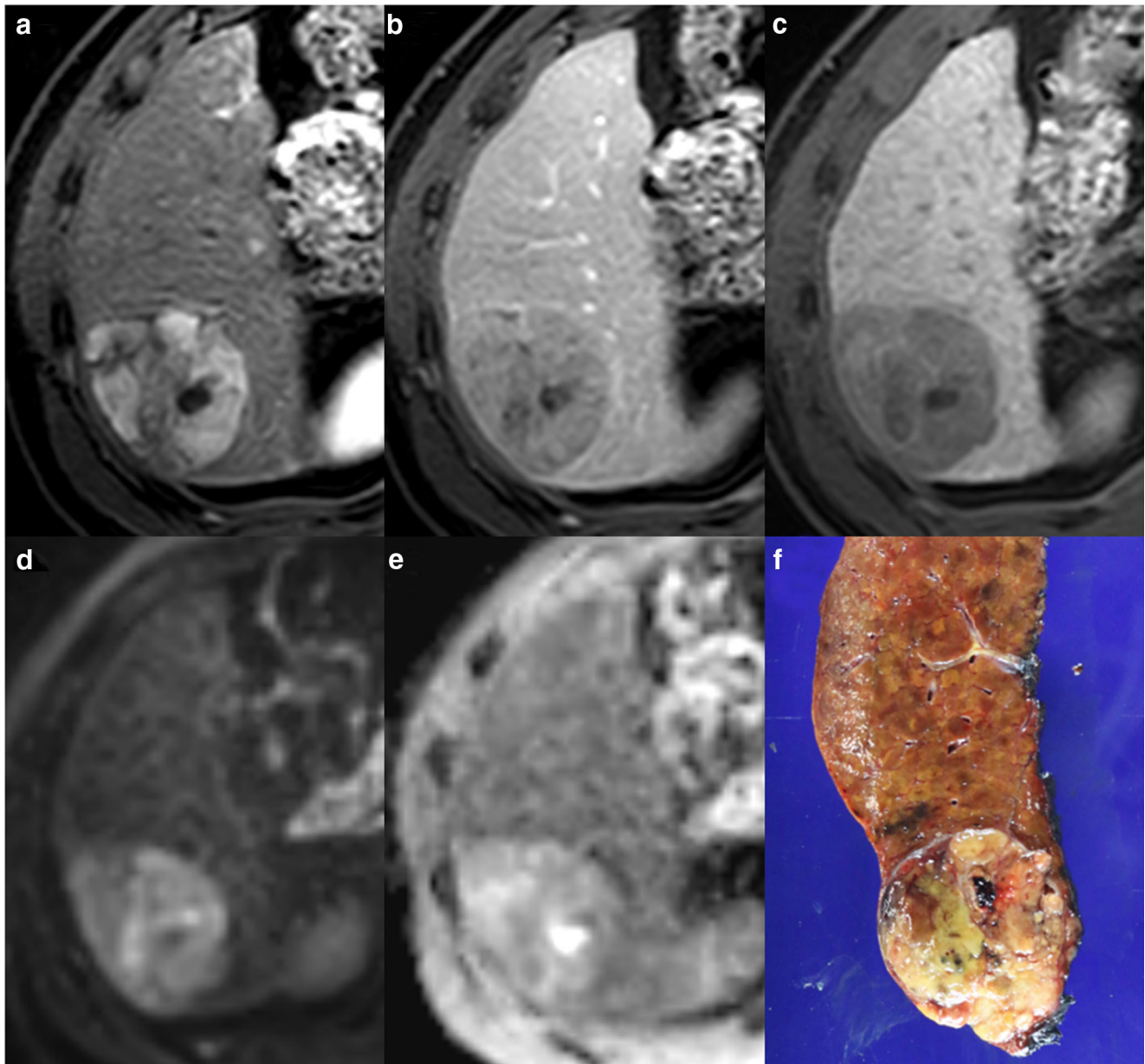


non-HCC malignancy, such as targetoid enhancement pattern including rim-like APHE, liver surface retraction, or biliary obstruction [39, 40]. However, another study indicated that cHCC-CCAs showed identical imaging features in 16 (23%)–18 (25%) of 70 cHCC-CCAs with those of HCC showing no obvious imaging features suggestive of non-HCC malignancy and that these may not be differentiable from HCC based on imaging features alone [41] (Fig. 2). Nonetheless, there is a great necessity for a correct diagnosis and identification of histologic characteristics of cHCC-CCA,

according to which the methods of surgical treatment and chemotherapeutic regimen may require to be adapted [42, 43].

### Mass-forming intrahepatic cholangiocarcinoma

Excluding perihilar cholangiocarcinoma, mass-forming intrahepatic cholangiocarcinoma (MF-iCCA) is less common than cHCC-CCA in cirrhotic liver, but should be another important differential diagnosis of HCC [44, 45]. MF-iCCA is typically characterized by an irregularly marginated mass with



**Fig. 2** Combined hepatocellular and cholangiocarcinoma in a 50-year-old man with B-viral cirrhosis. Gadopentate-enhanced arterial (a), portal (b), and hepatobiliary (c) phase images show a 5-cm mass with arterial phase hyperenhancement, washout, and capsule appearance. Diffusion-

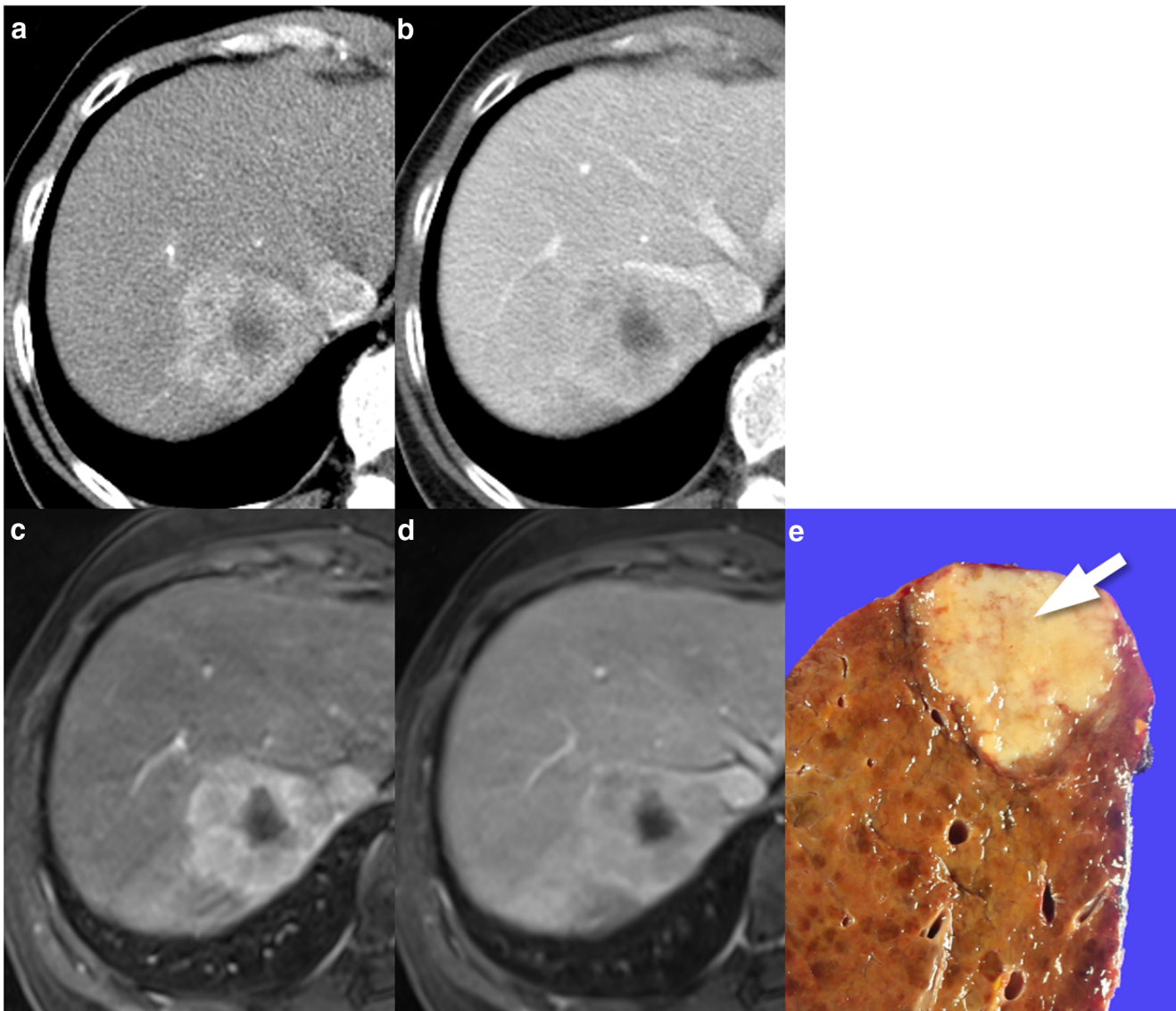
weighted (d,  $b = 800 \text{ s/mm}^2$ ) and apparent diffusion coefficient map (e) images show a mass with moderate diffusion restriction. f Gross specimen shows a mass with mosaic pattern and capsulation

rim-like enhancement on arterial phase and progressive central enhancement on late dynamic phase [46]. However, in cirrhotic liver, atypical global APHE and washout appearance may be more commonly seen in MF-iCCA than those arising in non-cirrhotic liver [45–47]. In a study by Huang et al [45], 7% of small iCCAs (3 cm or smaller) arising in cirrhotic liver showed wash-in and washout enhancement patterns, mimicking HCC. Moreover, peritumoral biliary dilation, which may be useful to correctly differentiate MF-iCCA from HCC, may be less common than that arising in non-cirrhotic liver [48]. MF-iCCA manifesting as HCC-like hypervascular enhancement pattern exhibits less fibrosis and more ductular components and can be subclassified into small duct-type cholangiocarcinoma [49, 50]

(Fig. 3). Studies have reported that MF-iCCA showing APHE tended to have better post-surgical outcomes than those showing classical rim-like or poor enhancement [49, 51–53].

### Sarcomatoid carcinoma

Sarcomatoid carcinomas in the liver are conventional carcinomas containing a spindle cell component, which do not have specific mesenchymal differentiation as that of a carcinosarcoma [54]. Sarcomatoid carcinoma can be divided into sarcomatoid HCC, sarcomatoid CCA, sarcomatoid cHCC-CCA, or unclassified sarcomatoid carcinoma [55, 56]. Sarcomatoid carcinomas usually present as large, irregular,



**Fig. 3** Cholangiocarcinoma in a 60-year-old woman with B-viral cirrhosis. On both post-contrast CT (**a, b**) and MRI (**c, d**), a mass shows arterial phase hyperenhancement (**a, c**) and washout appearance (**b, d**), mimicking hepatocellular carcinoma. Poorly enhancing area noted on

both CT and MR images corresponds to tumor necrosis. (**e**) Corresponding gross specimen shows an area of coagulative necrosis (arrow)

and peripherally enhancing masses with areas of central necrosis [55, 57, 58]. Therefore, typical imaging patterns indicating HCC (non-rim APHE and washout appearance) are less commonly seen in sarcomatoid carcinomas [59] and are mostly suspected as non-HCC malignancy in preoperative imaging. However, some sarcomatoid HCCs, especially those that are small, may show diagnostic imaging features of HCC and cannot be differentiated from HCC (Fig. 4). In our unpublished data, approximately 12% of sarcomatoid carcinomas could be classified as definitely HCC (LR-5) when the LI-RADS was applied. As sarcomatoid HCC may be considered a histologic variant of HCC, imaging diagnosis of sarcomatoid HCC as HCC may not be entirely incorrect. However, it is desirable to identify sarcomatoid carcinomas given that they have worse outcomes after treatment [59].

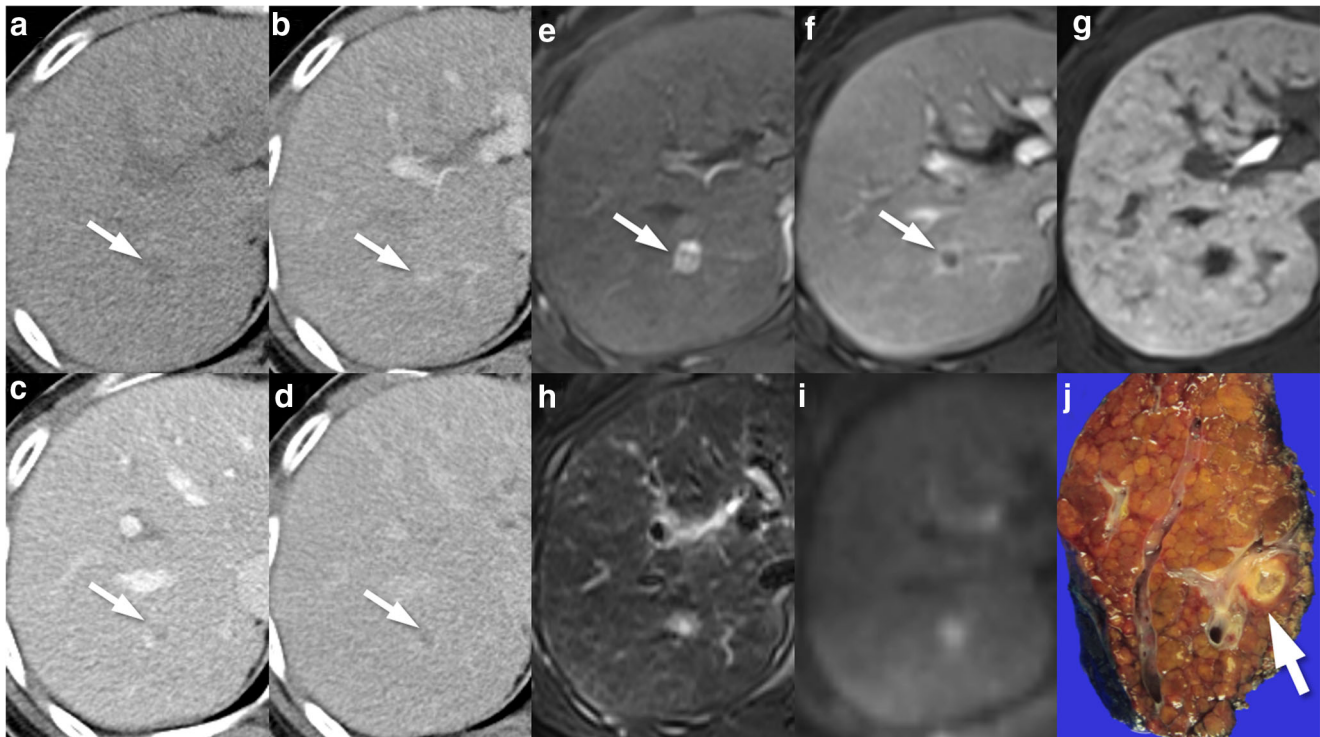
### Lymphoepithelioma-like carcinoma

Lymphoepithelioma-like carcinoma (LELC) is a rare tumor composed of pleomorphic epithelial cells with a prominent lymphoid infiltrate and may present as one of two forms: lymphoepithelioma-like hepatocellular carcinoma or lymphoepithelioma-like cholangiocarcinoma [60].

As both forms of LELC have different pathogeneses and a better clinical course than HCC and iCCA, they should be distinguished from HCC [61]. The imaging findings of LELC are not well known, but may mimic those of HCC by exhibiting APHE and washout appearance [62, 63] or those of iCCA by exhibiting rim-like APHE [64] (Suppl. Fig. 4). There is no report on a collective series of imaging features of LELC. However, according to a report by Lee et al [65] regarding the false-positive diagnosis of HCC in 837 liver resection patients, one LELC was recorded among the 18 (2.2%) false-positive diagnoses of HCC.

### Hepatoblastoma

Hepatoblastoma is the most common primary malignant hepatic tumor in children, mostly occurring at the ages of 6 months and 3 years, but is extremely rare in adults [66, 67]. Differential diagnosis of hepatoblastoma arising in adults from HCC is difficult even on pathological examination because the two tumors share similar gross and microscopic characteristics [66]. Similar to pediatric forms, adult hepatoblastoma commonly shows capsulation or pseudocapsule formation and elevation of serum alpha-



**Fig. 4** Sarcomatoid hepatocellular carcinoma in a 45-year-old man with B-viral cirrhosis. Precontrast (a), post-contrast arterial (b), portal venous (c), and equilibrium (d) phase CT images show a small nodular lesion with subtle arterial phase hyperenhancement and washout appearance (arrows). The lesion was not considered diagnostic of hepatocellular carcinoma at this examination. On the gadoxetate-enhanced MRI obtained

2 months after CT, the lesion shows obvious arterial phase hyperenhancement (e) and washout and capsule appearance (f). The lesion is hypointense on hepatobiliary phase image (g). T2-weighted (h) and diffusion-weighted (i,  $b = 800 \text{ s/mm}^2$ ) images show a diffusion-restricted lesion. j Surgical specimen shows a small nodular mass in a cirrhotic liver



fetoprotein level [66]. Approximately 25% of adult hepatoblastomas have been reported in cirrhotic liver [68]. Imaging diagnosis of adult hepatoblastoma is also challenging because of its extremely low prevalence in adults and similar tumor characteristics to those of HCC. However, hepatoblastoma may be characterized by a more heterogeneous texture because of its mixed histologic components [69] (Fig. 5). According to the abovementioned series of Lee et al [65], two hepatoblastomas were included among the 18 (2.2%) false-positive diagnoses of HCC.

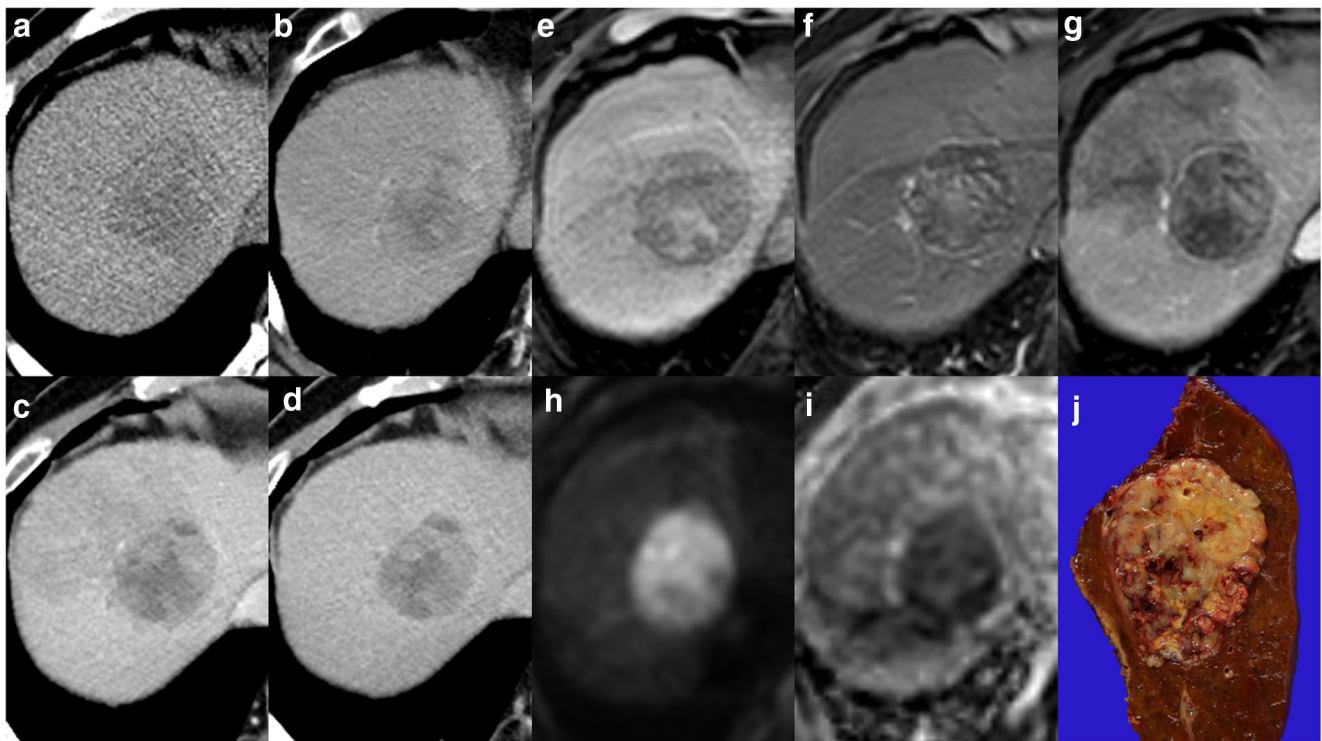
### Metastatic adenocarcinoma

Metastatic carcinoma is relatively uncommon in cirrhotic liver, probably due to alteration of hemodynamics and microstructural environment in the liver [8]. When metastatic cancers are found in cirrhotic liver, they usually show rim-like APHE and can be categorized as non-HCC malignancy according to the imaging criteria of LI-RADS [37]. However, when a metastasis in cirrhotic liver demonstrates both non-rim APHE and washout appearance, it can be misdiagnosed as HCC (Fig. 6). As the current guidelines do not recommend restraining imaging diagnosis in patients with extrahepatic malignancy when they have cirrhosis, imaging diagnosis of

HCC should be conducted with caution in patients with both extrahepatic malignancy and cirrhosis. According to our unpublished data, three (6.6%) out of 45 metastases arising in patients with cirrhosis or chronic hepatitis B could not be differentiated from HCC.

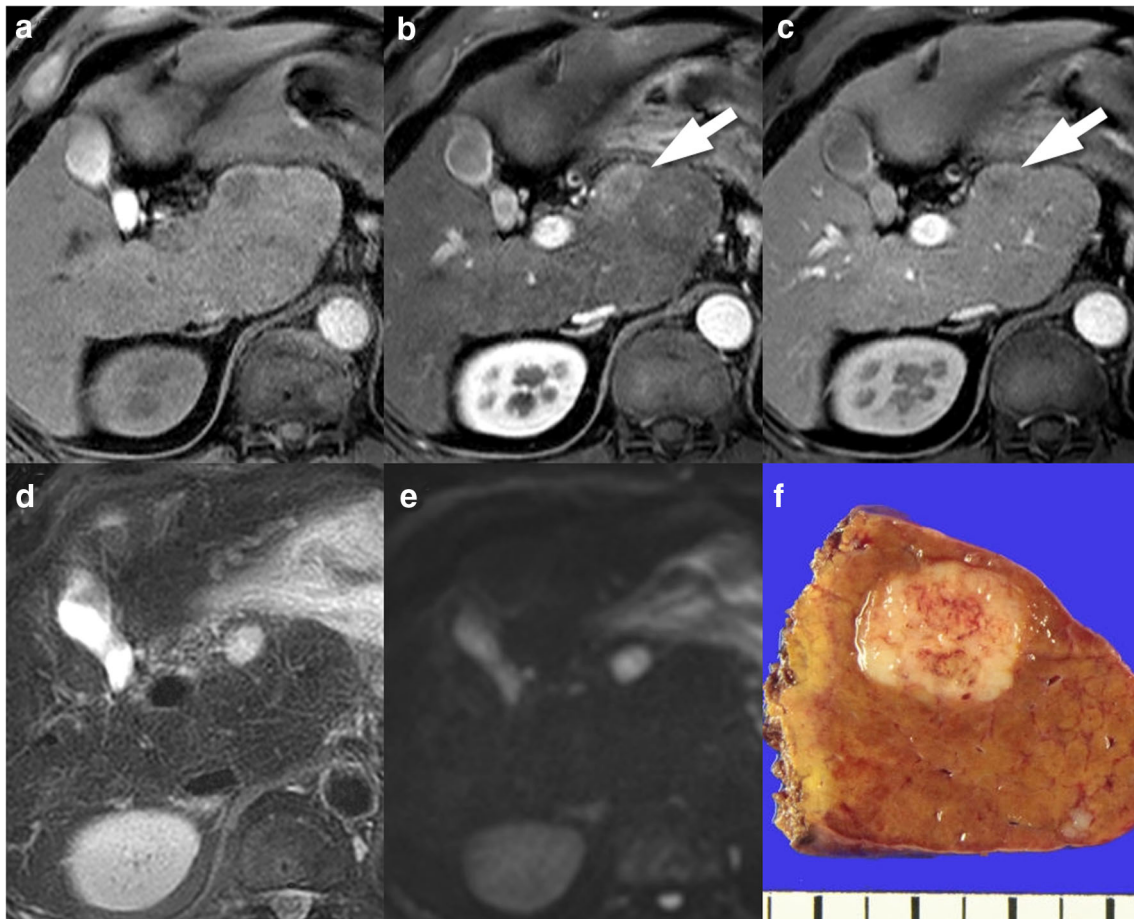
### Conclusion

We have illustrated benign and malignant lesions found in histologically proven cirrhotic liver, showing imaging features compatible with HCC. Other lesions that were not addressed in this review but have been reported in cirrhotic liver by mimicking HCC include bile duct adenoma [70], inflammatory pseudotumor [71], angiomyolipoma [65], and chronic abscess [72]. The lesions we presented above may have been diagnosed clinically as HCC and would have been treated as such, if imaging criteria alone had been used for planning a locoregional treatment without histologic diagnosis. Although we only presented HCC-like tumors found in cirrhotic liver, there could have been more diverse entities showing the typical appearances of HCC, if we had included cases found in patients with chronic B-viral hepatitis or with other risk factors for



**Fig. 5** Hepatoblastoma in a 75-year-old man with B-viral cirrhosis. Dynamic CT precontrast (a), arterial (b), venous (c), and equilibrium (d) phase images show a heterogeneously hypervascular mass with washout and capsule appearance. Gadoxetate-enhanced MRI, precontrast (e),

arterial (f), and venous (g) phase images show an encapsulated mass with arterial hyperenhancement and washout. Diffusion-weighted image (h,  $b = 800 \text{ s/mm}^2$ ) and apparent diffusion coefficient map (i) image show a mass with diffusion restriction. j Corresponding surgical specimen



**Fig. 6** Metastatic adenocarcinoma from gastric cancer in a 65-year-old man with B-viral cirrhosis. Gadoxetate-enhanced MRI, precontrast (**a**), arterial phase (**b**), and venous phase (**c**) images show a nodular lesion in the caudate lobe of the liver, presenting with arterial phase

hyperenhancement and washout appearance. T2-weighted fast spin-echo (**d**) and diffusion-weighted (**e**,  $b = 800 \text{ s/mm}^2$ ) images show a hyperintense lesion. **f** Gross specimen shows the corresponding lesion

HCC. Moreover, even though patients undergo locoregional treatment without histologic confirmation, they would be given a diagnosis of HCC and treated as such on further management.

Therefore, we suggest that lesions that were diagnosed as HCC on imaging alone should be referred to with a different term, such as HCCi, meaning “HCC diagnosed based on imaging but not pathologic examinations.” In contrast, HCCs that were diagnosed as HCCs based on pathology may be designated as HCCp when they need to be distinguished from HCCi. Distinction of HCCi and HCCp would be relevant because histologic evaluation is important not only for the correct diagnosis of HCC but also for the identification of distinct subtype for estimation of prognosis and planning targeted therapy [73]. By using different terms (HCCi or HCCp) for the different HCCs diagnosed histologically or by imaging, it will be possible to evaluate the potential differences in prognosis between HCCi and HCCp after a certain treatment, especially

locoregional treatment in which histological diagnosis is not typically obtained.

In conclusion, some benign and non-HCC malignant lesions can be diagnosed as HCC by satisfying imaging criteria. We propose distinguishing HCCs diagnosed based on imaging from those diagnosed by histologic examination using terms such as HCCi and HCCp.

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### Compliance with ethical standards

**Guarantor** The scientific guarantor of this publication is Myeong-Jin Kim.

**Conflict of interest** The authors of this manuscript declare no relationships with any companies, whose products or services may be related to the subject matter of the article.

**Statistics and biometry** Not applicable



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#### Methodology

• Illustrative Review

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