18 Benign Solid Focal Lesions and Incidentalomas of the Liver

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- *Hemangioma (the most common benign solid hepatic tumor) and Focal Nodular Hyperplasia (FNH) seldom pose a clinical significant risk requiring a surgical procedure.*
- *Hepatic adenoma is a rare tumor that may cause significant morbidity from bleeding, rupture, or malignant transformation. It represents the most frequent indication for surgical intervention among solid benign hepatic tumors.*
- *Oral contraceptives have been associated with hepatic adenoma and FNH. Nonetheless this association is not clear for hepatic hemangiomas.*
- *Other benign solid tumors are of exceedingly low frequency. They are difficult to diagnose and exceptionally require surgical treatment.*
- *Despite most of hepatic incidentalomas in patients with and without known cancer are benign, some of them require follow-up or treatment and management of incidentalomas is challenging.*

INTRODUCTION

Focal lesions of the liver are detected with increasing incidence due to the frequent use and technical advances of imaging studies of the abdomen.

The technical improvements (mainly contrast and spatial resolution), associated to an increasing number of imaging examinations performed, lead to an increase in the detection of incidental findings (incidentalomas).

Benign focal lesions can originate from hepatocytes, bile duct epithelium, mesenchymal tissue, or a combination of these. Cystic diseases, the most common focal hepatic lesions, are discussed on chapters 19 (Non-Parasitic Cystic Diseases of the Liver) and 20 (Parasitic Hepatic Cysts).

The most frequent benign solid tumors of the liver are hemangioma, focal nodular hyperplasia (FNH), and adenoma. Also, inflammatory pseudotumor, peliosis hepatis, focal fatty infiltration, hamartoma, and other rare conditions can appear as focal solid lesions in imaging studies. (**Table 1**)

Table 1. Main benign liver tumors.

Origin		Tumor
Epithelial	Hepatocellular	Focal nodular hyperplasia Hepatocellular adenoma Regenerative nodules
	Biliary	Bile duct adenoma Biliary cystadenoma Biliary cyst
Mesenchymal	Endothelial	Hemangioma Hemangioendothelioma
	Mesothelial	Benign mesothelioma
	Adipocyte	Lipomatous tumors
Other		Biliary hamartoma

Hepatic hemangioma and FNH are more frequent than hepatic adenoma, but symptoms are uncommon for any

of them. While hemangioma rarely presents diagnostic difficulties, differentiation between FNH and adenoma can be challenging.

In contrast to hemangioma and FNH, hepatic adenoma usually requires surgical resection due to the significant risk of morbidity from bleeding, rupture, or malignant transformation.

The presence of an underlying chronic liver disease (such as chronic hepatitis or cirrhosis) is uncommonly found in patients with benign hepatic lesions, and it should raise the suspicious of a malignant tumor.

This chapter encompass the main features on benign focal hepatic diseases and incidentalomas, including decisional algorithms and radiological examples of a diversity of focal hepatic lesions (**Figures 1** to **36**).

HEPATIC HEMANGIOMA

INTRODUCTION

Hepatic hemangioma is the most common benign solid focal lesion of the liver. It is found in 2% to 4% of the general population and up to 20% of necropsies.[1] It can be a single lesion (60% of cases) or multiple, ranging in size from some millimeters to many centimeters (more than 20 cm). Those with more than 5 cm are designated giant hemangiomas. Although hemangiomas can occur at all ages, they are diagnosed more frequently in individuals aged 30-50 years. Infantile hemangiomas, seen in 5-10% of children aged 1 year, typically regress during childhood.

The hepatic hemangioma is composed of masses of blood vessels that are atypical or irregular in arrangement and size, making the blood flow slower than in the normal hepatic parenchyma. Although uncertain, its etiology is probably a consequence of a congenital vascular malformation.

Despite the absence of a clear association with hormonal factors, steroids and estrogen (including pregnancy) can increase the size of an already existing hemangioma. In addition, hemangiomas occur more frequently in females, and symptoms are more likely in childbearing women.[2,3]

CLINICAL FEATURES

Hemangiomas of the liver are usually small and asymptomatic. They are most often discovered during imaging studies (mainly ultrasonography and computed tomography) performed for another reason. They will require a therapeutic intervention only exceptionally.

Despite the rarity of symptoms, pain or fullness may occur when large and/or multiple lesions exist. Up to 40% of patients with hemangiomas greater than 4 cm, and up to 90% of those with lesions greater than 10 cm, might have symptoms. However, even in the large hemangiomas, symptoms attributed to hepatic lesions can be due, in fact, to other gastrointestinal diseases, such as irritable bowel syndrome. Early satiety, nausea, and vomiting may occur when large lesions compress the stomach. Single large lesions are more likely to produce persistent pain, truly related to the hepatic hemangioma. Pain can occur due to thrombosis, infarction or hemorrhage into the lesion, or compression of adjacent tissues or organs. Globally, a third of hemangiomas will increase in size, specially single lesions.[4]

The physical examination is generally not remarkable. Rarely a hemangioma can present as an abdominal mass with or without an arterial bruit over the right upper quadrant. Other atypical presentations include cardiac failure (from massive arteriovenous shunting), jaundice (from compression of the bile ducts), gastrointestinal bleeding (from hemobilia), and fever of unknown origin.

Seldom, hemangiomas can occur in association with clinical syndromes. The Kasabach-Merritt syndrome is characterized by tumor bleeding, thrombocytopenia, and coagulopathy (due to intravascular coagulation). The Blumgart-Bornman-Terblanche syndrome is characterized by an inflammatory process with fever and abdominal pain. These syndromes can evoke minor and major complications and should be treated surgically in most of cases. The Osler-Rendu-Weber disease is characterized by numerous small hemangiomas on the face, nares, lips, tongue, oral mucosa, gastrointestinal tract, and liver. Also, in Klippel-Trenaunay-Weber syndrome, hepatic hemangiomas occur in association with congenital hemiatrophy and nevus flammeus, with or without hemimeganencephaly. Von Hippel-Lindau disease is marked by cerebellar and retinal angiomas, with lesions also in the liver and pancreas. Multiple hepatic hemangiomas have been reported in patients with systemic lupus erythematosus.[5]

Rupture, spontaneous or traumatic, is awfully atypical and can lead to acute hemorrhagic shock with upper abdominal pain. Reported spontaneous rupture occurred in lesions with a mean size of 11 cm. The overall mortality rate associated with rupture is 60-75%, with a 30 - 40% operative mortality rate in this situation.[6]

Hemangioma can be mistaken for other hypervascular lesions, including focal nodular hyperplasia, hepatic adenoma, hemangioendothelioma, metastasis, and hepatocellular carcinoma. Differentiation of each individual lesion is important as hemangioma and other lesions can coexist. Tumor markers, such as alpha-fetoprotein, CEA, CA19.9, are typically at normal levels. Their increase should raise the suspicious of a malignant condition. It is of note that malignant transformation of hemangioma has not been reported.

Hemangiomas are uncommon in cirrhotic livers, probably due to the fibrotic process.

IMAGING

The modalities that usually help in the diagnosis of hepatic hemangiomas include ultrasonography (US), dynamic contrast-enhanced computed tomography (CT) scanning, nuclear medicine studies using technetium-99m (^{99}Tc)-labeled red blood cells (RBC), magnetic resonance imaging (MRI), hepatic arteriography, and digital subtraction angiography. Some atypical hemangiomas may require multiple imaging tests due to patterns similar to other hypervascular hepatic lesions, such as hepatocellular carcinoma and certain metastases, especially from neuroendocrine tumors.

Ultrasonography

Hepatic hemangiomas are usually well circumscribed and uniformly hyperechogenic on conventional US (**Figure 5**), but their appearance can be variable. In large hemangiomas, heterogeneous areas occur within the hyperechoic mass. Changes of the hepatic parenchyma, such as diffuse steatosis, can make a typical hemangioma appear as a hypoechoic lesion.[7] Also, atypical features can include hypoechoic lesions with a thin hyperechoic rim or a thick rind and scalloped borders.[8] Color Doppler might improve specificity and sensitivity of US.

Contrast-enhanced ultrasonography (CEUS) provides data on blood flow and tissue perfusion. The accuracy of CEUS for the diagnosis of hepatic hemangioma is high (from 82% to 95%).[9–11]Hemangiomas show peripheral puddles and pools of enhancement that expand in a centripetal pattern during the portal phase. Later scans usually show a complete filled in lesion. The absence of complete enhancement might occur in large lesions due to central thrombosis or scarring. On the other hand, small lesion can present with complete and rapid centripetal enhancement during arterial phase.

Computed Tomography

Hemangiomas have characteristic dynamic features with the administration of contrast media. The typical triple phase CT with delayed imaging of a hepatic hemangioma shows: i) hypodense lesion on precontrast phase, ii) peripheral enhancement (ring or globular) of the lesion in arterial phase with hypodense center, iii) and progressive centripetal enhancement in portal phase and delayed images. The center of hemangioma may only become hyperdense in delayed images. The pattern of a peripheral, discontinuous, intense nodular enhancement during the arterial-dominant phase with progressive centripetal fill in on CT scans is considered pathognomonic for hemangiomas (**Figures 19** and **20**).

Wedge-shaped subcapsular or segmental perilesional enhancement may be noted adjacent to high-flow hemangiomas. These findings are possibly due to hemodynamic alterations in the liver.[12] Atypical features of hemangiomas include the presence of arterioportal shunts and capsular retraction.[13,14] Rarely, a centrifugal pattern of contrast enhancement is seen.[15]

On CT, such as on CEUS and MRI, small hemangiomas can show intense and uniform enhancement in arterial phase (**Figure 17**) and thus be mistaken for other hypervascular liver tumors such as hepatocellular carcinoma, FNH, adenoma, and hypervascular metastases.

Magnetic Resonance Imaging

MRI is a highly sensitive and specific method in the diagnosis of hepatic hemangioma. Hemangiomas appear as smooth, lobulated, homogeneous, sometimes septated, hypointense lesions on T1-weighted images. On T2-weighted images, they appear highly hyperintense relative to the liver. When gadolinium is used as an intravenous contrast agent, hemangiomas enhance in a similar fashion to that seen on dynamic CT, although the enhancement pattern is more easily depicted on MRI (**Figure 18**). Lesions of less than 2 cm may show a homogeneous enhancement on early phase images that persist on delayed images and can sometimes be indistinguishable from other hypervascular lesions. The sensitivity of MRI for detection of hepatic hemangioma is 90% to 100% and the accuracy is higher than 90%.[16]

Large hemangiomas may show cystic areas on MRI or CT as a result of hemorrhage or myxomatous degeneration. Exceedingly slow blood flow through the lesion can favor sedimentation of blood cells with the development of internal fluid levels.[17,18]

Nuclear Imaging

Planar scintigraphic studies using Tc-99m labeled red blood cells have an adequate accuracy in diagnosis of hemangiomas larger than 2 cm.[19] The association of single-photon emission computerized tomography (SPECT) using Tc-99m pertechnetate-labeled RBCs is even more accurate. SPECT seems to be more specific than MRI, but less sensitive. This is particularly true for lesions near the heart or major blood vessels.[20]

Arteriography

The diagnostic accuracy of noninvasive tests has obviated the use of angiography in most cases. Hemangiomas have early opacification of irregular areas, with persistence of a dense and nodular pattern into the venous phase. Branches of the hepatic artery may be displaced and crowded together or stretched around the lesion, with normal vascular tapering.

Practical use of imaging studies

MRI with extracellular contrast agents is the most accurate radiologic study to establish the diagnosis of a small hepatic hemangioma.

Patients with a typical hemangioma on US and no history of liver disease or malignancy may repeat the US within three

to six months to assure stability. Otherwise a confirmatory test such as CT o r MRI should be performed.

The sonographic diagnosis of a probable hemangioma can be confirmed by MRI and/or nuclear medicine studies. MRI is the test of choice in most centers.

CEUS is gaining acceptance as an emerging method for diagnosis of hemangioma.

Imaging in patients with cirrhosis requires greater caution due to the higher probability of hepatocellular carcinoma (HCC). Hemangioma-like lesions seen on CT and/or SPECT on cirrhotic patients with normal alpha fetoprotein proved to be HCC on fine needle aspiration biopsy.[21] On this setting, MRI may be useful for better lesion characterization.

BIOPSY

Percutaneous biopsy of a hepatic hemangioma carries an increased risk of hemorrhage and should be avoided, specially in large superficial lesions.[22,23] Percutaneous or laparoscopic biopsy may be reasonable to perform in cases where a small liver lesion must be differentiated from HCC (radiologic studies and alpha fetoprotein testing equivocal). Whenever possible the needle should pass through liver parenchyma before sampling the target lesion to diminish the risk of bleeding.

MANAGEMENT

Most hepatic hemangiomas remain asymptomatic and do not require any kind of treatment. It is unclear if radiological follow-up is needed, even in patients exposed to estrogen overload or large tumors (greater than 10 cm). However, any patient known to have a hemangioma presenting with a new onset of abdominal pain requires a contemporary imaging study in order to exclude some sort of complication.[2,24]

Although rare, treatment of hepatic hemangioma may be required in: i) symptomatic patients, ii) rapidly growing tumors, iii) doubt regarding the possibility of malignancy, and iv) the presence of complications.[25,26]

Unfortunately, it is difficult to assure if the symptoms are truly caused by the hemangioma. Some authors have advocated resection for large (greater than 10 cm) asymptomatic lesions because of the potential risk of spontaneous rupture, intratumoral hemorrhage, or high-output congestive heart failure. Although, these complications are seldom reported in the literature and a recent retrospective study concluded that operative treatment should be reserved for patients with severe symptoms or complications of their disease.[27] This cohort, including 289 patients with hemangiomas greater than 4 cm demonstrated that 23% of the 233 patients in the non-operative group reported hemangioma-related symptoms, but life-threatening complications occurred in only 2%. On the other hand, 7% of the 56 patients submitted to surgery experienced life-threatening complications.

Whenever needed, the main treatment option for hepatic hemangiomas is surgical resection. Very selected cases might benefit from non-surgical therapies, such as arterial embolization, radiofrequency ablation, and hepatic irradiation. There are even few reports of ortothopic liver transplantation in very exceptional circumstances.

Spontaneous rupture of a hemangioma is a feared and potentially life-threatening event. The approach in this exceedingly rare situation is challenging. Immediate surgical resection is associated with a very high mortality rate. Thus, hemorrhagic shock and associated coagulopathy should be treated before definitive tumor resection. Techniques used to reduce bleeding allowing hemodynamic stabilization include control of the arterial hepatic inflow and can be obtained by radiology (percutaneous arterial embolization) or surgery (hepatic artery ligation).[6] In exceptional cases liver packing and damage control could be considered.

The Kasabach-Merritt syndrome is characterized by consumptive coagulopathy caused by the hemangioma. Thus, the treatment goals include: i) control of coagulopathy and thrombocytopenia, and ii) tumor resection. Surgery is often difficult, but resection of the tumor is the treatment of choice and usually curative.[28]

Surgical resection

Surgical resection of hemangioma can vary from enucleation to anatomical resection. The choice of the procedure relies mainly on the size and location of the lesion. Typically, surgical resection is performed using an open approach, but laparoscopic surgery can be used in selected cases and probably associated with less morbidity. For further reading on laparoscopic approach refer to **Chapter 27** (Principles of Laparoscopic Liver Resections). Seldom, surgical resection requires total hepatectomy followed by liver transplantation.[29,30]

Mortality rates for surgical resection can reach zero in large series. Morbidity rates are typically low and dependent of factors such as the extent of resection. The average length of hospital stay is shorter than one week.[31,32]

A useful maneuver to reduce intraoperative bleeding during definitive surgery of a large and/or ruptured hemangioma is to control blood tumor inflow before resection (hepatectomy or enucleation). This can be accomplished by preoperative percutaneous arterial embolization or intraoperative extrahepatic surgical ligation of feeding vessels as the first step of surgery.[6,33]

Arterial embolization.

Arterial embolization of hemangioma is a safe procedure resulting in shrinkage of the lesion, that continue until 12 months after the procedure. [34] It is performed percutaneously with embolization of hepatic artery branches done with polyvinyl alcohol, pingyangmycin-lipiodol emulsion, or other

substances.[34–36] Morbidity includes transient impairment of liver function, which recovers in 2-4 weeks, and abscess formation. Both are seen more frequently in case of large tumors. Also, pain, fever, and nongranulomatous arteritis with eosinophilic infiltration are recognized complications.

The use of arterial embolization as a sole treatment option is useful for patients carrying a prohibitive surgical risk (severe comorbidities, massive or diffuse nature of the lesion, and vicinity to some vascular structures). In a series of 98 patients submitted to arterial embolization of hepatic hemangiomas, Zeng et al.[34] reported relieve of symptoms in all the 53 symptomatic individuals. Although, long-term efficacy of isolated arterial embolization (without subsequent resection) has not been proved.

Other treatments

Alternative therapies can be used in very selected cases. Percutaneous or laparoscopic radiofrequency ablation has been reported to reduce the lesion size in selected symptomatic patients.[37–39]

Irresectable tumors can eventually be treated by hepatic radiation therapy (15-30 Gy over several weeks) resulting in symptom relief and lesion regression with minimal associated morbidity. [40,41] Its use in young patients is a matter of concern due to the increased risk of secondary malignancy development. Although, selected cases of Kasabach-Merritt syndrome in childhood might benefit from this approach.

It should be noted that currently there is no approved medical therapy to reduce the size of hepatic hemangiomas.

FOCAL NODULAR HYPERPLASIA

INTRODUCTION

Focal nodular hyperplasia (FNH) is found in up to 8% of the general population. Following hemangioma, FNH is the second most common benign solid hepatic tumor. FNH is 8 to 9 times more frequent in women than men. The majority of them are seen among 20 to 50 year-old individuals. [42] FNH comprises up to 2% of liver tumors in children.[43] Most frequently FNH is solitary (80 to 95%) and with less than 5 cm in size. Although, multiple lesions and larger than 10 cm may also occur.

It is accepted that FNH represents a hyperplastic or regenerative response to hyperperfusion, probably due to a vascular anomaly. In fact, an anomalous central artery is commonly identified.[42,44] The association with hereditary telangiectasia (Osler-Weber-Rendu disease) strengthens the hypothesis of a congenital vascular anomaly.

Histologically, all the regular components of the liver parenchyma are present but in an abnormal organized pattern. This might be useful for diagnostic purposes since Kupffer cells are not typically seen in certain tumors eventually misdiagnosed with FNH, such as hepatic adenoma and HCC. A characteristic finding on pathology, the central stellate scar, might be present along with an disproportionately large artery with multiple branches radiating to the periphery. Its margin is usually sharp without capsule and may eventually be pedunculated.

Most of FNH are asymptomatic and incidentally diagnosed. FNH rarely presents with acute onset of hemorrhage, necrosis, or infarction. Despite its little clinical significance, FNH must be differentiated from other lesions.

Malignant transformation of FNH has not yet been reported. However it may be misdiagnosed with fibrolamelar hepatocellular carcinoma as they may share some imaging and gross features. The differential diagnosis between FNH and adenoma may be also challenging.

DIAGNOSIS FEATURES

The main diagnostic feature of FNH is the demonstration of a central scar. Unfortunately, a typical central scar is not always present (it is absent in 20 to 50% of cases). Non-classical variants comprise up to 20% of FNH and they almost always lack the central scar. On the other hand, a central scar may be found in fibrolamellar hepatocellular carcinoma, hepatic adenoma, and intrahepatic cholangiocarcinoma. Also, hypervascular metastasis, hemangioma, and regenerative nodules in a cirrhotic liver, may mimic FNH on imaging studies.

The most common variant was the telangiectatic type (often present in multiple FNHs, and associate to obesity and hepatic steatosis). This variant is characterized by the absence of nodular architecture and the presence of plates of hepatocytes fed by anomalous arteries. The telangiectatic type carries a risk of bleeding similar to that observed in patients with a hepatic adenoma.[45] In fact, telangiectatic FNHs are nowadays classified as inflammatory hepatocellular adenomas, described below in this text. Some authors suggest even to ban this term.[46]

Biochemical liver tests are frequently within the normal range, although minor elevations can be seen. Alpha-fetoprotein is not elevated.

IMAGING

Ultrasonography

US findings usually rise suspicious for FNH diagnosis. US is particularly useful when combined with duplex Doppler (**Figure 6**), and may even preclude from additional tests. Doppler differentiation of the arterial or venous flow may distinguish FNH from hepatic adenoma. In the setting of malignancy additional imaging studies, such as CT, MRI,

angiography, and radionuclide imaging, are needed to improve the diagnostic yield. It is of note that only 1% of FNHs have calcifications.

On conventional US, FNH can appear as a hyper, hypo, or isoechoic lesion with a central scar identified in only 20% of cases. The use of contrast-enhanced ultrasonography (CEUS) improves characterization of focal liver lesions, and might be useful when FNH is suspected.

Computed Tomography

Dynamic CT with non-enhanced and enhanced phases may be highly suggestive of FNH when a central scar is seen (**Figure 21**). On non-enhanced CT scans, FNH may appear as an isodense or slightly hypodense mass. Typically, FNH becomes hyperdense compared to the surrounding liver in the arterial phase. In the portal venous phase FNH is less conspicuous and becomes isodense compared with the hepatic parenchyma and keeps this pattern in the delayed phase.

The stellate central scar is hypodense with a core and radiating fibrous septa and becomes hyperdense in the portal venous and/or delayed phases. Central scar is identified by CT in only 15 to 33% of patients. The central artery traversing the central scar may show early enhancement in the arterial phase.

CT features of FNH can mimic other benign and/or malignant lesions (**Figure 7**).

Magnetic Resonance Imaging

Since FNH has the same components found in normal liver, its enhancement patterns on MRI are similar to those seen on CT. Typical FNH is isointense on T1-weighted images, and isointense or slightly hyperintense on T2-weighted images. Central stellate scar is more commonly seen on MRI and it is typically hyperintense on T2-weighted due to vessels or edema. The dynamic seen after gadolinium infusion is similar to that observed on enhanced-CT (**Figure 22**).

MRI with liver-specific contrast agent has higher sensitivity (97%) and specificity (100%) than US or CT for the diagnosis of FNH (**Figure 23**).[47] The use of gadolinium-based liver-specific contrast agents (Gd-BOPTA and Gd-EOB-DTPA), with both dynamic and hepatobiliary studies, increases the accuracy of MRI by providing functional and morphological features on FNH. Most nodules appear iso-hyperintense to the liver on hepatobiliary phase and central scar become hypointense due to lack of hepatocytes. The central scar is even more commonly seen on hepatobiliary phase.[48]

In most cases MRI can differentiate hypervascular liver lesions. However, false-positive diagnosis of FNH may occur with HCC (fibrolamellar and other well-differentiated forms), adenoma, and hypervascular metastases.

Nuclear Imaging

The detection of FNH using radionuclide scans with technetium-99m sulfur colloid depends on the burden of Kupffer cells in the lesion. As the concentration of these cells in FNH is not uniform, the uptake of technetium sulfur colloid is variable. On the other hand, hepatic adenomas will occasionally harbor Kupffer cells. Thus, in many centers, nuclear imaging has been largely replaced by Gd-BOPTA-enhanced MRI or dynamic multi-phase CT.

Angiography

Angiography has a little role in the diagnosis of FNH. The typical spokelike appearance (a dilated main feeding artery perforating the center of the tumor and peripheral arteries branching from it) is seen in only a third of cases. Up to 10% of FNHs are avascular. Vascularity may be decreased within the central stellate scar. Characterization of small FNHs is even more difficult. In small lesions, the supplying arteries break up into small branches, which appear to permeate the tumor, and form a reticular pattern.

LIVER BIOPSY

Findings on needle biopsy may substantially overlap those of well-differentiated HCC. Thus, open biopsy or surgical resection might be recommended when the imaging diagnosis is not clear.

MANAGEMENT

Since FNH is not associated with malignant potential and very few cases of complications have been reported, these lesions almost always do not require any intervention.[50] FNHs generally remain stable in size, although they can occasionally become smaller or bigger over time.

The uncommon symptomatic FNH should be treated by resection. Also, surgical resection or open biopsy should be considered for patients with unclear diagnosis.

Despite an inconsistent association, estrogen overload has been linked to FNH enlargement. Thus, it is reasonable to discourage the use of oral contraceptives and/or perform a follow-up examination every 6 to 12 months. Regarding pregnancy, small FNHs do not appear to pose any significant threat but close observation is strongly advised. It is wise to treat large lesions (more than 8 cm) with resection before pregnancy.

HEPATOCELLULAR HEPATIC ADENOMA

INTRODUCTION

Hepatocellular adenoma (HCA) is an uncommon benign hepatocellular neoplasm of presumable epithelial monoclonal

origin. Kupffer cells, whenever present, are reduced in number and usually nonfunctional. Despite its low frequency (approximately 0.004% of the general population) HCA represents the third most common benign focal hepatic lesion and the second most common benign hepatocellular neoplasm, after FNH. The risks of bleeding and malignant transformation reinforce its clinical importance. Overall, up to 30% of HCAs may bleed and almost 10% undergo malignant transformation.[45] Symptoms, specially right upper quadrant discomfort, may be present in up to 50% of patients with HCAs.[51]

Most HCAs are solitary and non-encapsulated, with size ranging from less than 1 cm to more than 20 cm.

There is a strong association between HCAs and estrogen overload (such as oral contraceptives and pregnancy). They occur mostly in women (female:male ratio 8-10:1) of childbearing age and are rarely seen in adult men and children.[52,53] Most of patients with HCA (85 to 95%) have used oral contraceptives (OCs) for more than 2 years.[54,55]

Oral contraceptives containing a high dose of estrogen, and even those with a low dose, especially when used for a long time, increase the risk of HCA.[56] According to Rooks et al.[57] the annual incidence of HCA among women who had never used OCs was 1.3 per million, while among long-term users of OCs this rate was much higher (34 per million). Also, HCAs are more numerous, larger, and more likely to bleed in patients who take OCs.[58–60] Despite HCAs can eventually be diagnosed after previous exposure to OCs, its discontinuation can lead to HCA regression.[61] During pregnancy HCAs can grow remarkably, increasing the risk of rupture and/or hemorrhage, and posing a threat for the mother and the fetus.[62]

HCAs are more frequent among patients with metabolic liver diseases, such as glycogen storage disease (GSD), tyrosinemia, galactosemia, steatohepatitis, and hemochromatosis.[63,64]Also, anabolic androgen steroid intake and familial adenomatous polyposis are associated to HCA.[65–68]

Actually, genetic studies indicate that HCAs comprise a group of tumors with specific pathologic abnormalities and biology. Therefore, HCAs are currently categorized into four distinct genetic and pathologic subtypes: i) inflammatory HCA, ii) hepatocyte nuclear factor 1 alpha (HNF-1α) HCA, iii) β-catenin-mutate HCA, and iv) unclassified HCA.[69,70]

Inflammatory HCA (I-HCA)

I-HCA represents 40 to 50% of all HCAs. They are seen predominantly in women, in association with obesity, alcohol use, and hepatic steatosis. Most of patients with this subtype have used OCs.[66]

Symptomatic individuals can present with a clinical systemic inflammatory syndrome (fever, leukocytosis, and elevated serum C-reactive protein levels), anemia or nephrotic syndrome. [71]The serum level of gama-glutamyl transferase may be elevated. Characteristic imaging is of a hypervascular hepatic mass with persistent enhancement in the portal venous and delayed phases. They are markedly hyperintense on T2-weighted images (corresponding to areas of sinusoidal dilatation). On CEUS, I-HCAs show arterial hypervascularity with centripetal filling and peripheral rim of sustained enhancement with delayed central washout. Many of these HCAs were misclassified as "telangiectatic focal nodular hyperplasia" in the past.

Inflammatory HCAs carry a definite increased risk of bleeding (up to 30%) and a risk of malignant transformation (5 to 10%).[65,72,73]

HNF1α inactivated HCA (HNF-HCA)

Hepatocyte nuclear factor-1 alpha (HNF1α) mutated HCA subtype represents 35 to 50% of HCAs. They occur exclusively in women and most of them have a history of OC use. HNF-HCA can also be associated with familial adenomatosis and maturity onset diabetes of the young type 3 (MODY3). Familial cases of adenomatosis can also occur in HNF-HCA. [74,75] They are characterized by diffuse intralesional steatosis (due to suppression of gluconeogenesis, activation of glycolysis, and promotion of fatty acid biosyntesis secondary to hepatocyte nuclear factor-1-alpha mutation). Thus, HNF-HCA may appear as a liver mass containing fat, which is better characterized on MRI than on CT. On CEUS, HNF-HCA is homogenously hyperechoic with mild to moderate arterial hypervascularity and becomes isoechoic on the portal venous phase.[65]

HNF-HCA may be multiple in up to 50% of cases.[65] It carries a low risk of bleeding, but there is no risk of malignant transformation.

β-catenin mutated HCA.

This subtype of HCAs (10 to 18% of all HCAs) originates from sustained activation of beta-catenin due to a gene mutation. Beta-catenin plays a major role in hepatocyte development, differentiation, zonation, proliferation, and regeneration. This aberrant activation is also seen in HCCs and hepatoblastomas. β-catenin mutated HCAs affect primarily male patients with glycogen storage disease and those individuals on androgen treatment. Up to 75% of patients with glycogen storage disease (type IA, II, IV and VI) may develop HCAs.[76]

HCAs with beta-catenin mutations may appear as homogeneous or heterogeneous hypervascular tumors that lack intralesional fat. Intense arterial enhancement may persist in delayed phases of dynamic CT and MRI. The presence of arterial enhancement and washout can simulate a HCC.

β-catenin mutated HCAs have a greater propensity than other subtypes to undergo malignant transformation (hepatocellular carcinoma): 5% to 10%.[51,52,77] In fact, 20 to 30% of malignant HCAs show beta-catenin mutations.[51,76,78]

Unclassified Adenomas

About 10% of all HCA do not have known genetic alterations or specific histological phenotype to be classified as I-HCA, HNF-HCA, or β-catenin mutated HCA.

The clinical impact of this histologic classification needs to be validated. Despite being the main feature of a subtype (β-catenin mutated HCA) the β-catenin mutation can also be found in 10% of I-HCAs. This predisposing condition to malignant degeneration is not present in HNF-HCAs. In the near future the typical radiological findings might define the approach for low and high-risk lesions of malignant transformation. Current evidence suggests that MRI and CEUS will be used with a high predictive value in subtype stratification of HCAs.[79,80]

HEPATIC ADENOMATOSIS

Hepatic adenomatosis (HA) is defined as the presence of more than 10 adenomas in the absence of classic risk factors for HCA (such as estrogen overload) in an otherwise normal liver. Patients with glycogen storage disease are excluded from this definition. Hepatic adenomatosis is very uncommon and affect equally men and women.[81]

HA is characterized by the development multiple HNF-HCA or I-HCA. These individuals should be submitted to periodical screening for early detection of diabetes. The mutation of the gene Hepatocyte Nuclear Factor 1-alpha (HNF 1-alpha), found in half of patients with HA, is associated with the development of maturity onset diabetes of the young type 3 (MODY3).

Differential diagnosis includes other multiples hypervascular tumors, such as multifocal HCC, FNH, or metastases. CT and MRI features can strongly suggest the diagnosis of adenomatosis.[82]

The rates of complications (bleeding and degeneration) for each individual lesion in adenomatosis are similar to those found on solitary HCAs. Therefore, the therapeutic approach should be based on the assessment of each nodule, considering its subtype and size, rather than the total number of hepatic lesions. [83] Currently, some authors suggest do not consider hepatic adenomatosis as a specific entity, and the term should mean many HCAs (more than 10).[9,65]

As for solitary HCA, resection is recommended for lesions greater than 4-5cm. Liver transplantation can eventually be needed in case of malignant degeneration, progressive liver failure, or unresectable disease.

CLINICAL FEATURES

Most of hepatic adenomas are asymptomatic and found incidentally during an abdominal imaging study for an unrelated reason. Although there is a clear distinction among the histological subtypes, they are not used yet to define the clinical approach. Pain and bleeding are the most common symptoms. Although rare, mass effect can be responsible for symptoms, such as early satiety and abdominal bloating.

Pain and bleeding

In general, right upper quadrant pain is present in 20-25% of cases and associated to hemorrhage in 30-40% of them. In this subset of patients hemorrhage is intralesional in one third and subcapsular or intraperitoneal in two third of cases. Bleeding into the lesion does not represent a life-threatening event in most of cases, however subcapsular and intraperitoneal haemorrhages need immediate evaluation and treatment to avoid fatal complications. The global risk of bleeding from HCA is likely to be between 20% and 40%.[84]

The risk of relevant clinical hemorrhage increases in adenomas larger than 4-5 cm and during pregnancy, but massive bleeding from lesions of only 3.5cm had already been reported. Every patient known to have HCA should undergo a new imaging examination in case of new setting of abdominal pain or clinical signs of hypovolemia. Also, evidence of minimal silent intratumoral bleeding is often present. Lesions near the surface of the liver are more prone to cause hemoperitoneum. In a systematic review including a total of 1176 patients, the overall frequency of hemorrhage was 27.2% (15.8% of all lesions). Rupture with intraperitoneal bleeding was reported in 17.5% of patients. [85] Rupture and acute bleeding of a previously unknown adenoma can occur at 10-30% of cases and is associated with a mortality of up to 8%. [86]In case of intraperitoneal bleeding leading to shock a mortality rate of 25 to 30% can be expected. Adenoma rupture during pregnancy is associated with high rates of maternal and fetal mortality.[87–89]

Malignant transformation

The estimated global risk of malignant transformation is 4% to 10%.[90,91]This risk is not completely understood, but it is enhanced in patients with male hormone use, familial polyposis, and β-catenin mutated subtype of HCA.[87]

Large lesions (greater than 5 cm), even in asymptomatic patients, carry an increased risk of complications (bleeding and malignancy).

IMAGING

The imaging methods with the best yield for HCA diagnosis are MRI and CEUS (**Figure 26**). It is difficult to describe typical radiological findings as the imaging features of HCAs vary on the basis of associated complications and pathologic subtype.

The absence of Kupffer cells may be a hint for the HCA diagnosis. HCAs usually have large blood vessels on

the surface and a fibrous capsule may be present or not. The capsule absence may predispose to intrahepatic or extrahepatic hemorrhage. Necrosis may be seen in lesions that outgrow their arterial blood supply.

The subtype classification can be suggested by MRI and CEUS. HNF-HCAs are typically associated to diffuse fat distribution (intralesional steatosis) and I-HCAs present sinusoidal dilatation.[80,92]

The similar patterns of enhancement can become a real challenge in the differentiation of HCA from FNH and well-differentiated HCC. The typical findings of an uncomplicated HCA (isointense or isodense lesion, with homogeneous enhancement at the arterial phase and becoming isointense or isodense at the portal venous phase) can be seen also in FNH and well-differentiated HCC. Imaging is useful to identify high-risk lesions, such as HCA that are large, peripheral on the liver, and without lipid content. It is of note that more than one type of HCA can be present in the same patient.

Magnetic Resonance Imaging (MRI)

The use of gadolinium-based liver-specific contrast agents (Gd-BOPTA and Gd-EOB-DTPA) in MRI facilitates the differentiation of HCA and FNH (sensitivity of 92% and specificity of 91%).[93] However, the differentiation from well differentiated HCC may be problematic in some cases.

The MRI is able to identify steatotic and hemorrhagic components in the lesions. The aspect of HCAs on MRI is heterogeneous, but some patterns are useful to characterize the main subtypes of HCAs.

The most common subtype of HCA is the inflammatory, characterized by intense plymorphous inflammatory infiltrates, marked sinusoidal dilatation or congestion, and thick-walled arteries. They appear at MRI as lesions diffusely hyperintense on T2-weighted images, with a higher signal intensity in the periphery of the lesion (correlating with dilated sinusoids). These lesions are isointense or mildly hyperintense on T1-weighted images. There is an intense enhancement during the arterial phase after administration of gadolinium, which persists in the portal venous and delayed phases.[69,80,94] These findings provide a sensitivity of 85% and a specificity of 87% for I-HCA.

The HNF-HCA subtype is predominantly hyper- or isointense on T1-weighted images, with diffuse signal drop-off with use of a chemical shift sequence, due to the intracellular steatosis.[69] Also, the hepatic parenchyma commonly presents steatosis. HNF-HCAs appear isointense to slightly hyperintense on T2-weighted images. After gadolinium injection moderate enhancement occurs in the arterial phase, with no persistent enhancement in the portal venous and delayed phases (sensitivity 86% and specificity 100%).[69,80]

Notably, b-catenin-HCAs have no specific MRI pattern. They show homogeneous or heterogeneous hyperintensity on T1- and T2-weighted images, according to the presence of hemorrhage and/or necrosis.

No specific image patterns are identified on unclassified HCAs.

MRI characteristics according to HCA subtype are depicted in **Table 2**.

HCAs with hemorrhage may have hyperintense T1-weighted imaging with subcapsular hemosiderin rings in 30% of patients.

Non-Contrast-Enhanced Ultrasonography

Regular ultrasonography has no specific findings for HCA. The lesions may be hypoechoic, isoechoic, or hyperechoic relative to liver parenchyma. Doppler flow patterns in HCAs are venous, as compared to the arterial pattern noted in FNH.

Contrast-Enhanced Ultrasonograhy (CEUS)

The main subtypes of HCAs (I-HCA and HNF-HCA) have typical CEUS patterns.

I-HCAs show arterial hypervascularity with centripetal filling, a peripheral rim of sustained enhancement, linear vascularities, and central washout in the late venous phase. These findings provide a sensitivity of 64% and specificity of 100% for diagnosis of I-HCA.[95,96]

The CEUS aspects of HNF-HCAs are of homogeneous hyperechoic lesions with isovascularity or moderate hypervascularity with mixed filling in the arterial phase,

Table 2. MRI features of subtypes of hepatocellular adenoma. (Modified from Katabathina et al.[69])

Subtype	T1-weighted Gradient-Echo	T2-weighted	Gadolinium-enhanced T1-weighted
Inflammatory	Isointense or mildly hyperintense, without signal loss on chemical shift imaging	Diffusely hyperintense	Intense enhancement during arterial phase that persists in the portal venous and delayed phases
HNF-1α-mutated	Hyper- or isointense, with diffuse signal loss on chemical shift imaging	Isointense to slightly hyperintense	Moderate enhancement in the arterial phase, with no persistence enhancement in the portal venous and delayed phases
β-Catenin-mutated	No specific MRI patterns; may mimic HCC (strong enhancement during arterial phase, with portal venous washout)		

MRI: Magnetic Resonance Imaging; HCC: Hepatocellular carcinoma.

and isoechogenicity in the portal and late portal venous phases. The homogeneous hyperechogenicity correlates with diffuse fat infiltration and provide a sensitivity of 88% and specifity of 91% for diagnosis HNF-HCA. This pattern may be misdiagnosed with hemangioma.[95]

Like in MRI, b-catenin-HCAs and unclassified HCAs have no specific patterns on CEUS.

Computed Tomography (CT)

Most HCAs are encapsulated on CT scan. The lesions can have a central necrotic area or calcifications.

Non-enhanced CT images generally show HCAs as well-circumscribed isodense or hypodense lesions. After contrast injection a heterogeneous or centripetal pattern of enhancement is seen on arterial phase, and the lesions become iso- or hypodense on portal venous and delayed phases.

The CT scan is not useful to distinguish the HCAs subtypes.

Nuclear Imaging

Nuclear imaging can be useful to differentiate HCA from FNH and HCC. Typically, HCAs and HCCs appear as defects on sulfur-colloid scans, due to their low content or absence of Kupffer cells. With the use of hepatobiliary radiotracers, HCAs can be distinguished from HCC as they appear hot on early and delayed images. For differentiation between HCA and FNH, nuclear imaging has been replaced by MRI with liver-specific contrast agents.

Angiography

Currently, angiography does not have a significant role in the diagnostic workup of HCA.

BIOPSY

HCAs are a mass of normal-appearing hepatocytes and the conventional histologic evaluation has a low yield for its diagnosis. However, immunohistochemistry testing can be helpful not only to differentiate HCAs from other lesions, but also to identify its subtypes. In fact, the immunohistochemistry results can guide the approach of HCAs.

In selected cases resection may be required as the most specific way to confirm diagnosis.

OTHER TESTS

Liver function tests are typically normal. However, serum aminotransferase, alkaline phosphatase, and gamma-glutamyl transferase levels can be mildly elevated in multiple adenomas. These findings can also be observed when intratumoral bleeding and/or a mass effect are present. Tumor markers, such as alpha-fetoprotein, are within the normal range.

MANAGEMENT

Regardless of the management strategy, in all cases of HCAs the offending drugs (such as oral contraceptive pills and androgens) should be stopped whenever possible. Although complete resolution is atypical, this allows regression in the size of the majority of the tumors. However, the risk of malignant transformation remains even after the contraceptive or steroid use has been discontinued.[52,97]

The approach of HCAs should be based on the presence of symptoms and the risk of complications (bleeding and malignant degeneration). In case of more than one lesion, the characteristics of each individual HCA, rather than the total number of lesions, should guide the therapeutic approach.

Asymptomatic HCA

Most HCAs are incidental findings in asymptomatic patients. These individuals can be managed according to the algorithm in **Figure 1**.

Size greater than 5 cm is associated with a high risk of bleeding and malignant transformation.[52,65] Also, men and patients with glycogen storage disease (GSD) have a higher risk of malignant degeneration (up to half of HCAs in men and ¾ of HCAs in patients with GSD).

Thus, all HCAs occurring in men and those greater 5 cm, irrespective of gender, should be treated by surgical resection.[52,65,98]

An individualized approach of HCAs with less than 5 cm in females is based on its subtypes. The imaging features

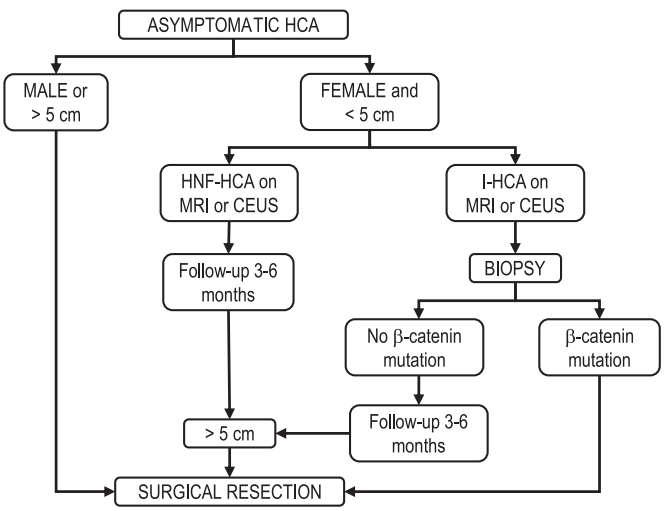

Figure 1. Individualized approach to asymptomatic hepatocellular adenoma. HCA: Hepatocellular adenoma; HNF-HCA: Hepatocyte nuclear factor-1 alpha mutated HCA; I-HCA: inflammatory HCA; MRI: magnetic resonance imaging; CEUS: contrast-enhanced ultrasonography. (Note: if biopsy or immunohistochemistry is unavailable HCAs with less than 5 cm in females should be followed and surgical resection considered for growing lesions – see the main text).

in this population can suggest the subtype and guide the need of a biopsy. HNF-HCAs on MRI or CEUS carry a very low risk of b-catenin mutation and can be precluded from biopsy.[52,77,86]

On the other hand, I-HCAs on imaging should be biopsied to explore the risk of malignant degeneration. All HCAs with evidence of b-catenin activation should be resected due to the risk of malignant degeneration. HCAs with no evidence of b-catenin mutation can be followed with regular year imaging (MRI) examination until menopause, at least.

The individualized approach of HCAs according to their subtypes relies on imaging technics and sophisticated immunohistochemistry analysis of tumor samples. However, tumor biopsy carries risks such as tumor rupture/seeding, hemorrhage, and sampling errors. Also, the lack of widespread adequate immunohistochemistry and the occasional difficulties on differential diagnosis with core biopsy limit the clinical application of biopsy-based approach.

For those centers where biopsy and/or immunochemistry are not available, the traditional approach should still be used. In this setting HCAs with less than 5 cm in asymptomatic females should be followed after stopping offending drugs.

It is judicious to treat lesions diagnosed as HCAs in patients with elevated alpha-fetoprotein irrespective of size and/or symptoms.

HCA and pregnancy

The estrogen overload during pregnancy represents an increased risk of HCA growth and bleeding. Thus, the management of HCAs in women of childbearing age requires particular attention.

The natural history of HCAs during pregnancy and labor is poorly understood due to the rarity of the situation. Prognostic factors on rupture and malignant degeneration during pregnancy remain unknown. The traditional management guidelines have been based on case reports and/or retrospective small case series, most of them of complicated patients.

Lesions greater than 5 cm, as for non-pregnant women, should be treated before pregnancy, with resection whenever possible or other less invasive techniques (rafiofrequency ablation, arterial embolization). However, the management of small HCAs during pregnancy remains controversial. Current data suggest that it is acceptable to observe lesions of up to 4-5cm. In a recent prospective series of 17 pregnancies (12 patients) only 5 of more than 30 HCAs grew during pregnancy. Thus, pregnancy should not be completely discouraged to all women with small HCAs, as long as the risks are discussed with the patient and close follow-up performed (imaging every 6 weeks). It seems reasonable to treat only growing lesions that reach over 5 cm. Although elective surgical treatment of benign liver tumors carries a low morbidity and mortality risk in non-pregnant women, non-urgent surgical procedures in pregnant ones, especially during the second trimester, seem to be safe with laparoscopy being an important emerging tool. Other options in case of growing HCA include radiofrequency ablation, cesarean section, and arterial embolization. Treatment options should be tailored according to gestational age and risks related to radiation exposure.

Rupture and bleeding of an HCA during pregnancy is a life-threatening situation for both, the mother and fetus. Rupture occurring during pregnancy should be managed as in non-pregnant patients.

HCA and hemorrhage

Hemorrhage associated with HCAs may be limited to the tumor (intralesional bleeding) or not (subcapsular hematoma and/or hemoperitoneum). Diagnosis of bleeding is easily confirmed by abdominal imaging methods. Although rare, HCA rupture with hemodynamic instability might occur. All patients with HCAs who present with abdominal pain and/or signs of bleeding must undergo immediate imaging assessment.

The **intratumoral bleeding** is more common and generally does not need immediate procedures. Symptomatic patients should be given analgesics and observed. In the absence of pain relief a new imaging study should be performed.

Tumoral rupture can result in **subcapsular hematoma and/or hemoperitoneum.** These are life-threatening situations requiring immediate management.

The initial approach includes the assessment of hemodynamic stability and ordinary resuscitation management. Patients with hemodynamic instability require an immediate procedure to stop the bleeding. Whenever possible, selective arterial hepatic embolization should be the procedure of choice in this setting.[99–101] In case of failure or unavailability of arterial embolization urgent laparotomy should be performed.[102] Indeed, even patients without hemodynamic instability will benefit from selective arterial hepatic embolization to stop or limit the bleeding and to reduce the tumor mass. Occasionally, patients with no signs of shock and/or active bleeding can be managed without arterial embolization during the acute phase with rest and observation.

Elective surgical resection is the definitive treatment of choice for ruptured adenomas. The reabsortion of the hemoperitoneum and/or hematoma, generally 4-6 weeks after the acute event, allows a safer and more limited hepatic resection.[65,101] Lately, some authors have favored a non-surgical approach after a successful embolization resulting

in small tumor size (less than 5 cm).[99] Patients with high-surgical risk can be managed with transarterial embolization or radiofrequency ablation.

Summary

In summary, surgical resection of HCA is warranted in the following cases: i) male gender, ii) lesions greater than 5 cm, iii) growing tumors, iv) b-catenin mutated adenomas and, v) elevated serum AFP.[25,73,103]

TREATMENT OPTIONS

Usual therapeutic procedures for HCAs include surgical resection, local ablation, and arterial embolization.

Surgical resection

Surgical resection is the definitive treatment of choice for HCAs. Complete tumor clearance of the target lesions abolishes the risk of bleeding and malignant degeneration. Once an HCA is completely resected, the rare event of recurrence is associated with lesions that had already degenerated.[104] After a first resection of HCA up to 25% of patients require another surgery due to another lesion.[91,105]

Limited segmental hepatic resection is enough in most of cases. Major liver resections can be needed in case of large and/or central lesions. Elective resection of benign tumors carries a low morbidity (approximately 13%) and mortality (less than 1%). [91,105]On the other hand, in case an emergency hepatic resection is performed, the mortality rate is exceedingly high (5-25%). [103,106,107]

Feasibility of laparoscopic approach for benign liver tumors has already been shown. The preference of open or laparoscopic procedures should be based on localization and size of the tumor as well as the team expertise. For further details refer to **Chapter 27** (*Principles of Laparoscopic Liver Resections*).

Seldom, liver transplantation has been described as an alternative for the treatment of patients with multiple adenomas and glycogen storage disease.[81,108]

Emerging approaches

Less invasive emerging approaches for the treatment of HCAs include selective arterial embolization and local ablation by radiofrequency.

Selective arterial embolization is the treatment of choice for the management of acute bleeding. Outside the emergency setting, selective arterial embolization has been proposed for the management of multiple HCAs not amenable to surgical resection, poor surgical candidates, and for reduction of tumor volume. Although selective arterial embolization can be used as a sole treatment it is unknown if the reduction of the size of the lesion represents a truly reduction in the risk of malignant degeneration.

Local radiofrequency ablation seems to be efficient for the treatment of small lesions. Large tumors can be treated with multiple ablations or after size reduction by previous selective arterial embolization.[109] Long-term results are still lacking, but it is reasonable to consider this less invasive approach for poor surgical candidates or those that would require a major liver resection.

FOLLOW-UP

Despite the lack of evidence, all patients with diagnosis of HCA and lesions left in situ should undergo regular follow-up. There are no clear guidelines for the optimal interval, duration and screening methods, but it is suggested yearly imaging (US or MRI) and assessment of alfa-feto-protein until menopause, at least. It is also reasonable to follow patients that underwent surgical resection of HCA due to the risk of de novo lesions in up to 25% of patients.[51,65,109–111]

OTHER SOLID BENIGN TUMORS

Among the less common solid benign tumors and pseudotumors of the liver are included the inflammatory pseudotumor, the lipomatous tumors, and the nodular regenerative hyperplasia. Other rare benign tumors will not be discussed here.

INFLAMATORY PSEUDOTUMOR

Inflammatory pseudotumor of the liver is a localized mass of proliferating fibrovascular tissue infiltrated by inflammatory cells.[112,113] It represents a chronic inflammatory lesion of uncertain histogenesis and may be secondary to portal phlebitis, such as originated from recurrent cholangitis.[114] Inflammatory pseudotumor is a benign lesion and can present spontaneous regression, but usually mimic other hepatic tumors on imaging.[115–117]

LIPOMATOUS TUMORS

Lipomatous tumors of the liver, such as lipoma, hibernoma, angiolipoma, myelolipoma, angiomyelolipoma, angiomyolipoma, angiomyomyelolipoma, present different elements in variable proportions.[118] The variability of the different tissue components rend radiological images heterogeneous. In fact, the heterogeneity of these tumors makes difficult the diagnosis even by needle biopsy. MRI is the most specific radiological method for the detection of lipomatous component. However, the definitive diagnostic is the histopathologic study, associate to immunohistochemical markers,

of the resected specimen.[119]

Despite most of **angiomyolipomas** are asymptomatic and found incidentally; some of them may reach a large size and cause symptoms. Abdominal discomfort, nausea, hepatomegaly, and even Budd-Chiari syndrome were reported.[120] The combined study of dynamic CT, MRI and contrast-enhanced US allows for the detection of a vascular pattern with a prominent efferent tumor vein. [119,121,122] The specificity of this vascular pattern, however, has not been documented yet. Asymptomatic angiomyolipomas no need treatment and should be monitored on regular basis, since rupture or malignant transformation are exceeding rare.

Epithelioid angiomyolipoma is a mixed mesenchymal tumor that usually occurs in the kidney.[123] It is characterized by a triad of tortuous, thick-walled blood vessels, smooth muscle cells, and adipose tissue in varying proportions.[118] Most of angiomyolipomas has no propensity for metastasis or malignant potential. Multiple hepatic angiomyolipomas are found in patients with tuberous sclerosis and particularly in those with multiple renal angiomyolipomas.[124]

NODULAR REGENERATIVE HYPERPLASIA

Nodular regenerative hyperplasia is characterized by diffuse hyperplastic nodules composed of cells resembling normal hepatocytes, without fibrosis around the nodules. Nodular regenerative hyperplasia is of uncertain etiology and represents a regenerative hepatocellular activity. Nodular regenerative hyperplasia is usually associated with organ transplantation myeloproliferative or lymphoproliferative diseases, or autoimmune processes, and lesions usually enhance similar to the liver parenchyma on radiological studies. Computed tomography and MRI can show multiples nodules mimicking metastatic disease or cirrhosis. It can present with portal hypertension.[125,126] This condition should be differentiating from large **regenerative nodules**, which are often associated with Budd-Chiari syndrome and result in contrast enhancing liver lesions. Regenerative nodules do not present fibrosis between the nodules.[127,128]

SUMMARY

In fact, the main clinical challenge during evaluation of a hepatic focal lesion is the exclusion of a primary hepatic or a metastatic malignancy. Efforts should be directed to obtain preoperative diagnosis based on imaging and/or needle biopsy, with special immunohistochemical markers when necessary. If definitive diagnosis is not established, the approach should be based on the clinical scenario additionally to radiological features, that even when not diagnostic, a stratification risk of worrisome may be possible. Approach to incidental hepatic lesions is suggested below.

HEPATIC INCIDENTALOMA

INTRODUCTION

Hepatic incidentaloma refers to asymptomatic hepatic lesions identified incidentally. Hepatic incidentalomas (HI) are most commonly detected during radiological investigations for other pathologies although eventually they may be identified during a laparotomy or laparoscopy. HI are identified on up to 15% of radiological studies and most of them are non-threatening benign lesions, however some of them will require additional evaluation, follow-up, or even treatment. Indeed, approximately 10% of HI are malignant lesions. Workup of HI can be challenging since additional studies or procedures may lead to unnecessary costs and risks, and even be misleading.[129–132]

MANAGEMENT

The approach of HI aims to identify significant lesions, i.e. malignant tumors or benign lesions with potential for complications (mainly bleeding and malignant degeneration). There are no evidence-based guidelines regarding the best approach to HI. However, it is usually possible distinguish hepatic incidental lesions with no clinical meaning from those that require a specific treatment or follow-up. The clinical scenario, including anamnesis, physical examination, simple laboratory tests, review of imaging already performed, and selective use of further imaging are the basis for the management of HI.

Thus, the initial approach should be based on the clinical scenario, the imaging modality performed, and the lesion features.

The clinical scenario

Patients can be stratified according to the presence of known risk factors for potentially significant lesions. Mainly, hepatocellular carcinoma, liver metastasis, and adenoma have well-known risk factors. Thus, three groups can be depicted: i) **high-risk group** includes patients with a known malignancy with a propensity to metastasize to the liver (including gastrointestinal and breast tumors, and melanoma), cirrhosis of any etiology, or other hepatic risk factors (chronic viral hepatitis, autoimmune hepatitis, sclerosing cholangitis, hemochromatosis, hemosiderosis, hepatic dysfunction, long-term oral contraceptive or anabolic steroid use); ii) **moderate-risk group** comprises patients older than 40 years of age without known malignancy and no hepatic risk factors; and iii) **low-risk group** includes young patients (<40 years-old), with no malignancies or other hepatic risk factors.[133]

Tests that might be useful for the inclusion of a patient into one of the three groups include liver function tests, serum ferritin, serological tumor markers (CEA, alpha-fetoprotein, CA19.9) and serological markers of viral hepatitis and autoimmune hepatitis. In a similar way, radiological signs of chronic underlying liver disease can be informative. Other tests, such as upper endoscopy, colonoscopy, mammography, and chest imaging, should be used very selectively when a liver metastasis is suspected in a patient without known malignancy.

IMAGING MODALITIES AND LESION FEATURES

Hepatic incidentaloma may be detected on different imaging methods, most frequently US, CT and MRI. The first imaging examination is commonly enough for adequate characterization of the lesion and for definition of the clinical significance or even of the definitive diagnosis of a HI.

An algorithm based on the imaging modality that detected the incidental lesion and the lesion features is summarized on **Figure 2** and discussed below.

PROPOSED ALGORITHM TO APPROACH OF HI

The algorithm represented on **Figure 2** is based on imaging modalities and lesions features. Numbers cited on specific items of the flowchart are used to locate the respective discussion of these items in the text below.

The outcomes of this approach include no-need of further evaluation (discharge), follow-up imaging, or additional evaluation. Treatment and follow-up according to specific diagnosis are discussed in other chapters of this textbook.

HI on ultrasonography (US)

Hepatic incidentalomas are frequently found on US. This method is useful to distinguish cystic ① from solid ② lesions.

Cystic lesions ① can be classified as simple or complexes. Simple cyst ③ (**Figure 3**) is sharply delimited, anechoic, homogeneous, with posterior reinforcement, and with no vascular flow with Doppler US. A complex cyst ④ (**Figure 4**) is characterized by the absence of simple cyst features, presence of septae, mural nodules, heterogeneous content, or solid component.

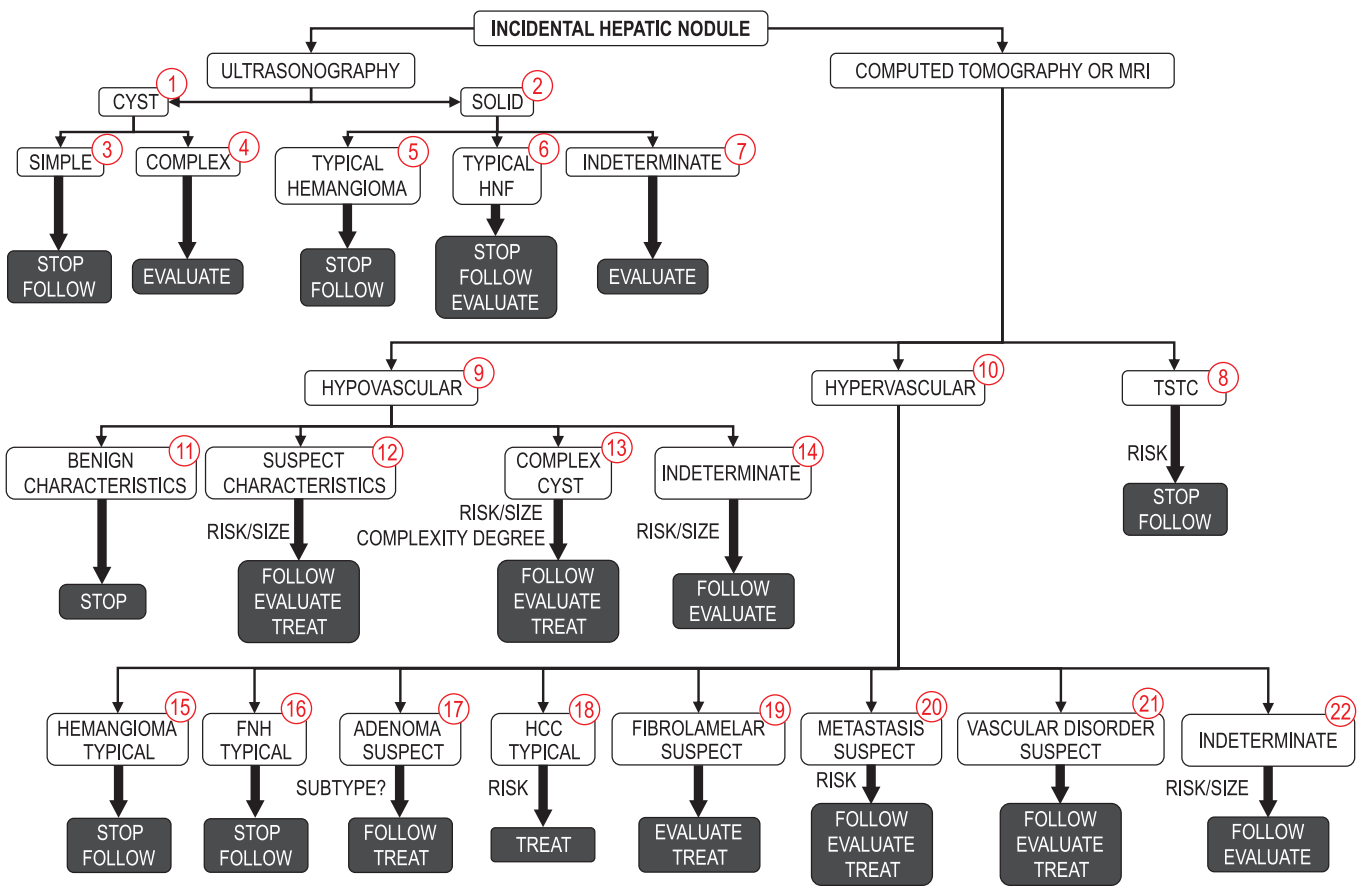

Figure 2. Approach to hepatic incidentaloma according to imaging features. Numbers are used to locate details on the main text. MRI: Magnetic resonance imaging; TSTC: to small to characterize; FNH: Focal nodular hyperplasia; HCC: hepatocellular carcinoma.

Solid lesions ② may be ultrasonographically characterized as typical for hemangioma, typical for focal nodular hyperplasia (FNH), or indeterminate. Typical hemangioma ⑤ (**Figure 5**) is sharply delimited, homogeneous, hyperechogenic, with posterior acoustic reinforcement, and no signs with Doppler US. Typical features of a FNH ⑥ (**Figure 6**) are a homogeneous nodule, with variable echogenicity, with no hypoechogenic halo (capsule), with a central scar that may be hyper- or hypoechogenic and that presents arterial flow with Doppler US. Solid nodules with unspecific ultrasonographic characteristics are indeterminate lesions ⑦ (**Figure 7**).

Complex cysts ④ and indeterminate nodules ⑦ should be evaluated with a dynamic study, such as contrast enhanced CT or MRI.

HI on Computed Tomography (CT) and Magnetic Resonance Imaging (MRI).

These are largely available and useful methods to characterize hepatic lesions. Hepatic nodules can be classified as: i) to small to characterize (TSTC) ⑧, ii) hypovascular nodules ⑨, and iii) hypervascular nodules ⑩. Accuracy of MRI seems better than that of CT for detection and characterization of focal hepatic lesions. Thus, some indeterminate nodules on CT might have a distinct classification using MRI. Main features of each group of HI found on CT or MRI are described below.

Lesions to small to characterize (TSTC) ⑧ (Figures 8 and 9)

Lesions TSTC are generally indeterminate due to their small size and atypical imaging features and usually their categorization is not reliable. They also called subcentimeter lesions, however this is not a size-based classification. Indeed, the progress on imaging methods has more frequently allowed characterization of nodules of less than one centimeter.

In a study [134] published in 1992 comprising 1,500 patients that underwent abdominal CT, TSTC lesions were found in 17% of cases. No TSTC was identified in patients with no known primary malignancy. Among those with known primary malignancy, the number of TSTC lesions was associate with the risk of malignancy, i.e., for 1 TSTC lesion

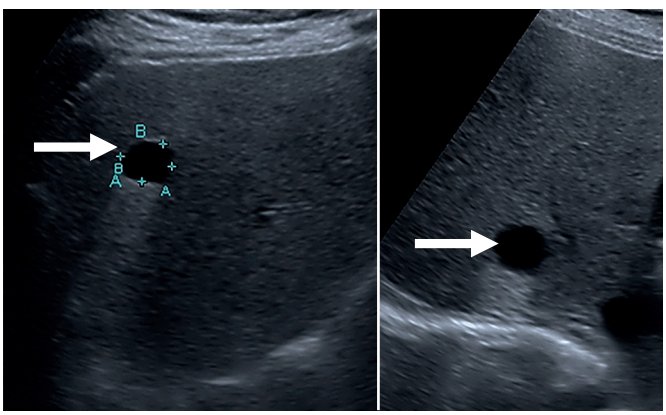

Figure 3. Simple cysts on ultrasound (arrows): anechoic, homogeneous, sharply delimited, and with posterior reinforcement.

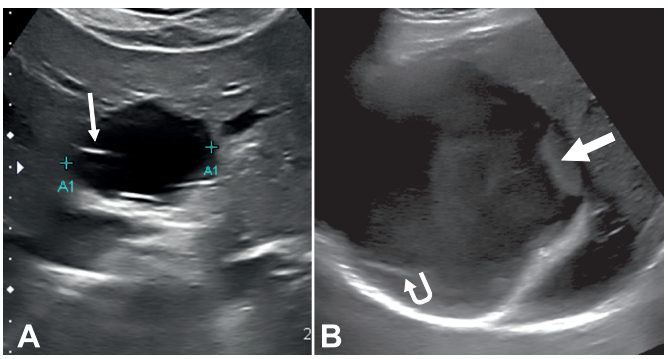

Figure 4. Complex cyst on ultrasound. **A)** Anechoic cyst with thin septum (arrow). **B)** Large cyst in the right liver with a thick septum (curved arrow), echogenic content (asterisk) and mural nodule (arrow).

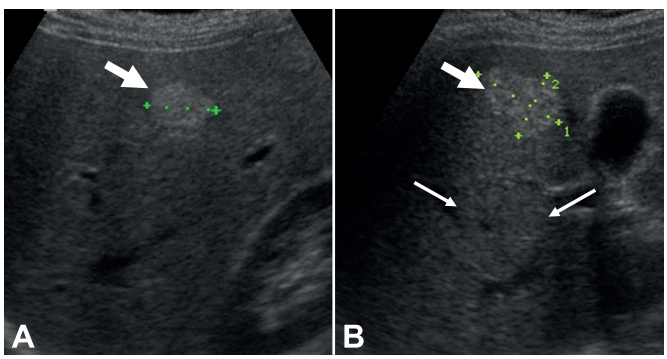

Figure 5. Typical hemangioma on ultrasound. **A** and **B**) Well-defined, homogeneous and hyperecogenic nodule (thick arrows) with posterior acoustic enhancement (thin arrows) and no signal on Doppler scan. (*courtesy of Dra. Iara R. S. Lucena, Hospital de Clínicas, Porto Alegre, Brazil*)

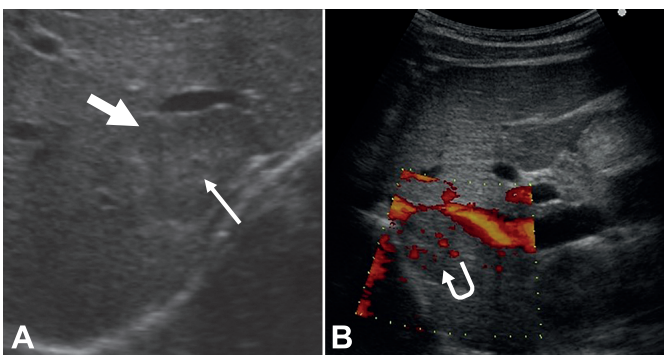

Figure 6. Typical focal nodular hyperplasia (FNH) on US. **A** and **B**) Homogeneous lesion (thick arrow) with variable ecogenicity and with no peripheric hypoecogenic halo (capsule). A hypoecogenic central scar (thin arrow) with arterial vessels on Doppler US (curved arrow), a characteristic finding on FNH, is seen.

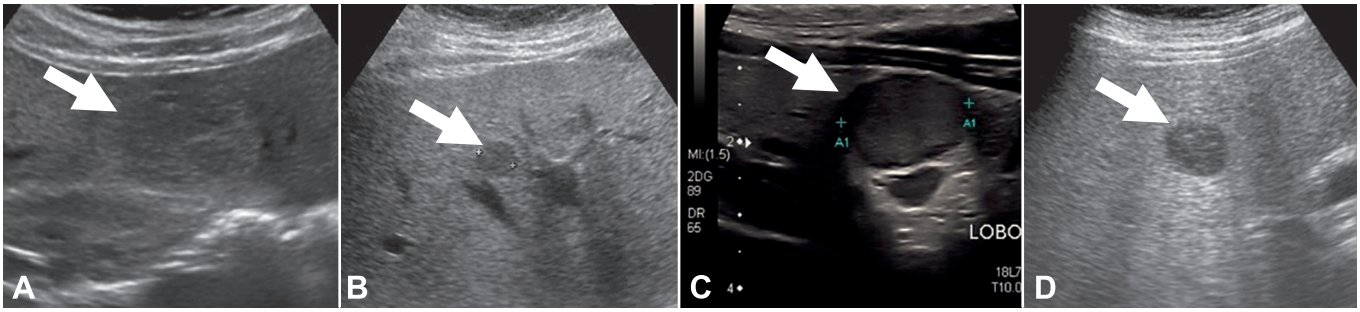

Figure 7. Indeterminate nodules on ultrasound. Nodules that do not fit features for specific diagnosis on ultrasound (US) should be considered indeterminate and evaluated by a dynamic imaging method. A large range of benign and malignant lesions may have similar US appearance becoming specific diagnosis impossible. **A**) Hemangioma. **B**) Focal nodular hyperplasia. **C**) Liver metastasis from endocrine tumor. **D**) Hepatocellular carcinoma.

the risk of malignancy was 5%, for 2 to 4 TSTC lesions this risk increased to 19%, and for those with 5 or more TSTC lesions the risk of malignancy reached 76%. However, it is of note that this study was performed before the advent of multidetectors CT. Another study [130], published in 1999, including 2,978 patients with known primary malignancy, reported a prevalence of 12% of TSTC lesions, and only 12% of them (1.4% of patients) were metastases. TSTC were more frequently malignant when the primary site was a breast tumor. This found is in agreement with the observation that liver metastases from breast cancer are usually small and multiple, in opposition of those from colorectal origin, for example.

More recently, a study [135] reported a correlation between the size and edge aspect of TSTC lesions and the risk of malignancy, as summarized on **Table 3**. Also, a cohort including breast cancer patients with no known liver metastasis found that those with TSTC lesions (present in 35% of cases) developed liver metastasis in 28% of cases.[136] This risk was similar to those patients with no TSTC after a median follow-up of 584 days. Thus, despite most of TSTC lesions are benign, multiple TSTC lesions in patients with known malignancy represent an increased risk to malignancy.

Hypovascular nodules ⑨

Hypovascular nodules represent a large group of lesions, including most of liver metastases. On the flowchart hypovascular lesions were classified as i) benign ⑪, ii) suspicious ⑫, iii) complexes cysts ⑬, and iv) indeterminate ⑭.

Table 3. Probability of a lesion being benign using size and edge as characterization. (Modified from Robinson et al.[135])

Size	Ill-defined	Sharply defined
<5mm	90%	94%
5-10mm	71%	81%
10-15mm	62%	71%

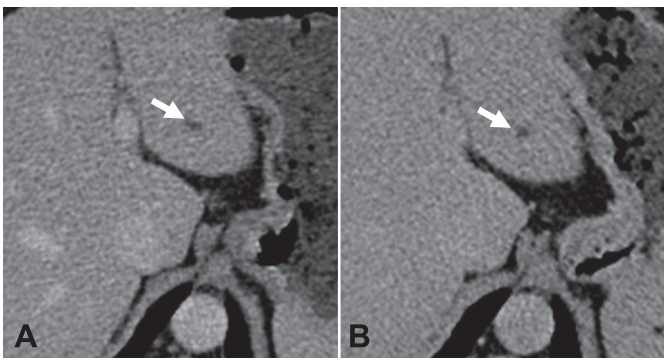

Figure 8. A small nodule (arrows) on portal-venous (**A**) and delayed (**B**) phases of dynamic CT. The nodule remains hypodense and shows the same aspect on both phases, suggesting a cyst.

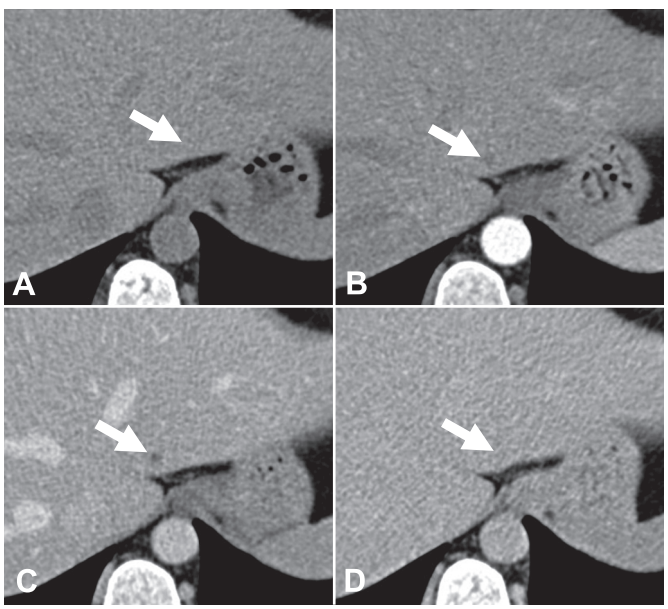

Figure 9. To small to characterize (TSTC) nodule. A small nodule (arrows) on pre-contrast (**A**), arterial (**B**), portal-venous (**C**), and delayed (**D**) phases of a dynamic CT. The nodule shows contrast enhancement, however, it is not possible to characterize the pattern of enhancement.

Typical benign hypovascular nodules ⑪ (**Figure 10**) are sharply defined, homogenous, with low density (up to 20 HU) on CT, and with no contrast enhancement. Margins may be irregular but well defined. Hepatic cysts are the more common lesions in this category.

Suspicious hypovascular nodules ⑫ (**Figures 11** to **14**) have ill-defined margins, contrast enhancement (more than 20 HU), and heterogeneity. Metastasis is the more frequent lesion in this category and most metastases presents with these imaging features. However, this group is heterogeneous and include many different diagnosis. Cholangiocarcinoma for example normally is included in this category. Inflamatory pseudotumor, a benign lesion, usually also shows imaging features of this category.

Complex cystic lesions ⑬ (**Figures 15** and **16**) are characterized by the presence of septa and wall thickening with contrast enhancement, heterogeneous content, calcifications, and solid component. Complex cysts can be subdivided according to the degree of complexity into mild, intermediate and accentuate. Mild complex cysts have non-perceptible walls, with thin septa (less than 3 mm) and no solid compound. Intermediate complex cysts have little thicker wall and/or septa (between 3 and 5 mm), without solid compound. Finally, accentuate complex cysts have thick (more than 5 mm) and irregular walls and/or septa and may have solid compound that enhances after contrast

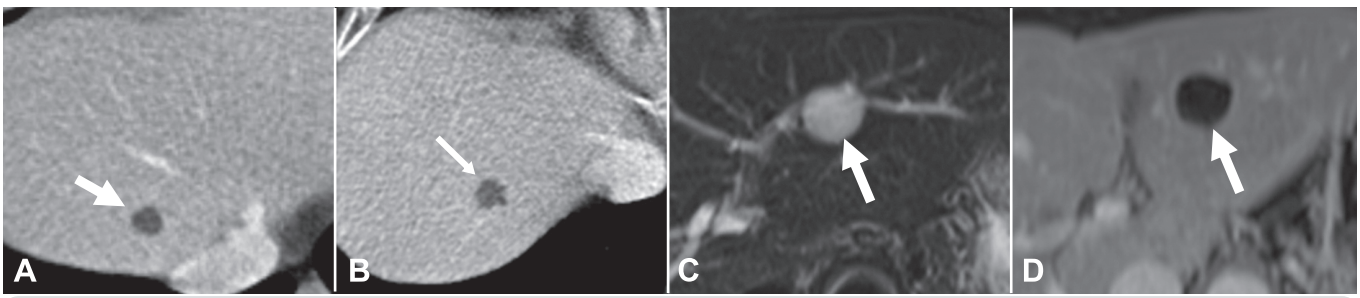

Figure 10. Benign hypovascular lesions. **A**) Portal-venous phase CT showing a well-defined and homogeneous nodule (arrow), with low density (lower than 20 HU) and no contrast enhancement. **B**) Portal-venous phase CT showing a nodule with irregular, but sharply defined, margins (arrow). **C** and **D**) MRI of a well-defined and homogeneous nodule (arrows), hyperintense on T2-weighted image (C) and with no enhancement on dynamic post-contrast scan (D).

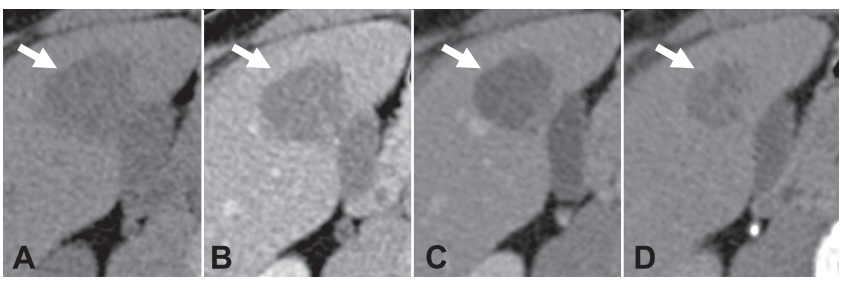

Figure 11. Suspicious hypovascular lesion on dynamic CT. Nodule (arrows) with ill-defined margins, heterogeneity, and contrast enhancement (better appreciated on delayed phase). Lesion was proved to be a colorectal metastasis. Pre-contrast (**A**), arterial (**B**), portal-venous (**C**), and delayed (**D**) phases of dynamic CT.

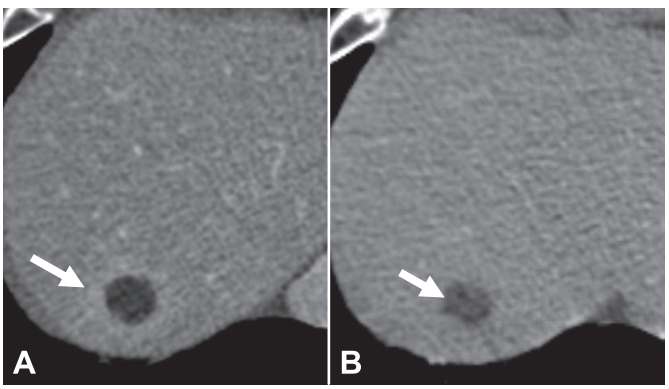

Figure 12. Suspicious hypovascular lesion on dynamic CT. **A**) portal-venous phase showing subtle peripheric enhancement (arrow). **B**) Delayed phase with little enhancement (better noticed by reduction of lesion's size). It was proved to be a metastasis from pancreatic cancer.

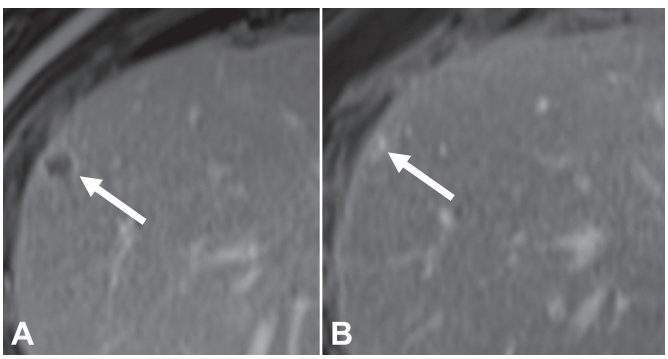

Figure 13. T Suspicious hypovascular lesion on portal-venous phase of dynamic MRI (MRI). **A**) Initial imaging showing a nodule with peripheric enhancement (arrow). **B**) After chemotherapy there was a size reduction (arrow). The nodule was a liver metastasis from breast cancer. Increasing of size on follow-up study or reducing of size after treatment are suspicious characteristics.

media administration. Etiology of complex cysts is variable and includes complicated simple cyst (bleeding or infection of simple cyst), ciliated cyst, hydatid cyst, abscess, bilioma, hematoma, cystadenoma, cystadenocarcinoma, cystic primary hepatic tumors, and cystic metastases. Management of complex cysts depends on clinical features and specific characteristics. For example, a hepatic cyst with calcified wall and no contrast enhancement in a patient from an endemic area is probably a hydatid cyst.

Indeterminate hypovascular lesions ⑭ represent the other hypovascular lesions, which its characteristics are not included in the former hypovascular categories. They might be submitted to additional evaluation or follow-up, according to their size and group of risk of the patient.

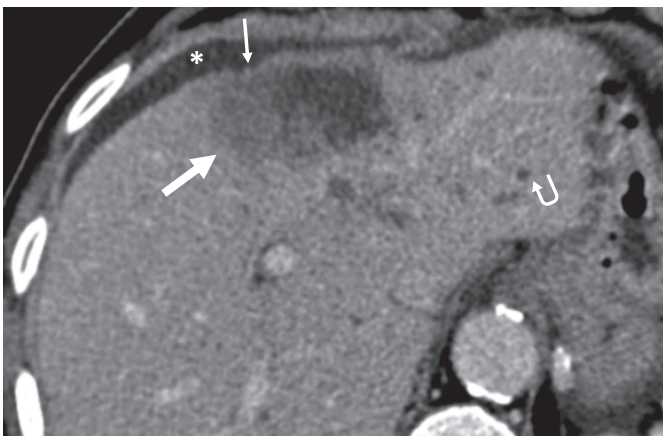

Figure 14. Suspicious hypovascular lesion on portal-venous phase of dynamic CT. An ill-defined and heterogeneous lesion (thick arrow) is shown, associated to minimal capsular retraction (thin arrow), intrahepatic biliary dilatation (curved arrow), and ascites (asterisk). The lesion was an intrahepatic cholangiocarcinoma, a diagnosis usually found on this category.

Hypervascular nodules ⑩

Hypervascular lesions are further divided in: i) typical hemangioma ⑮, ii) typical focal nodular hyperplasia (FNH) ⑯, iii) suspicious adenoma ⑰, iv) typical hepatocellular carcinoma ⑱, v) suspicious fibrolamelar carcinoma ⑲, vi) suspicious metastases ⑳, vii) suspicious vascular disorder, and viii) indeterminate ㉒.

Typical **hemangiomas** ⑮ (**Figures 17** to **20**) may present three patterns of contrast enhancement. In type I, typical of small (less than 1.5 cm) hemangiomas, there is an intense and uniform contrast enhancement of the lesion during the arterial phase, followed by a progressive slow reduction of the enhancement, but remaining hyperdense/hyperintense in late phase, in a similar way of vascular structures. There may be perfusion abnormalities surrounding the nodule during arterial phase. In type II, most frequent on hemangiomas up to 5 cm, the lesion enhancement is nodular, initially peripheral and non-homogeneous, with progressive centripetal enhancement resulting in a homogeneously isodense/isointense aspect to the vessels in late phases. Type III enhancement is found in large hemangiomas and characterized by nodular, initially peripheral and non-homogeneous, with centripetal enhancement on subsequent images, similar to type II lesions, however, in this pattern a central scar is present, with no enhancement even in late phases. Atypical patterns of enhancement are not discussed here; however they usually have non-specific imaging findings leading its diagnose challenging and unsafe. Usually the pattern of enhancement of hemangiomas is better characterized by MRI than by CT. The typical signal hyperintensity on T2-weighted images might be useful for the diagnose of hemangioma on MRI. In type III lesions, the central scar is even more hyperintense on T2-weighted images.[137]

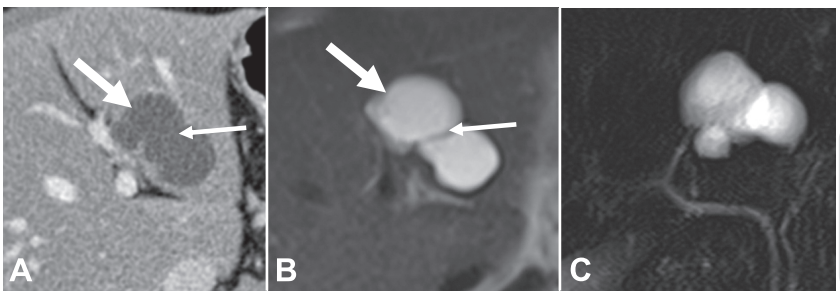

Figure 15. Complex cyst (thick arrows) on portal-venous phase of dynamic CT (A), T2-weighted MRI (B), and T2-weighted MRI cholangiography (**C**). Note the lobulated contour and the thin septum (thin arrow, better depicted on MRI).

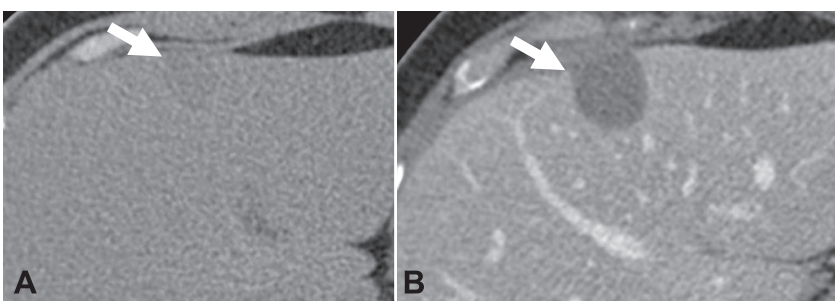

Figure 16. Complex cyst on pre-contrast (A) and portal-venous (B) phases of dynamic CT. A dense cyst (45 HU without contrast enhancement) on this location should raise suspicion for ciliated cyst.

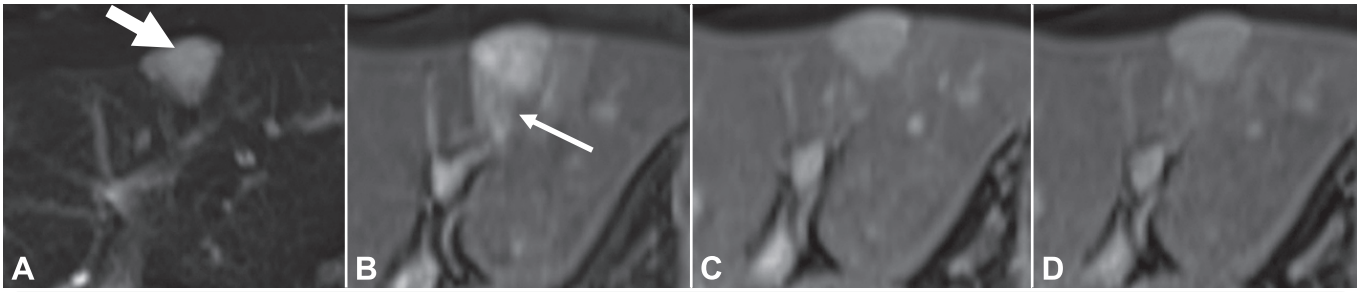

Figure 17. Type I hemangioma on dynamic MRI. **A**) T2-weighted image showing a well-defined hyperintense nodule (arrow). **B**) Arterial phase with intense enhancement and peripheric perfusion abnormality (arrow). **C** and **D**) Hyperintensity remains on portal-venous (C) and delayed (D) images, similar to the vessels.

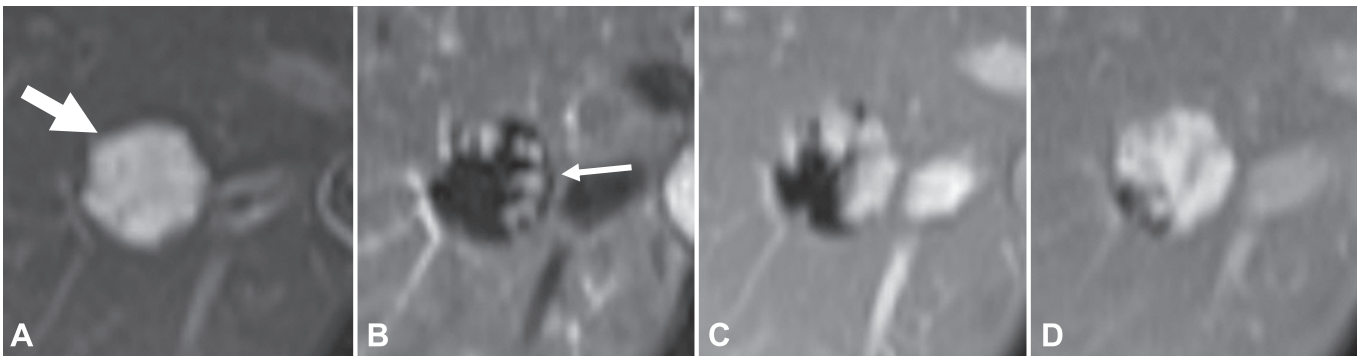

Figure 18. Type II hemangioma on MRI. **A**) T2-weighted image showing an hyperintense well-defined nodule (arrow). **B**) Arterial phase showing intense peripheric discontinuous nodular enhancement areas (thin arrow). **C**) On portal-venous-phase those nodular areas increase in size and tend to converge centripetally. **D**) On delayed phase the lesion tends to become homogeneously hyperintense, similar to the vessels.

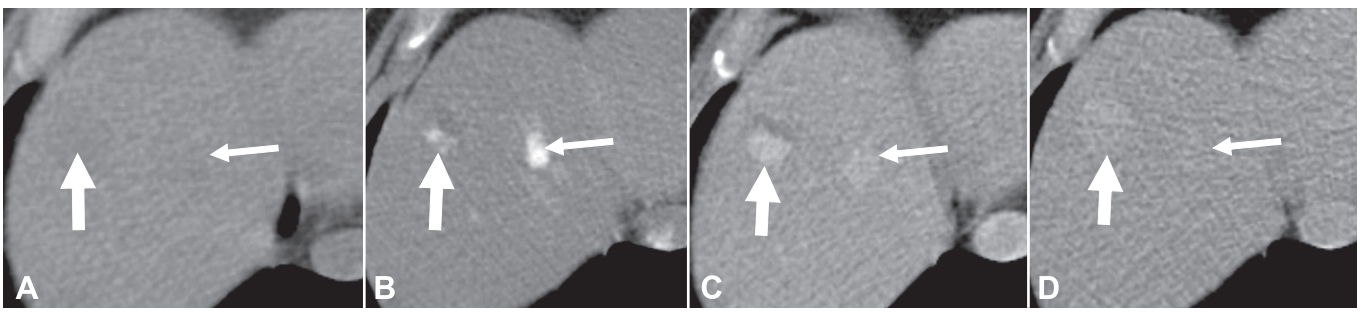

Figure 19. Type I (thick arrows) and type II (thin arrows) hemangiomas on dynamic CT. Pre-contrast (**A**), arterial (**B**), portal-venous (**C**), and delayed (**D**) phases are shown. Note the enhancement of lesions similar to that of vessels.

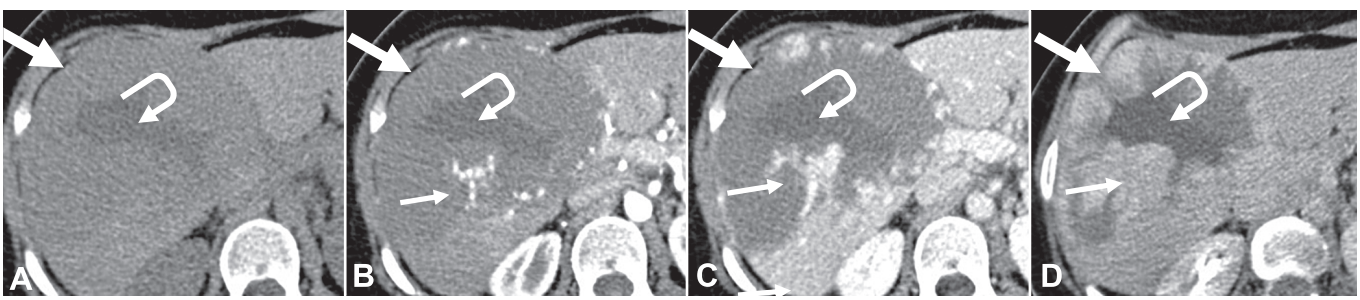

Figure 20. Type III hemangioma on pre-contrast (**A**), arterial (**B**), portal-venous (**C**), and delayed (**D**) phases of dynamic CT. A large liver lesion (thick arrow) with similar enhancement pattern of type II hemangioma (Centripetal discontinuous nodular enhancement – thin arrows). However, there is a "central scar", which is more hypodense than the lesion itself and do not enhance, even on delayed images. In MRI that "central scar" would be brighter than the lesion on T2-weighted images.

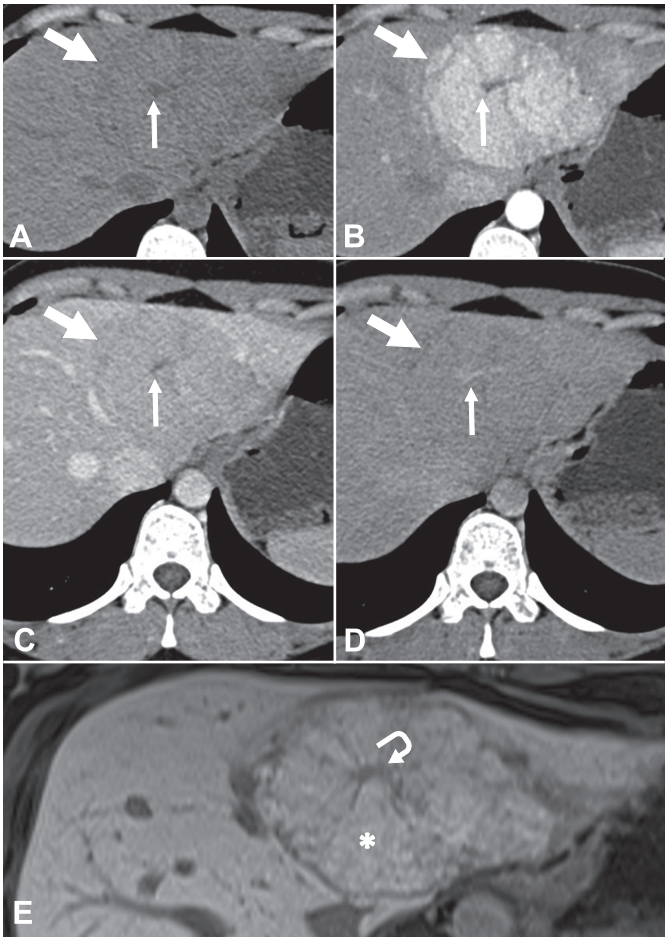

Figure 21. Typical focal nodular hyperplasia (FNH). **A** to **D**) Dynamic CT. The nodule has density close to liver parenchyma on pre-contrast phase (A), intense enhancement on arterial phase (B) and again density similar to liver parenchyma on portal-venous (C) and delayed (D) phases. A central scar (thin arrow) and radiating septa are seen, hypodense on pre-contrast and arterial phases, with progressive enhancement that is persistent on delayed phase. **E**) MRI after hepatobiliary contrast. Uptake is seen in the lesion (asterisk) but not in the central scar and septa (curved arrow). FNH usually has lobulated contour.

On CT, typical **FNH** ⑯ (**Figures 21** to **23**) appears as an isoattenuating nodule on images with no contrast (except if the rest of the liver is fatty, when FNH may appears hyperattenuating). The lesion is enhanced rapidly and transiently during the arterial phase, becoming isodense on portal and late phases. The central scar is hypodense on early phases and become iso- or hyperdense on delayed phases. Enlarged central arteries may be seen. On MRI, typical FNH is homogenous, well delineated, with lobulated aspect, and with signal intensity similar to liver parenchyma on T1-weighted and T2-weighted (or slightly low signal on T1-weighted and high signal on T2-weighted).

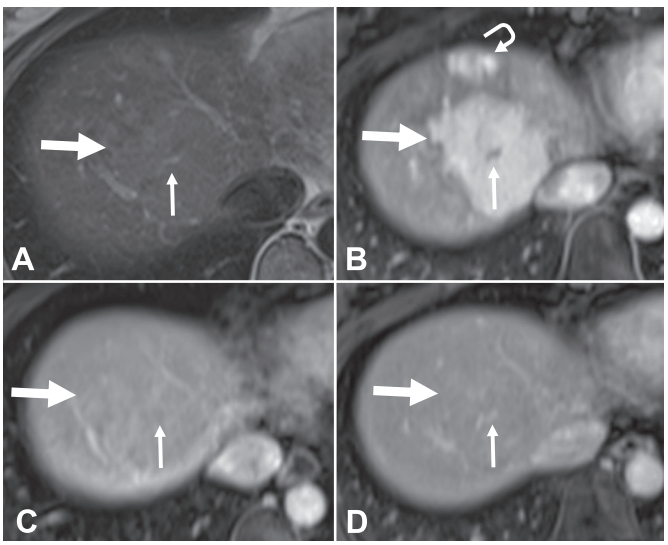

Figure 22. Typical focal nodular hyperplasia (FNH) on MRI. **A**) On pre-contrast T2-weighted the nodule has signal intensity close to liver parenchyma (thick arrow). **B** to **D**) Similar to CT, there is intense enhancement on arterial phase (B), and signal similar to the liver parenchyma on portal-venous (C) and delayed images (D). The central scar (thin arrows) is hyperintense on T2-weighted image (A) and no contrast enhancement occurs on arterial phase (B); on delayed phase it becomes hyperintense. The adjacent small nodule (curved arrow) seen on arterial phase (B) is another FNH.

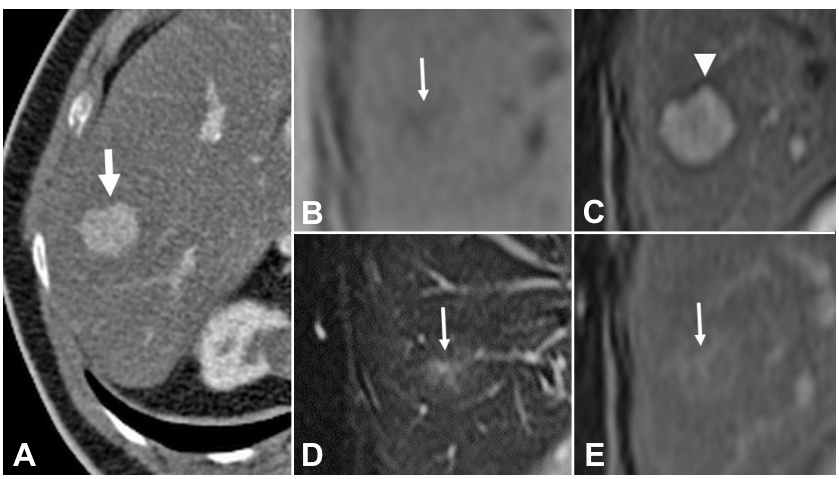

Figure 23. Focal nodular hyperplasia (FNH). **A**) Arterial phase of dynamic CT showing an indeterminate hypervascular nodule (arrow), not visible on the other phases (not shown). **B** to **E**) MRI depicted a central scar (arrows) with hypointensity on T1-weighted (B) and hyperintensity on T2-weighted (C) pre-contrast images. On post-contrast images the hypervascular nature of nodule (arrowhead) is depicted on arterial phase (D). On delayed phase (E) the central scar remains enhanced (arrow). These founds on MRI allows diagnosis of FNH.

Pattern of enhancement is similar to that of CT. The central scar is more frequently identified on MRI than on CT, and is typically high signal on T2-weighted when recognized.[137]

Suspected hepatic **adenoma** ⑰ (**Figures 24** to **26**) demonstrates early and relatively homogeneous enhancement returning to near isodensity on portal venous and delayed phase image. A peripheral halo may be seen in adenomas, contrarily to FNH. Fat and blood may also be found especially in large, complicated, and peripheral lesions. Microscopic fat can be detected using chemical shift on MRI. Also MRI can be helpful on distinguish histopathological and genetic subtypes: i) **inflammatory** adenomas are usually isointense or slightly hyperintense on T1-weighted, without loss of signal intensity on chemical shift imaging, and diffusely hyperintense on T2-weighted; there is intense enhancement during the arterial phase that persists on delayed images; ii) **HNF-1 (Hepatocyte Nuclear Factor 1) alpha-mutated** adenomas are usually hyper- or isointense on T1-weighted images, with signal loss in chemical shift imaging, and are isointense or slightly hyperintense on T2-weighted, with moderate enhancement during arterial phase and without enhancement persistence on delayed phases. The intensity of enhancement during the arterial phase varies according to the amount of fat inside the tumor, and nodules with large amount of fat may even do not show arterial enhancement.; iii) **beta-catenin-mutated** adenomas have no specific pattern on MRI and

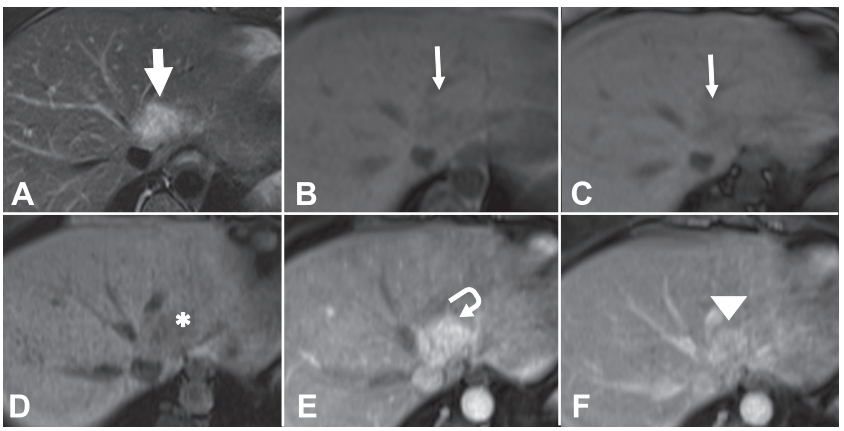

Figure 24. Suspected hepatic adenoma. MRI showing usual imaging features of inflamatory adenoma, presented as an hyperintense heterogeneous nodule (thick arrow) on T2-weitghted image (**A**), with no fat (thin arrow) on in-phase (**B**) and out-of-phase (**C**) images. The nodule is hypointense (asterisk) on pre-contrast phase (**D**), with intense enhancement (curved arrow) on arterial phase (**E**), that persist hyperintense (arrowhead) on portal-venous (**F**) and delayed phase (not shown)

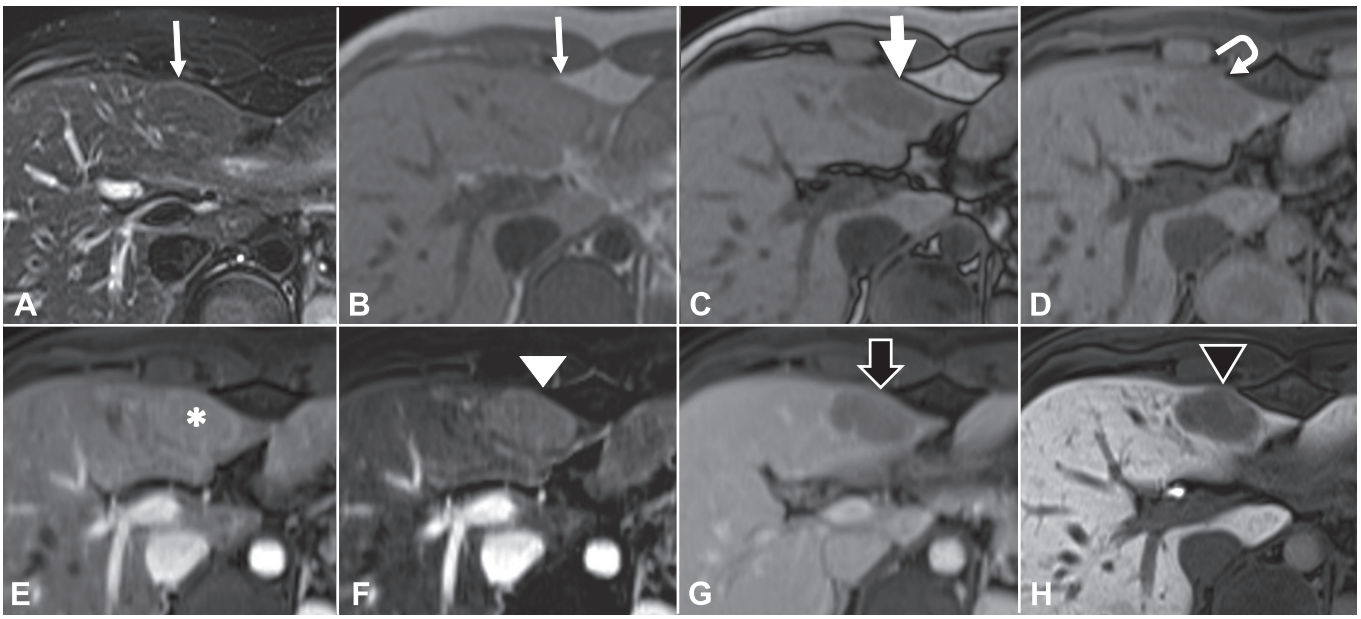

Figure 25. Suspected hepatic adenoma. MRI showing usual imaging features of HNF-1α-mutated adenoma. Signal intensity on T1- and T2-weighted images varies according the amount of fat inside. This nodule have signal intensity similar to liver (thin arrow) on T1-weighted (**A**) and T2-weighted (**B**) images. There is a signal drop (thick arrow) of the lesion on out-of-phase image (**C**) related to fat and a loss of signal (curved arrow) on fat-suppressed pre-contrast phase (**D**). On dynamic contrast images, the intensity of enhancement (asterisk) on arterial phase (**E**) is related to the amount of fat, better seen (arrowhead) in this case on subtracted image (**F**). There are hypointensity (open arrow) on portal-venous phase (**G**) representing washout and reduced contrast uptake (open arrowhead) on hepatobiliary phase (**H**).

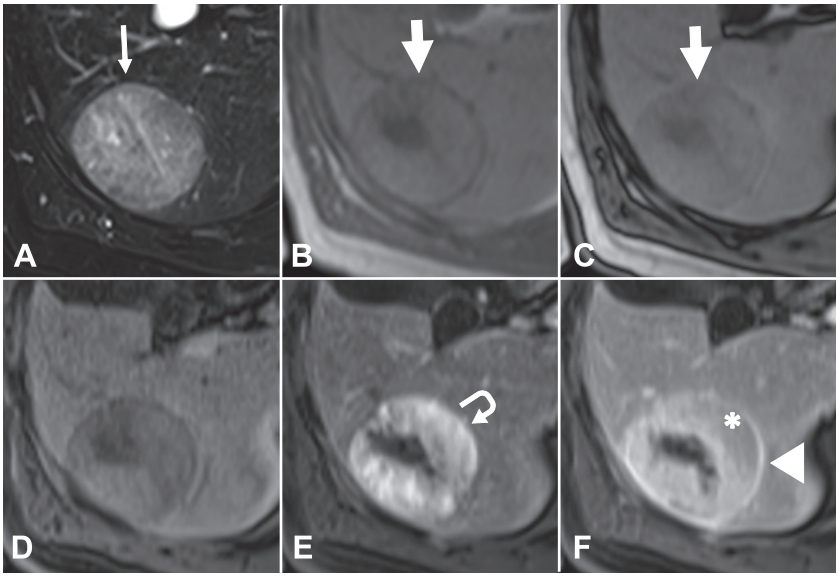

Figure 26. Hepatic adenoma (diagnosis proved after resection) with imaging features similar to hepatocellular carcinoma. There is mild heterogeneous hyperintensity (thin arrow) on T2-weighted image (**A**), with no evidence of fat (thick arrow) on T1-weighted in-phase (**B**) and on out-of-phase (**C**) images. On dynamic contrast study (**D** to **F**), there is arterial enhancement (curved-arrow) on arterial phase (**E**), with hypointensity (asterisk) and pseudo-capsule (arrowhead) on portal-venous phase (**F**).

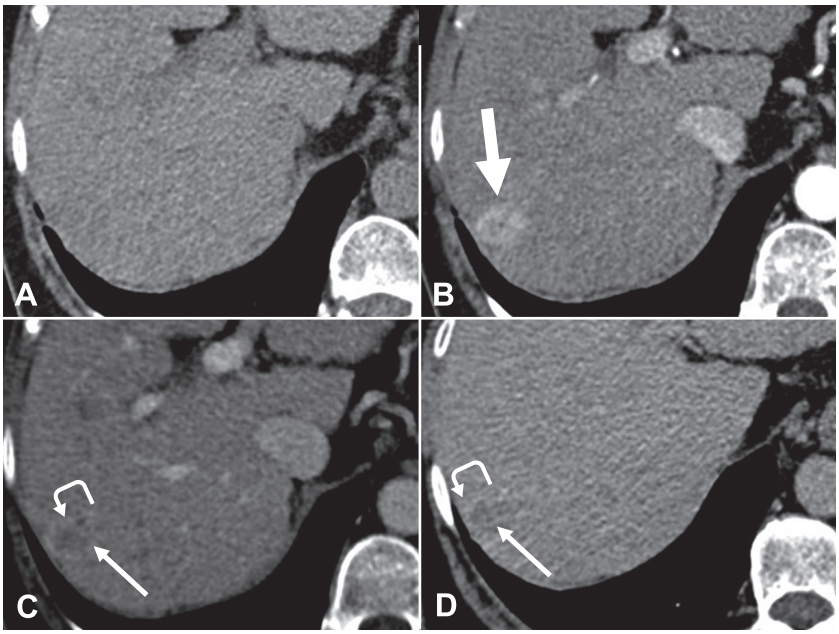

Figure 27. Typicaly hepatocellular adenocarcinoma on CT. Pre-contrast (**A**), arterial (**B**), portal-venous (**C**), and delayed (**D**) phases of a dynamic CT showing a typical small HCC with three major features: arterial enhancement (thick arrow), "washout" (thin arrow) on portal-venous and delayed phases (hypodensity related to the liver parenchyma), and pseudocapsule (curved arrow) on portal-venous and delayed phases. These features are in keeping with a LI-RADS 5 lesion.

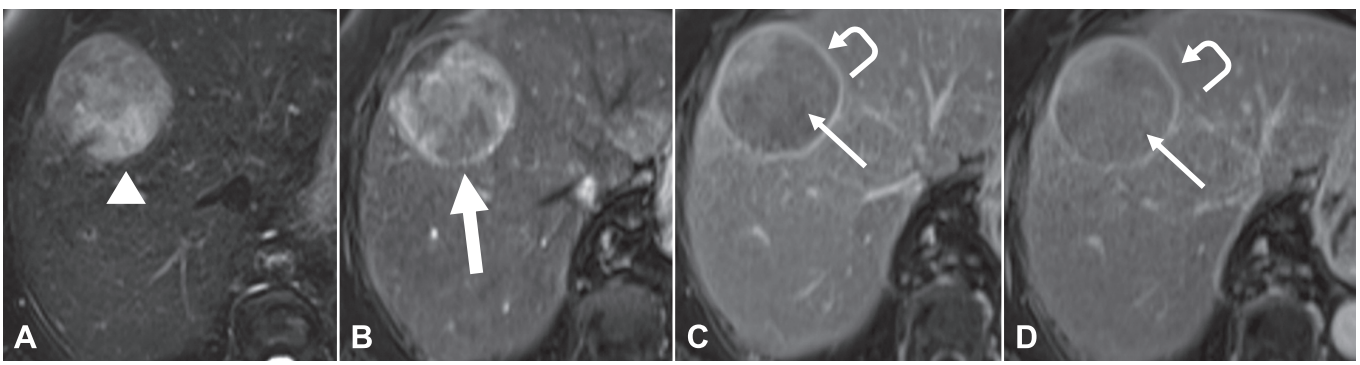

Figure 28. Typicaly hepatocellular carcinoma (HCC) on MRI. T2-weighted (**A**), arterial (**B**), portal-venous (**C**) and delayed (**D**) MRI images showing a typical large HCC with three major features: Intense enhancement (thick arrow) on arterial phase, "washout" (thin arrow), and pseudocapsule (curved arrow) on portal-venous and delayed phases. On T2-weighted image, the lesion is hyperintense and heterogeneous (mosaic architeture). These features correspond to a LI-RADS 5 lesion.

differential diagnosis with hepatocellular carcinoma is difficult. Of note that nearly 10% of adenomas are not included in the cited subtypes.

Hepatocellular carcinoma (HCC) ⑱ (**Figures 27** and **28**) features are discussed on **Chapter 13** (*Hepatocellular Carcinoma*) and this tumor should be included on the differential diagnosis of any hypervascular hepatic nodule. Typically HCC shows enhancement during arterial phase and non-homogeneous contrast washout during portal and/or delayed phases, with enhanced pseudocapsule on late phases. MRI is more accurate than CT on detecting HCC on chirrosis. LI-RADS (Liver Imaging Reporting and Data System) classification of nodules in patients at risk of HCC should be used to stratified risk according to imaging characteristics. Typical HCC represents category LI-RADS 5 with 100% certainty for HCC.

Fibrolammelar carcinoma ⑲ (**Figure 29**) should be included in differential diagnosis of nodules that are large, heterogeneous, with calcifications (70% to 95% of these tumors), with large central scar (usually more than 2 cm) which is hypointense on T2-weighted images on MRI, associate to increased hilar lymphnode (65% of cases), and occurring in non-cirrhotic liver.

Hypervascular liver **metastases** ⑳ (**Figures 30** and **31**) can be originated especially from renal clear cells tumor, melanoma, and endocrine tumor. Less frequently hypervascular metastases are from carcinoma of breast, pancreas, colon and lung, also from coriocarcinoma and sarcomas. Large metastases may present hypovascular central area in case of necrosis.

Vascular disorders ㉑ (**Figures 32** and **33**) on the liver may present diffusely or focally, sometimes mimicking focal lesions. Transient hepatic attenuation difference (THAD), hepatic infarction, arterio-portal shunt, passive congestion, peliosis hapatis, Budd-Chiari syndrome, hereditary hemorrhagic telangectasia (Osler-Weber-Rendu Syndrome), superior vena cava obstruction are examples of vascular disorders that occasionally may simulate focal lesions on radiological images.

Indeterminate hypervascular lesions ㉒ (**Figures 34** and **35**) should be evaluated according size of the nodule and the patient group risk. Small lesions on patients with low risk are usually benign and no additional evaluation or treatment is required. Large lesions or those occurring in patients with high risk should receive further evaluation.

Additionally, fat liver disorders may result on radiological images that simulate focal lesions (**Figure 36**). Focal area of steatosis or spared area on steatotic liver simulating focal lesions usually occur on hepatic peripheral or perivascular area, mainly adjacent to gallbladder, porta hepatis and falciform ligament, with no expansive effect, and generally with a triangular or geographical aspect. The MRI is the method of choice in doubtful cases.

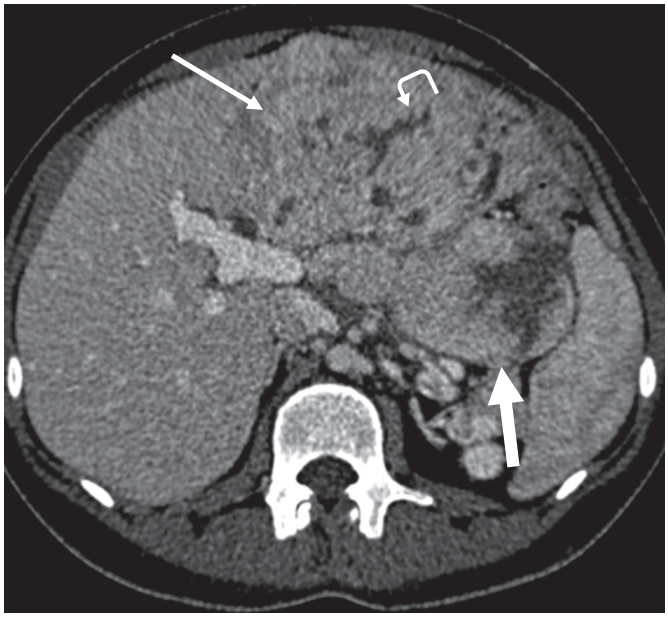

Figure 29. Fibrolamelar hepatocellular carcinoma. It should be suspected when there is a large heterogeneous nodule (thin arrow), usually with calcifications and/or large central scar (curved arrow) in a liver without characteristics of chirrosis. Enlarged lymph nodes are comum (thick arrow).

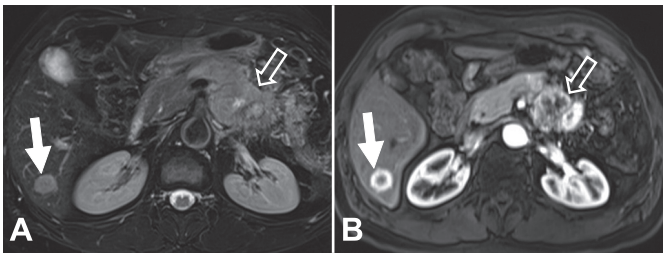

Figure 30. Hypervascular metastasis. Hepatic nodule (arrow) slightly hyperintense on T2-weighted image (**A**) with intense rim enhancement (arrow) on arterial phase of dynamic study (**B**), proved to be a metastasis. The primary tumor is depicted in the body/tail of pancreas (open arrow).

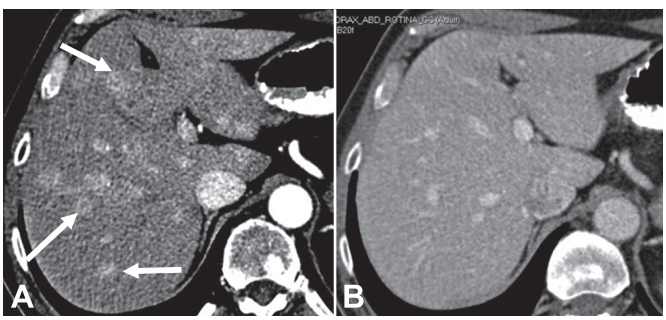

Figure 31. Hypervascular metastasis. **A**) Arterial phase of dynamic CT showing several hypervascular metastases from a bronchial endocrine tumor (some of them with a rim enhancement pattern). **B**) Portal-venous phase of dynamic CT at the same level of (A). No lesion is visible on this phase, disclosing the need of the arterial phase to detect some liver lesions.

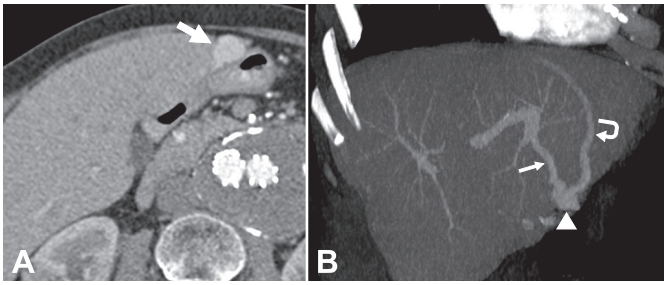

Figure 32. Portal-systemic shunt. **A**) Arterial phase of dynamic CT with a hypervascular nodular image in the left liver. **B**) MIP reformatation showing the communication (arrowhead) between a left portal vein branch (thin arrow) and the left hepatic vein (curved arrow), which has prompt enhancement due to the vascular shunt.

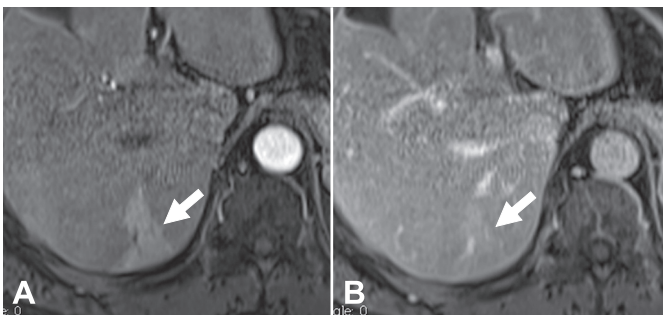

Figure 33. Transient hepatic attenuation/intensity differences (THAD/THID). Arterial (**A**) and portal-venous (**B**) phases of dynamic MRI showing a peripheric wedge-shaped area (thick arrow) of enhancement on arterial phase that become homogeneous on subsequent phases in keeping with a perfusion abnormality. Care should be taken about concomitant nodule (specially in the apex of wedge-shaped area), which can be the cause of the perfusion abnormality.

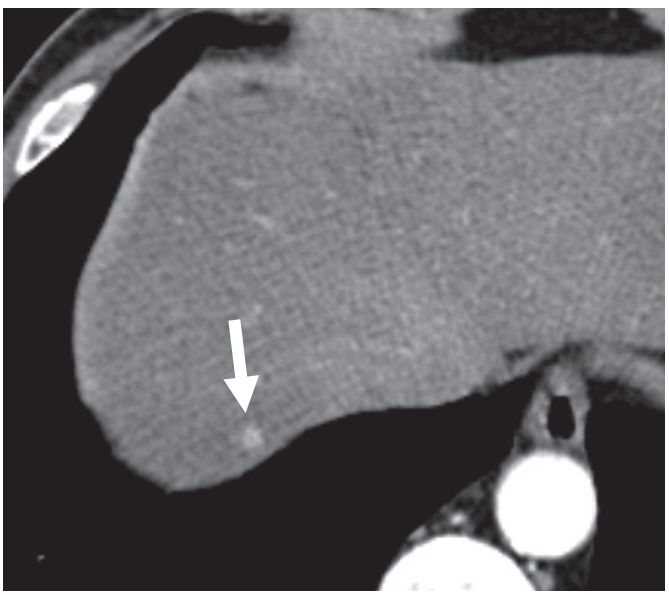

Figure 34. Hypervascular indeterminate nodule. Arterial phase of dynamic CT showing a tiny liver nodule visible only on this phase, in keeping with an indeterminate hypervascular nodule.

ADDITIONAL EVALUATION

Despite only a minority of incidental lesions requires supplemental investigations for a definite diagnosis, some methods may be helpful on management or definitive diagnosis of incidentalomas.

Hepatic MRI with liver-specific contrast

This method has replaced otheHHr radiological methods such as labeled red blood cell scans, sulfur colloid scans, and visceral angiography. Liver-specific contrast MRI combines vascular and hepatocyte-specific properties, being called bimodal contrast agents. Liver-specific contrast MRI is particularly useful in hypervascular lesions that are not hemangioma. Sensitivity and specificity to distinguish FNH and adenoma are up to 96% and 100%, respectively.[47,93] A recent meta-analysis evaluating the accuracy of MRI with liver-specific contrast agent for HCC detection showed an area under the ROC curve of 0.98 for overall HCC, 0.98 for HCC in patients with cirrhosis, and 0.99 for HCC 2.0 cm or smaller in diameter.[138] However, severe hepatocellular dysfunction (cirrhosis Child C) and cholestasis may prevent sufficient contrast uptake to obtain an adequate hepatocellular phase. In summary, liver-specific contrast play a special role on hepatocellular adenoma, focal nodular hyperplasia, hepatocellular carcinoma (mainly small one), and liver metastases. Biliary leakage may also be evaluated by these liver-specific contrast agents due to their partially biliary excretion of contrast, however, usually more delayed images are required.

Positron emission tomography – computed tomography (PET/CT).

18F-fluorodeoxyglucose (FDG) PET/CT has been used in the management of liver lesions, particularly it has a high sensitivity and specificity for detection of liver metastases from a range of primary cancers. Detection of additional metastases, intra- or extrahepatic, may change clinical management. However, false negatives can be seen in small lesions (less than 1 cm) and tumors that exhibit low glucose uptake (such as metastases from well-differentiated neuroendocrine tumors and some hepatocellular carcinomas) or have suffered significant necrosis.[139] False positive results are rare, but were described for abscesses and other inflammatory lesions (especially granulomatous ones) and liver adenomas.[93,140,141] Other biomarkers than FDG has been explored to increase sensitivity of PET/CT for hepatocellular carcinoma and other tumors.

Technetion-99m Labelled Red Blood Cell (RBC)

Labelled RBC Scintigraphy has a high specifitiy and positive predictive value for hepatic hemangioma. The standard pattern of images on this radiological method is a perfusion/

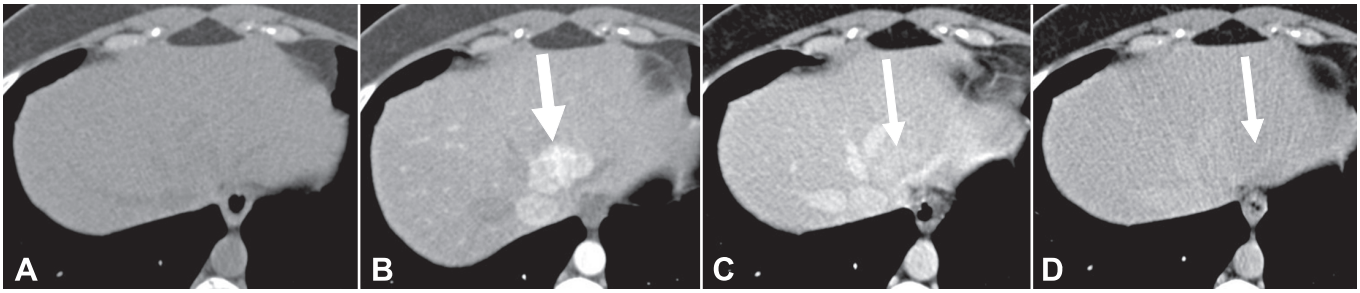

Figure 35. Hypervascular indeterminate nodule. Pre-contrast (**A**), arterial (**B**), portal-venous (**C**), and delayed (**D**) phases of a dynamic CT showing a large hypervascular liver nodule in segment 4, which has arterial enhancement (thick arrow) and becomes isodense to liver on the later phases. There is no sufficient specific findings to a precise diagnostic. This lesion should be considered a indeterminate nodule on CT. Further MRI (not shown) showed features suggesting adenoma and diagnosis confirmed after resection.

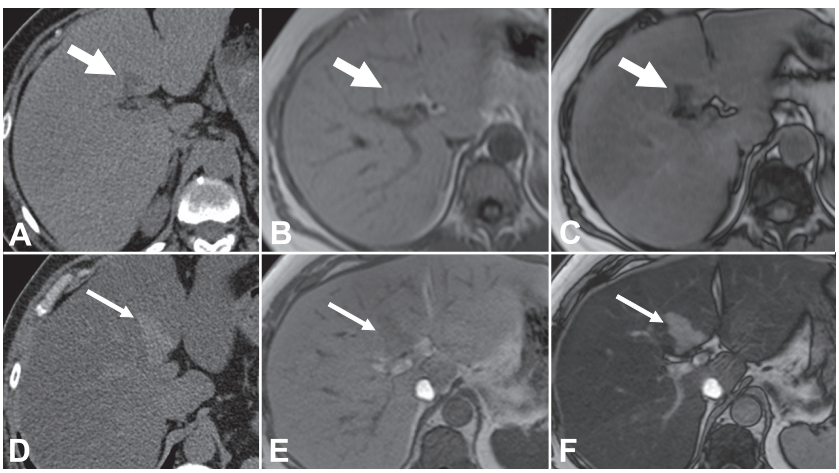

Figure 36. Hepatic steatosis. **A** to **C**) Area of focal steatosis on pre-contrast CT (A), in-phase T1-weighted MRI (B), and out-of-phase T1-weighted MRI (C). **D** to **F**) Area spared of steatosis (another patient) on pre-contrast CT (D), in-phase T1-weighted MRI (E), and out-of-phase T1-weighted MRI (F).

blood pool mismatch, i.e. a decreased perfusion on early dynamic images and a gradual increase in activity on blood pool images. This pattern of activity is rarely seen in other causes of liver nodules. On the other hand, labeled RBC scintigraphy has a limited sensitivity for the detection of small hemangiomas or those located adjacent to the heart or major vessels. Also, false negative results may occur on large hemangiomas with extensive thrombosis or fibrosis.

Technetion-99m Sulphur Colloid Scintigraphy

Uptake of technetion-99m sulphur colloid is seen in around 80% of patients with FNH and may be useful in evaluating indeterminate liver lesions. However, it has limited utility in differentiating FNH and adenoma, because adenomas occasionally demonstrate tracer uptake.

Pathological diagnosis

Sample tissue for histologic assessment can be obtained through biopsy or tumor resection. Most of the data on percutaneous biopsy comes from patients with known or suspected malignancies, when its global accuracy is close to 90%. However, it carries a non-negligible risk of morbidity (mainly bleeding and tumor seeding) of 2 to 4.8% and even mortality (0.05%).[142–145] Nonetheless, modern imaging methods can reach similar or even greater accuracy than percutaneous biopsy. Thus, needle biopsy is most appropriate in patients with an apparent malignancy of unknown origin in whom resection is clinically contraindicated or not technically possible.

For small size HI percutaneous biopsy can be challenging due to the technical issues and the difficulties for the pathologist to give a definitive diagnosis with limited samples. Moreover, very rarely pathological analysis of HI results in a modification of the patient management. Whenever necessary, tissue sample is more appropriate obtained by surgical excision. Despite of that, percutaneous biopsy could have a place in patients not candidates for a surgical resection.

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