

Hepatocellular carcinoma with macrovascular invasion: multimodality imaging features for the diagnosis

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ABSTRACT

Hepatocellular carcinoma (HCC) is frequently associated with macrovascular invasion of the portal vein or hepatic veins in advanced stages. The accurate diagnosis of macrovascular invasion and the differentiation from bland non-tumoral thrombus has significant clinical and management implications, since it narrows the therapeutic options and it represents a mandatory contraindication for liver resection or transplantation. The imaging diagnosis remains particularly challenging since the imaging features of HCC with macrovascular invasion may be subtle, especially in lesions showing infiltrative appearance. However, each radiologic imaging modality may provide findings suggesting the presence of tumor thrombus rather than bland thrombus. The purpose of this paper is to review the current guidelines and imaging appearance of HCC with macrovascular invasion. Knowledge of the most common imaging features of HCC with macrovascular invasion may improve the diagnostic confidence of tumor thrombus in clinical practice and help to guide patients' management.

Hepatocellular carcinoma (HCC) is the most common primary liver malignancy and the third leading cause of cancer death worldwide (1). HCC most commonly arises in the background of cirrhosis secondary to viral hepatitis, nonalcoholic steatohepatitis, or alcohol abuse. The prognosis of patients with HCC largely depends on the stage of the disease at the time of the diagnosis. According to the Barcelona Clinic Liver Cancer (BCLC) staging criteria, HCC patients should be classified as advanced stage once macrovascular invasion has manifested (2). Macrovascular invasion is associated with an extremely poor prognosis, with a median survival of 6 to 8 months (3). Moreover, its diagnosis significantly narrows the therapeutic options in HCC patients, due to the high rate of tumor recurrence, and it represents one of the most common tumor-related contraindications for locoregional treatments with curative intent (3).

The diagnosis of HCC in cirrhotic or high-risk patients is reached noninvasively with different contrast-enhanced imaging modalities when demonstrating the typical HCC landmarks in lesions larger than 1 cm, including arterial phase hyperenhancement (APHE), washout on portal venous or delayed phases, and the presence of enhancing capsule (3, 4). Although each imaging modality also provides suggestive or conclusive imaging features to rule out the presence of macrovascular invasion, the diagnosis remains challenging in clinical practice. Histopathologic characterization of thrombus is considered the reference standard for the diagnosis of macrovascular invasion, but it is usually not feasible in routine clinical practice since it is an invasive procedure not immune to complications or sampling errors (3).

Macrovascular invasion often coexists with advanced HCC or lesions with infiltrative appearance. However, the latter refers to the macroscopic growth pattern characterized by tumor nodular spreading throughout cirrhotic parenchyma with permeative growth (Fig. 1), regardless of the presence of tumor thrombus (5). The presence of infiltrative HCC makes the diagnosis of macrovascular invasion challenging since discrete enhancing HCC nodules are difficult to distinguish from background cirrhosis and it may not be visualized in up to 40% of patients (5, 6). Moreover, macrovascular invasion is not pathognomonic for HCC. Other non-HCC hepatic malignancies (i.e., intrahepatic cholangiocarcinoma, combined hepatocellular-cholangiocarcinoma) may occasionally manifest with tumor thrombus (7). Prior stud-

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ies have reported macrovascular invasion in 10%–24% of non-HCC primary hepatic malignancies, including intrahepatic cholangiocarcinoma and combined hepatocellular-cholangiocarcinoma (8, 9). Cirrhotic patients also tend to develop nontumoral portal vein thrombosis in up to 16% of cases, especially in Child-Pugh B-C stages, which may resolve with anticoagulant therapy (3). Therefore, the accurate imaging diagnosis of HCC with macrovascular invasion has important implications for patients' treatment and management.

This article aims to review the current guidelines and multimodality imaging features of HCC with macrovascular invasion and to provide pearls for a noninvasive imaging diagnosis.

Macrovascular invasion in current HCC guidelines

Even though several scientific organizations have developed different definitions and diagnostic criteria for the diagnosis of HCC, the presence of macrovascular invasion, alternatively termed as "tumor thrombus" or "tumor in vein" (TIV), is considered to be one of the worst prognostic factors in the management of HCC (3, 4, 7, 10). According to the clinical practical guidelines recently released by the European Association for the Study of the Liver (EASL) (3), macrovascular invasion of the main portal vein or hepatic veins represents an absolute contraindication for liver resection or transplantation due to the low survival and high post-transplant recurrence. The two imaging findings recommended by EASL for the diagnosis of macrovascular invasion on contrast-enhanced imaging include the

presence of arterial phase hyperenhancement and restricted diffusion within the portal thrombus (3). Similarly, the Korean Liver Cancer Association-National Cancer Center Korea Practice Guidelines (10) mention the presence of vascular infiltration as a mandatory contraindication for liver transplantation.

The LI-RADS perspective

The Liver Imaging Reporting and Data System (LI-RADS), released by the American College of Radiology and endorsed by the American Association for the Study of Liver Diseases (AASLD) practice guidance, aims to standardize the interpretation of liver lesions based on the probability of being HCC in high-risk patients (4, 7). The classification of lesions with macrovascular invasion has been significantly redefined and evolved among the subse-

quent LI-RADS versions (11). Initially, HCC with the presence of TIV was categorized as LR-5V in the LI-RADS v2013 and v2014. The LI-RADS v2017 included a major update for the classification of HCC with macrovascular invasion, renaming LR-5V as LR-TIV, since also other non-HCC primary hepatic malignancies may manifest with macrovascular invasion (Fig. 2). The LR-TIV is defined as "unequivocal enhancing soft tissue in vein, regardless of visualization of parenchymal mass" (Table) (7). Other imaging features that suggest the presence of TIV but do not establish its diagnosis according to LI-RADS algorithm are: occluded vein with ill-defined walls, occluded vein with restricted diffusion, occluded or obscured vein in contiguity with malignant parenchymal mass or heterogeneous vein enhancement not attributable to artifacts (7). Finally, in the latest

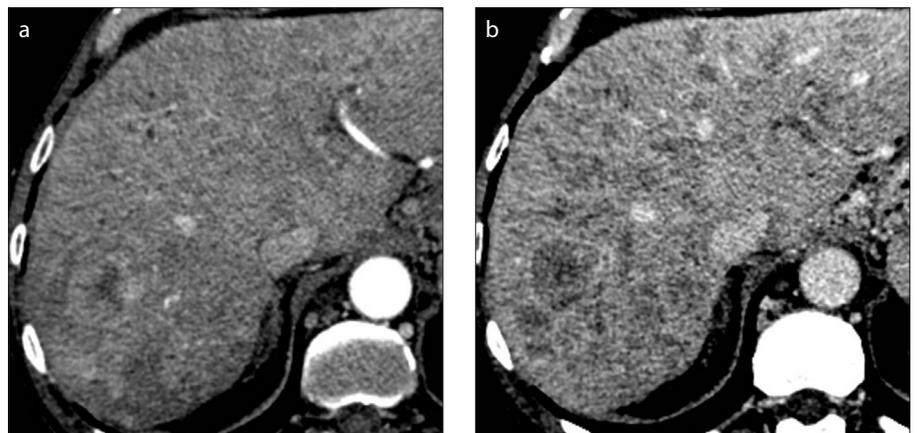


Figure 1. a, b. A 61-year-old woman with hepatitis C virus (HCV)-related cirrhosis and infiltrative HCC. Contrast-enhanced CT on hepatic arterial (a) and portal venous (b) phases show innumerable tumor nodules with permeative growth spreading through the liver parenchyma with mild heterogeneous enhancement and washout on portal venous phase.

Main points

- Hepatocellular carcinoma with macrovascular invasion is associated with an extremely poor prognosis, and its recognition represents one of the major tumor-related contraindications for locoregional treatments with curative intent.
- Imaging features of hepatocellular carcinoma with macrovascular invasion may be subtle on different contrast-enhanced imaging modalities, especially in lesions showing infiltrative appearance.
- Unequivocal enhancing soft tissue within the vein, restricted diffusion of the thrombus and vessel expansion are the most characteristic imaging findings suggesting the presence of tumor thrombus.

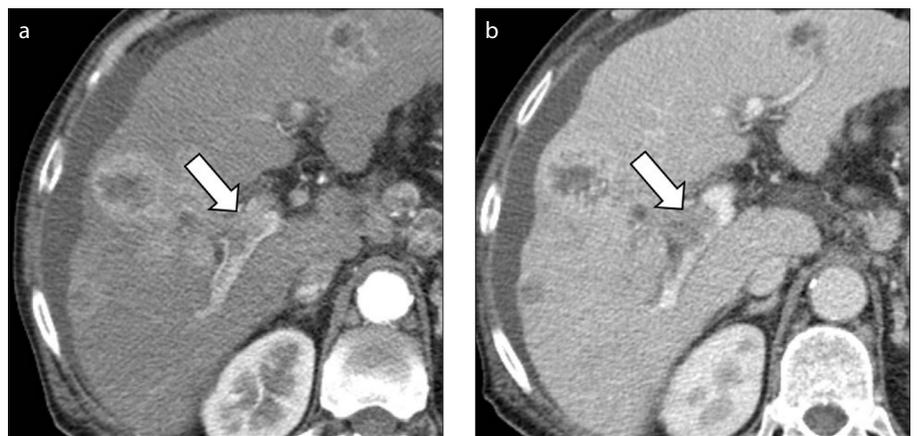


Figure 2. a, b. A 70-year-old man with cirrhosis and multifocal intrahepatic cholangiocarcinoma. Contrast-enhanced CT on hepatic arterial (a) and portal venous (b) phases demonstrate a hepatic mass with rim arterial phase hyperenhancement and macrovascular invasion in the main portal vein (arrows).

Table. Liver imaging reporting and data system (LI-RAD) v2018 (7) criteria for tumor in vein

Tumor in vein (LR-TIV):

- Unequivocal enhancing soft tissue in vein, regardless of visualization of parenchymal mass

Other imaging features that suggest the presence of TIV but do not establish its diagnosis:

- Occluded vein with ill-defined walls
- Occluded vein with restricted diffusion
- Occluded or obscured vein in contiguity with malignant parenchymal mass
- Heterogeneous vein enhancement not attributable to artifact

Reporting:

- If contiguous with targetoid mass report as “LR-TIV, may be due to non HCC malignancy”
- If contiguous with LR-5 mass report as “LR-TIV, definitely due to HCC”
- Otherwise report as “LR-TIV, probably due to HCC”

76%–87% and a specificity of 75%–89% as predictor of non-HCC malignancies.

Ultrasonography

Ultrasonography (US) is the most common imaging modality for HCC surveillance in high-risk or cirrhotic patients. At US surveillance, the main portal vein should always be scrutinized since portal vein thrombosis may be incidentally found even in asymptomatic patients with cirrhosis. In case of bland thrombus, US images show the presence of hyperechoic material with variable echogenicity within the lumen of hepatic vessels, distention of the portal vein and absence of flow at color- or pulsed-Doppler. However, the ability to characterize venous thrombi is low and conventional US does not allow a definitive diagnosis to rule out the presence of malignant thrombus since the thrombus echogenicity is not specific. Findings suggestive of tumor thrombus (Fig. 3) rather than bland thrombus are the new onset of portal vein thrombosis at subsequent US examinations, the presence of an adjacent liver mass with direct intravascular extension and color signal within the thrombus at Doppler evaluation (13, 14). However, color Doppler has demonstrated significantly lower sensitivity (20%–87%) for the characterization of tumor thrombus compared to contrast-enhanced imaging modalities (14–16). In contrast, the presence of collateral vessels with cavernous transformation of the portal vein is pathognomonic of long standing thrombosis and may be suggestive of bland thrombus since the low survival of patients with macrovascular invasion does not give enough time for cavernous transformation (13).

When using the LI-RADS US algorithm for HCC screening (17), the presence of a new thrombus in vein, whether considered bland or TIV, should be categorized as LI-RADS US-3 positive and a further multiphasic contrast-enhanced diagnostic exam should be recommended for characterization.

Contrast-enhanced ultrasonography

Contrast-enhanced ultrasonography (CEUS) allows to characterize liver lesions in cirrhotic patients according to the vascular pattern after the intravenous administration of a sulphur-hexafluoride microbubbles-based contrast agent (18). CEUS may be performed in case of visible nodule detected during the US screening in high-risk patients or as second

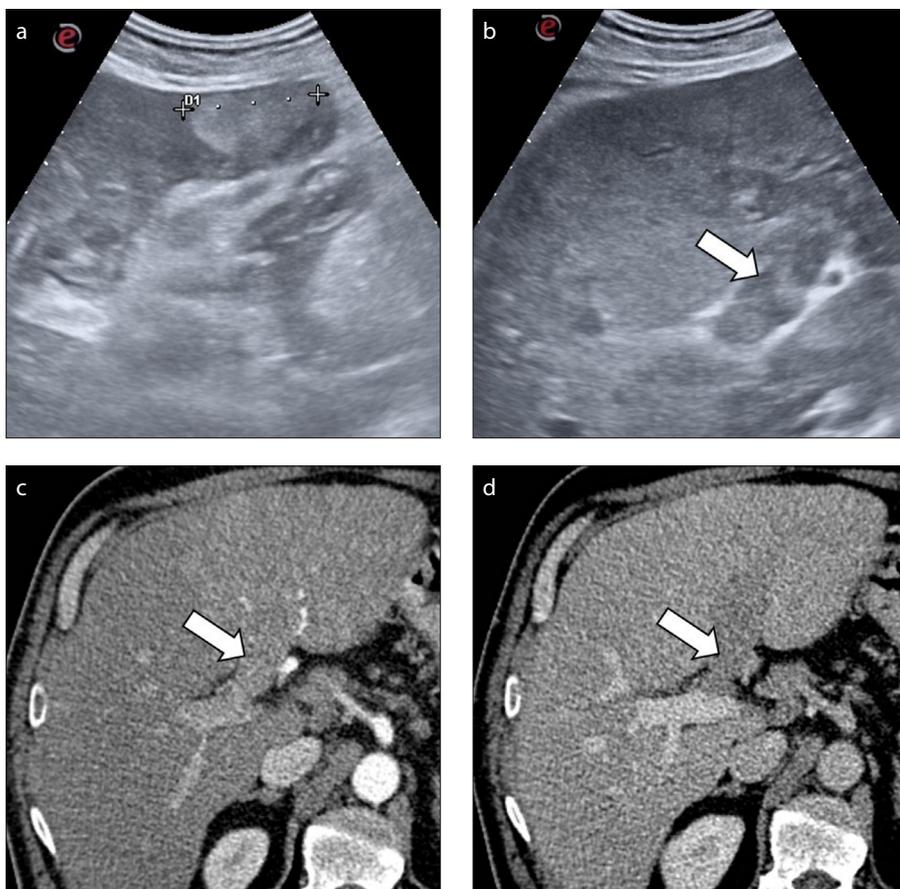


Figure 3. a–d. A 47-year-old man with alcohol-related cirrhosis. Conventional ultrasound examination depicts the presence of a hyperechoic lesion in the left hepatic lobe (a) and a heterogeneously hyperechoic thrombus (b, arrow) expanding the left portal vein. Subsequent contrast-enhanced CT (c, d) confirmed the presence of a tumor thrombus in the left hepatic vein (arrows).

CT/MRI LI-RADS v2018 algorithm the LR-TIV was sub-classified in three categories including: “LR-TIV, definitely due to HCC”, if in continuity with a LR-5 observation; “LR-TIV, may be due to non-HCC malignancy”, if adjacent to a targetoid mass; otherwise “LR-TIV, probably due to HCC” (Table) (7). A recent study performed by Ludwig et al.

(12) demonstrated that the combination of LR-TIV definitely due to HCC and LR-5 had a sensitivity of 57%–67% and a specificity of 85%–90% as predictor of HCC. On the contrary, the categorization as “LR-TIV may be due to non-HCC malignancy” combined with LR-M showed a sensitivity of

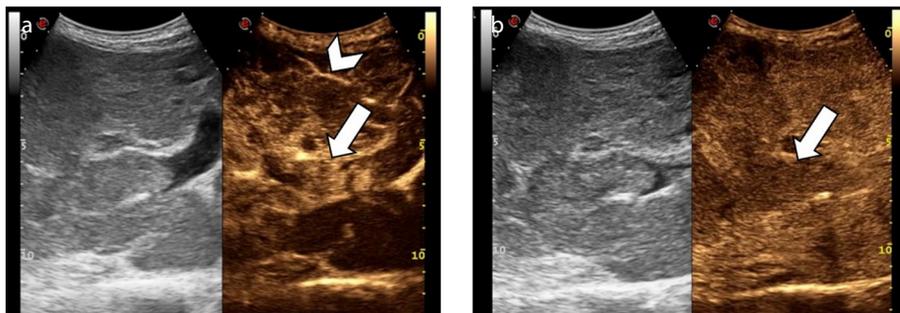


Figure 4. a, b. An 84-year-old man with hepatitis B virus (HBV)-related cirrhosis and tumor thrombus. Contrast-enhanced ultrasound image (a) at 13 seconds after the intravenous administration of contrast agent demonstrates the presence of an enhancing thrombus within the main portal vein (arrow), simultaneously with the intra-hepatic artery (arrowhead). Image acquired at 180 seconds (b) shows washout of the tumor thrombus (arrow).

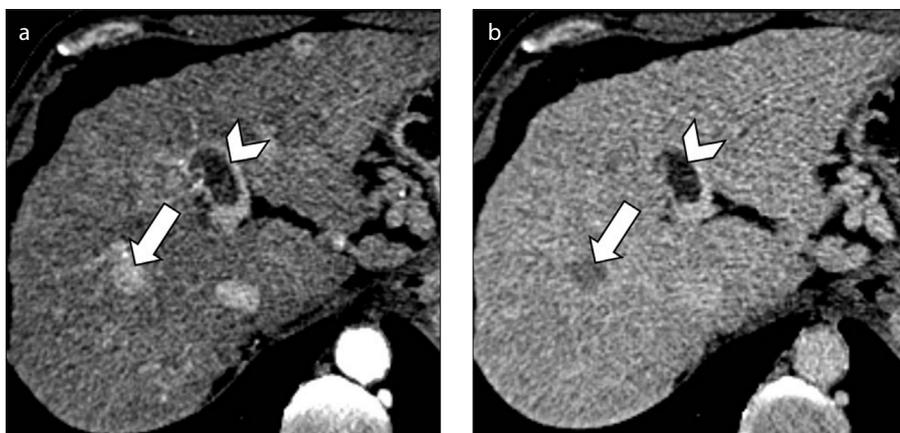


Figure 5. a, b. A 52-year-old man with HCV-related cirrhosis and multifocal HCC. Contrast-enhanced CT depicts a 1.5 cm HCC with arterial phase hyperenhancement (a, arrow) and washout (b, arrow) on delayed phase. In the same images, a coexistent nonenhancing bland thrombus (arrowheads) is seen in the left portal branch, not in contact with the HCC lesion.

step in patients with main contraindications or inconclusive contrast-enhanced computed tomography (CT) or magnetic resonance imaging (MRI) (3). According to the WFUMB-EF-SUMB practice guidelines (19), CEUS is listed among the possible imaging modalities for the differential diagnosis of portal venous thrombosis. CEUS has shown significantly higher sensitivity for the differentiation of portal vein tumor thrombus from bland thrombus compared to ultrasound with color Doppler (14, 15, 20). The sensitivity and specificity for the diagnosis of portal vein tumor thrombus have been reported as 88%–100% and 66%–100%, respectively (13, 16, 20, 21). The main advantage of CEUS is the real-time imaging examination, which may allow to detect arterial phase hyperenhancement of the thrombus even if missed or equivocal on multiphasic contrast-enhanced CT or MRI (20). Moreover, CEUS is fast, well tolerated even in patients with renal failure, and can be performed in the same session when the thrombus is detected. However, CEUS allows the evaluation of only

one or few lesions after contrast injection, limiting the applicability in patients with multiple hepatic findings, and shares the same limitations of US, including large body habitus, poor acoustic window and movement artifacts in poorly cooperative patients (18).

The arrival time of the contrast agent in the portal vein compared to the hepatic artery is the most important feature to differentiate malignant thrombosis from bland thrombus. Normally, the microbubbles of contrast agent reach the portal vein about 10 seconds after the opacification of the hepatic artery (22). Bland portal vein thrombi are typically avascular and do not demonstrate enhancement on early arterial phase. In contrast, in patients with macrovascular invasion there is an early (13–15 seconds after contrast injection) and almost simultaneous enhancement of the hepatic artery and portal vein thrombus, which is suggestive for malignant thrombosis (Fig. 4) (22). Washout on the extended portal venous phase may also be observed (23). Other

findings that may be observed using CEUS are the presence of formed small arterial vessels within the thrombus or portal vein expansion (16).

CT imaging

Multiphasic contrast-enhanced CT is performed as a noninvasive imaging modality for HCC diagnosis. Portal vein thrombosis is frequently encountered in cirrhotic patients undergoing contrast-enhanced CT for HCC diagnosis, therefore the radiologist should carefully scrutinize the presence of unequivocal findings of malignant thrombosis rather than bland non-neoplastic thrombus.

In cirrhotic patients bland thrombosis may coexist with HCC lesions, making the differential diagnosis particularly challenging (Fig. 5) (24). Bland portal vein thrombosis manifests as hypodense filling defect within the main portal vein or its branches, without contrast enhancement in any phase, and shows no continuity with concomitant HCC lesions (25, 26). Of note, radiologists should be aware that bland thrombosis may appear as hypodense luminal defect on unenhanced CT with vessels expansion in the acute phase (25, 26). Chronic thrombosis may develop calcifications within the thrombus or the vascular wall (Fig. 6), which should not be mistaken for enhancing tissue (27). Another common pitfall is the presence of contrast mixing artifacts during the hepatic arterial phase which may be misinterpreted as enhancing tissue (27). However, these artifacts completely resolve in the portal venous and delayed phases.

HCCs with macrovascular invasion typically manifest as tumor thrombus adjacent to a liver lesion showing the typical landmarks of HCC. Macrovascular invasion usually tends to be associated with larger HCC lesions (i.e., >5 cm) (Fig. 7) compared to bland thrombus (6, 28). CT imaging characteristics suggesting the presence of tumor thrombosis are the increased diameter of the portal vein and unequivocal enhancing soft tissue within the vein on arterial phase, with subsequent washout on portal venous and delayed phases (Fig. 8). Unequivocal arterial phase hyperenhancing tissue has demonstrated the highest sensitivity (76%–100%) and specificity (87%–91%) as standalone feature on CT images (28, 29), and it is the only criterion for definitive diagnosis of TIV according to LI-RADS algo-

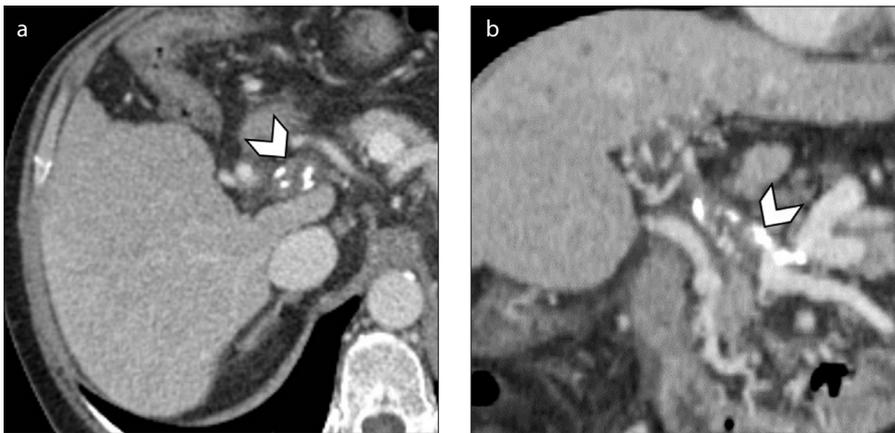


Figure 6. a, b. Axial (a) and coronal (b) contrast-enhanced CT on portal venous phase of a 60-year-old man with HCV-related cirrhosis shows chronic thrombosis of the main portal vein with wall calcification (arrowheads) and associated cavernous transformation of the portal vein at the level of hepatic hilum.

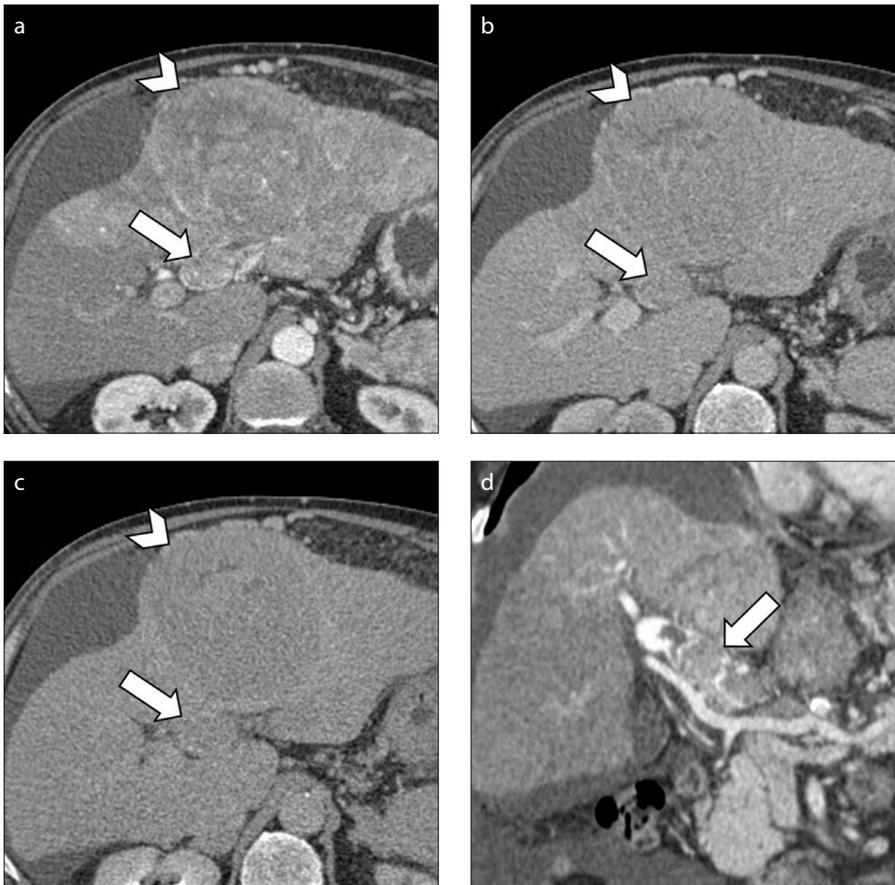


Figure 7. a–d. A 75-year-old man with HCV-related cirrhosis and HCC with macrovascular invasion. Contrast-enhanced hepatic arterial (a), portal venous (b) and delayed (c) phase CT images show macrovascular invasion (arrows) of the portal vein adjacent to a 12 cm HCC lesion (arrowheads). Coronal image (d) of the same patient demonstrates enhancing soft tissue (arrow) within the main portal vein.

rhythm (7). When combining the enhancing thrombus with portal vein diameter larger than 23 mm, the study performed by Tublin et al. (30) has demonstrated a sensitivity and specificity for the diagnosis of tumor

thrombus on contrast-enhanced CT of 86% and 100%, respectively. CT is also helpful in detecting macrovascular invasion into the hepatic veins, although this is less frequently encountered.

CT represents the gold standard modality to evaluate the extension of tumor thrombus which can range from segmental portal vein invasion to occlusion of the main portal vein trunk. Radiologists should also meticulously scrutinize the involvement of extra-hepatic portal system and superior mesenteric vein in case of portal vein invasion, or the inferior vena cava and right atrium in case of hepatic vein invasion (Fig. 9). Of note, large progressed HCC lesions may also demonstrate macrovascular invasion in both portal vein branches and hepatic veins or inferior vena cava (Fig. 10). When evaluating the extension of macrovascular invasion, radiologists should also be aware that tumor thrombosis may also coexist with bland thrombus in the same patient (Fig. 11). A correct differential diagnosis is important for precise tumor staging since a recent study performed by Mähringer-Kunz et al. (31) have reported how involvement of main trunk or contralateral portal vein branch to the primary involved lobe carries worse overall survival in HCC patients.

Finally, macrovascular invasion may manifest even in HCC treated with locoregional therapies (Fig. 12). In this setting, the new onset of tumor thrombosis is an unequivocal sign of tumor viability, even if an enhancing nodule is not visualized in the treated area.

Magnetic resonance imaging

Magnetic resonance imaging (MRI) has high sensitivity for the noninvasive diagnosis of HCC, allowing the investigation of vascular changes (i.e., APHE and washout) as well as the detection of several ancillary findings (i.e., intralesional fat, T2 hyperintensity, restricted diffusion, hepatobiliary phase hypointensity). MRI is a highly accurate modality to diagnose portal vein thrombosis as well as HCC with infiltrative appearance (32). Bland thrombus usually appears as a non-enhancing filling defect on post-contrast images, and it may show hyperintensity on T1-weighted images in acute phase.

Several MRI findings are associated with the diagnosis of malignant tumor thrombus (Fig. 13). Macrovascular invasion usually demonstrates hypointensity on T1-weighted images, presence of arterial phase hyperenhancement within the thrombus and subsequent washout on portal venous and delayed phases (32). On T2-weighted images the macrovascular invasion may demonstrate moderate-to-high T2 hyperintensity (Fig. 14).