Diagnostic approach to focal liver lesions at cross-sectional imaging: a primer for beginners

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Abstract. – Liver imaging encompasses a broad spectrum of diseases in different clinical backgrounds. The available literature is vast and reported data often lacks standardization. Because of all these issues, the differential diagnosis and the characterization of liver lesions can be challenging for the beginner. The aim of this narrative review is to provide the basics for an algorithm approach to liver lesions on cross-sectional imaging. First, some tips for the optimization of Computed Tomography (CT) and Magnetic Resonance Imaging (MRI) protocols will be provided. Liver Imaging Reporting and Data System (LI-RADS, version 2018) working group is proposing the adoption of their standardized lexicon beyond the original target population of LI-RADS (i.e., liver cirrhosis). Thus, the main imaging findings will be defined following the LI-RADS lexicon. Since the contrast study is the most important for lesion characterization, this narrative review separates the lesions into avascular, hypovascular, and hypervascular, with a focus on chronic liver disease (CLD) and hepatocellular carcinoma (HCC).

Key Words: Liver, Liver lesion, Computer assisted tomography, Magnetic resonance imaging, Hepatocellular carcinoma, Cholangiocellular carcinoma, Metastasis, Focal nodular hyperplasia, Hepatocellular Adenoma, Hepatic Hemangioma, Liver Imaging Reporting and data system, LI-RADS.

Introduction

The detection of an incidental liver lesion is becoming increasingly frequent thanks to technological advances and the widespread use of cross-sectional imaging¹. Accurate characterization is fundamental to avoid unnecessary, invasive, and potentially harmful procedures². Differential diagnosis may be challenging for the beginner due to the wide spectrum of disease, the overlap of imaging findings, and the need for integration with the clinical background². The published literature on the characterization of liver lesions at cross-sectional imaging is huge, and it can be difficult to be summarized due to the variability in lexicon and definitions³. Among liver lesions, the radiological features of hepatocellular carcinoma (HCC) have been...
standardized, and the diagnosis can be placed only on the imaging findings. The standardization of the radiological lexicon is one of the main aims of the Liver Imaging Reporting and Data System (LI-RADS). Knowing the advantages and the increasing diffusion of the standardized assessment of imaging findings in different fields, the LI-RADS Commission is pushing the adoption of the lexicon beyond the cirrhotic condition.

Different LI-RADS criteria have been developed for ultrasound (US), computed tomography (CT) and magnetic resonance imaging (MRI). However, multiphasic contrast-enhanced CT and MRI remain the cornerstone for the characterization of liver lesions in all clinical scenarios. This narrative review starts with an overview of the optimization of CT and MRI protocols in liver imaging will be provided. Then, some clarifications about the LI-RADS standardized lexicon will be discussed. Therefore, the liver lesions will be divided into avascular, hypovascular, and hypervascular, in cirrhotic and non-cirrhotic liver to describe an algorithmic approach to their differential diagnosis.

The Basics: Proper CT and MRI Techniques

CT

Multi-detector CT (MDCT) is usually the first examination performed for the evaluation of a liver lesion; therefore, it is important to implement the appropriate protocol to achieve the best diagnostic result. An inadequate examination would strongly affect the possibility of placing the right diagnosis.

The standard liver protocol usually includes a pre-contrast (basal) acquisition, even if, in some cases, it is considered optional. Specifically, the basal scan is used to detect the presence of blood, fat, proteinaceous material, or hyperdense remnants (e.g., iodized oil) from the previous treatments. Also, the accuracy of the measurements of liver metastases and the assessment of pseudolesions or lesions with faint enhancement is significantly improved when the basal acquisition is used as reference.

The basal acquisition is followed by the multiphasic, post-contrast study, with an arterial phase (AP), a portal venous phase (PVP), and a delayed phase (DP). The AP highlights hypervascular lesions against the poorly enhanced liver parenchyma and classified as “early” or “late”. The “early” AP is characterized by the enhancement of the hepatic artery without significant enhancement of the portal vein nor the liver parenchyma. Conversely, the “late” AP is considered optimal when the arterial enhancement of the hepatic parenchyma, the initial enhancement of the portal vein without forward enhancement of the hepatic veins, are present. Some liver lesions can be missed at the “early” AP, so the “late” AP is considered the most accurate for the detection of hypervascular liver lesions. Since the time window of the “late” AP is relatively narrow, protocols including bolus tracking or test bolus techniques are warranted. If the bolus tracking technique is used, the “late” AP is typically acquired with a delay of 10-30s after the aortic threshold of 100-150 HU. For the test bolus, 10-20s after the aortic peak are considered acceptable. A more detailed description is provided in Bae et al.

The PVP has a wider time window, between 60s to 90s after the start of the injection of the contrast material (CM). It provides the optimal enhancement of liver parenchyma and its vascular structures. For these reasons, PVP is the most reliable phase for the evaluation of hypovascular lesions (e.g., metastases), wash-out, residual enhancement of HCC, biliary abnormalities, or intrahepatic vessels.

The DP is usually acquired at 3-5 min; it was previously known as the “equilibrium” phase. As the name suggest, in this phase the CM is substantially “equilibrated” across the vascular and the interstitial compartments. This is helpful for the assessment of hypovascular tumors and wash-out.

Two principles must be considered for the optimization of the CM in liver studies. First, the arterial phase is more dependent on the cardiac output and iodine delivery rate (given by the concentration and the injection rate of the CM). Second, the optimal enhancement of the liver parenchyma during the portal phase (≥50HU) requires a dose of contrast material tailored to the anthropometric data.

The radiation dose is another aspect to be considered in the optimization of the CT protocol. The technological advances in tubes and detectors allow for the routine acquisitions at low kV, with a significant reduction in radiation dose and iodine load, with better contrast of liver lesions. In this scenario, the image quality can be further improved by the introduction of iterative Reconstruction (IR). The advantages of IR in terms of dose re-
Focal liver lesions for beginners

Conventional liver imaging methods, such as ultrasonography, computed tomography (CT), and magnetic resonance imaging (MRI), have been developed to overcome the limitations of IR. Material decomposition on Dual-energy CT (DECT) opens new perspectives on CT imaging. Specifically, virtual unenhanced images form DECT datasets that have the potential for dose reduction by avoiding basal acquisitions. Virtual monochromatic images can be used for contrast optimization and iodine maps that may be helpful for a better lesion characterization.

MRI

Magnetic Resonance imaging (MRI) provides a comprehensive, multiparametric assessment of the liver; therefore, it is considered a problem-solving technique. The standard protocol for the liver study relies on T1, T2, diffusion-weighted images (DWI), and the post-contrast study. The advanced techniques, such as fat and iron quantification, and MRI perfusion, are beyond the scope of this paper and are exposed elsewhere.

The examination usually starts with a Single Shot Fast Spin Echo (SSFSE), T2w sequence on the coronal plane: it provides a fast, general overview of the upper abdomen with acceptable image quality. The protocol continues with axial, usually Fast Spin Echo (FSE) or SSFSE, moderately T2 weighted (w) images (optimal echo time, TE, 80-100ms). Two main points must be discussed. First, the FSE sequences are prone to J-coupling with abnormal hyperintensity of fat, so fat saturation is necessary; the preferred techniques are spectral fat saturation or inversion recovery techniques. Second, some authors suggested to both acquire moderately and heavy T2w images (TE>160 ms). This would allow a more accurate differentiation of benign and cystic-like lesions (which maintain the hyperintensity), from “solid” lesions (more hypointense at longer TE).

For T1 images, Gradient Recalled Echo (GRE) sequences are used. These images are useful to assess substances with high signal on T1 images, such as fat, hemorrhage, protein materials, or glycogen. Moreover, GRE sequences are sensitive to susceptibility artifacts, optimal for the detection of metals (such as iron compounds), calcium, and air. In the basic protocol, the dual-echo GRE has the echo times set at phase coherence and opposition of fat and water signals. Conventionally, to distinguish and reduce the T2* effect while assessing steatosis, the out-phase (OP) images have shorter TE than the in-phase (IP). More recently, 3D sequences, and Dixon techniques for optimal water/fat separation, are increasingly used.

The DWI evaluates the Brownian motion of the water molecules; several different models have been developed to assess tumor cellularity. DWI has a relevant role for lesion detection, with higher conspicuity and better detection of subcentimetric lesions. The data regarding DWI for lesion characterization are encouraging, but the effectiveness is still limited.

Similarly to CT, the post-contrast study is necessary for accurate lesion detection and characterization. Rapid, spoiled T1w 3D GRE sequences with a high temporal resolution are used. Pre-contrast series are acquired for subtraction and basal assessment. The acquisition times of post-contrast phases reflect the principles discussed for CT but consider the filling mode of the k-space. The CM routinely administered are Gd-chelates with vascular-interstitial kinetics, except for two (Gd-BOPTA and Gd-EOB-DTPA) which are actively assimilated by the hepatocytes in variable proportions. The hepatospecific contrast agents (HSCA) have several advantages: they provide metabolic information about the hepatocytes and lesions, improve lesion detection and conspicuity, and allow the assessment of the biliary tree. However, their use requires adjustments in protocols (e.g., longer acquisition times) and in image interpretation. Since Gd-EOB-DTPA is characterized by an early uptake, the lesion washout can be assessed only on the PVP, and the delayed phase cannot be named “equilibrium” phase but “transitional” phase.
The Basics: Some Considerations About Liver Parenchyma and Prevalence of Liver Lesions

The American College of Radiology (ACR) defines the focal liver lesion detected during an examination for unrelated reasons as “incidental”. The accurate characterization of the finding is fundamental for the adequate management. The assessment starts from the clinical background. Several clinical conditions influence the prevalence of focal liver lesions in adult patients. Karkunen et al. evaluated an autopic case series of 95 adult men dead of cardiovascular accidents or violent death. The authors found a liver lesion in 49 (52%) of cases: 26 subjects (27%) had benign lesions of the bile ducts (hamartomas or adenomas), 19 (20%) had hepatic hemangiomas (HH), and 3 (3%) subjects had focal nodular hyperplasia (FNH). Other lesions were rare: 1% case of hepatocellular adenoma, 1% case of nodular regenerative hyperplasia, 1% subject with peliosis, and 1% with colorectal liver metastases. The lesions were globally small (the mean diameters ranged from 1.3 mm of the biliary lesions to 8 mm of the FNH), the prevalence increased with age, and in at least 40% of cases, were multiple. This trend is confirmed by ultrasound (US) studies in large populations. Kaltenbach et al. presented similar US findings on 45,319 patients. They recorded 2,839 focal fatty changes (6.26%), 2,631 (5.81%) cysts, 1,640 (3.62%) HH, 81 (0.18%) FNH, and 19 (0.04%) HA. Oshibuchi et al. reported similar findings in a previous study on a smaller population.

The circumstances are different for symptomatic or oncological patients. Although most of the liver lesions radiologically detected in this setting are benign (up to 80%-92%), metastases have a significant prevalence (nearly 4-22%). These findings are comparable to the autopic case series of Ono et al.: they found liver metastases in 38 cases (27%) in 142 patients with urologic malignancies.

Liver cirrhosis represents another different scenario. Here, regenerative-dysplastic and HCC nodules are the most frequent findings, with an incidence rate of up to 6/100,000 per year. Dodd et al. reported the imaging and pathological findings in 508 explanted cirrhotic livers. The authors found dysplastic nodules in 57 (11%) of livers and HCC in 46 (9%) livers. Caroli-Bottino et al. evaluated 30 explanted cirrhotic livers. In 11/30 (36.7%) cases, there was a known radiological diagnosis, while in the remaining 19/30 (63.3%), there was an incidental detection of HCC – all livers had at least 1 HCC. Regarding benign lesions, Dodd et al. found only 9 HH (1.8%) in their case series. Moreover, the occurrence of liver metastases in oncological patients with cirrhosis is lower (23.7% vs. 37.3% in the metanalysis of Seymour et al.).

In conclusion, a liver lesion should be evaluated first on the basis of the patient risk profile, i.e., healthy subjects, patients with known malignancy, and chronic liver disease. The ACR white paper on incidental liver lesions defines a “high-risk category” including the latter two conditions; another useful classification is based only on the presence or absence of chronic liver disease.

Characterization of Liver Lesions: Main Findings, Lexicon, and Standardization

The groundwork for an accurate characterization of a liver lesion relies on univocal definitions of the observed findings. This allows a concise and precise report (eventually a structured report), ensuring the correct communication with other specialists. However, the available radiological literature on liver lesions is vast, and incongruences in terms and definitions are widespread. As an example, arterial phase hyperenhancement (APHE) of HCC is defined as “arterial enhancement” in Freeman et al., “arterial wash-in” in a version of the Latin American for the Study of the Liver (LAASL) guidelines, and as “hypervascularization”, “arterial-phase hypervascularity”, or “arterial-phase enhancement” in Bolondi et al.

The LI-RADS criteria (updated in 2018) by the ACR, aims to provide a diagnostic algorithm for the radiological diagnosis of HCC in at-risk populations. The Committee also provides a standardized, comprehensive lexicon to improve the image interpretation, even in less-experienced readers, with beneficial effects on clinical communication, education and research. The LI-RADS lexicon was further upgraded in 2021. In this version, the Working Group provides the Context of Use of each term (namely “Broad” or “Restricted to LI-RADS” target populations) with the aim to expand the utilization beyond cirrhotic patients. Interestingly, 69 of 81 terms defined are applicable in the broad scenario.

In this context, it is worth summarizing the main definitions to provide a framework for the assessment of a liver lesion. First, a focal abnormality in the liver is hierarchically defined as an observation. First, a focal abnormality in the liver is hierarchically defined as an observation.
to a pathological abnormality, while, if not, it is a pseudo lesion\textsuperscript{104}. If the lesion is <2 cm, it is a nodule. If the lesion causes distortion/destruction of anatomical structures, it is defined as a mass, otherwise, it is a nonmass-like lesion\textsuperscript{4,9,102,105}.

The characterization of a liver lesion considers the features at basal acquisitions paired with the behavior after CM injection. While basal acquisition in CT provides limited information, lesion characterization on MRI starts with the assessment of basal T2w, T1w, and DWI images\textsuperscript{11}. The qualitative assessment signal of liver lesions on T1w and T2w images derives from the early investigations showing altered relaxation times of neoplastic nodules\textsuperscript{106}. The most accepted biological model involves the differences in the interactions between water and macromolecules in normal or pathological tissues, leading to the typical signal characteristics on T1w and T2w images\textsuperscript{107-109}.

The LI-RADS system distinguishes the mild-moderate and the marked T2 hyperintensity\textsuperscript{9,102,109}. In the first case, the lesion is mildly hyperintense than the liver on T2w images, with a signal similar to the spleen. This is suggestive of general malignancy, but it can be noticed also in benign lesions (Figure 1)\textsuperscript{109-112}. Conversely, a markedly T2 hyperintense lesion (Figure 2) has a signal intensity similar to static fluids (eventually maintained at longer echo times); it is suggestive of benignity, with the exception of cystic or hypervascular malignancies\textsuperscript{109,113,114}.

The next sequence to be evaluated is the DWI. In the LI-RADS lexicon, the restricted diffusion is defined as the combination of hyperintensity of the observation at medium-high b values (≥400 s/mm\textsuperscript{2}) together with a signal lower than the liver on the ADC map. The consensual assessment of the two images is strongly recommended to avoid the T2 shine-through artifact (Figure 2)\textsuperscript{109}. In general, the biological basis of restricted diffusion relies on multiple, complex factors leading to the limitation of the Brownian motions of the water molecules in the neoplastic tissues compared to the normal ones\textsuperscript{57,63}. The LI-RADS system includes the

\begin{figure}[h]
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\includegraphics[width=\textwidth]{Figure1}
\caption{Hepatocellular Adenoma (HA, a-g) and Focal Nodular Hyperplasia (FNH, h-p) on MRI with gadoxetic acid. a-h, T2w images. b-i, DWI b=800 s/mm\textsuperscript{2}; (c,l) ADC map (mm\textsuperscript{2}/s). d-g, m-p, 3D GRE, fat-suppressed, T1w images. Contrast study: basal, (m), late arterial (e,n), portal venous (f,o), and hepatobiliary phases (g,p). Images show lesions with mild-moderate hyperintensity on T2w images, with variable restriction on DWI-ADC images, nonrim APHE, with hypointensity (HA), (g) and iso-hyperintensity (FNH), (p) on the hepatobiliary phase.}
\end{figure}
DWI-ADC among the imaging features suggestive of malignancy; it distinguishes a nontargetoid and a targetoid restricted diffusion. A qualitative, visual assessment of the images is recommended, and a marked or mild restriction are distinguished. It is acknowledged that DWI-ADC has a lower sensitivity for HCC than for other malignancies, due to several factors (e.g., differentiation). A difference in fat or iron content between a lesion and the surrounding liver is helpful for the characterization. A lower intralesional fat content than the surrounding liver is suspicious of any malignancy, while a higher intralesional fat suggests the hepatocellular origin of the lesions, which can be malignant or benign. On CT, a lesion with increased fat is significantly hypoattenuating (<10 HU) if compared to a less or non-steatotic liver. Conversely, a hyperattenuating lesion, more than a steatotic, surrounding liver (liver attenuation ≤40 HU) has a reduced fat content. On MRI, the differences in fat content between the lesion and the liver are assessed by the signal decay on the in-phase images or on the fat-only or fat-fraction maps. The iron content is preferably assessed on MR. While the increased intralesional iron suggests benignity (e.g., dysplastic nodules in chronic liver disease), reduced iron content is suggestive of a malignant lesion. The effects of iron on T2* relaxation causes signal decay in the sequences with long echo times (i.e., hypointensity on T2w sequences or signal decay on out-phase images) or on R2* maps.

The assessment of the contrast study is fundamental for the differential diagnosis of a liver lesion. In general, liver lesions are characterized by assessing the contrast enhancement at specific times.
time points after the injection, i.e., the post-contrast phases already described\textsuperscript{109}. First, there is Arterial phase enhancement (APHE), when the enhancement of the lesion is higher than the surrounding liver either during the early or late AP. However, as previously mentioned, APHE can be confidently assessed on the late AP independently from the findings on the early AP\textsuperscript{106,109}. Therefore, the late AP is crucial for the contrast study of the liver. In fact, the APHE cannot be excluded if it is absent on the early AP. Moreover, if the early AP is the only available AP and the APHE is absent, this finding must be considered as non-characterizable\textsuperscript{109}. Two subcategories of APHE are identified into the LI-RADS system: the nonrim and the rim APHE. The first reflects a diffuse arterial blood supply of the lesion, which can be considered as benign or malignant (i.e., the gradual, diffuse neoangiogenesis of the HCC) (Figure 1; Figure 3). Conversely, the rim APHE is a sign of neoangiogenesis at the tumor periphery, which is typical of other malignancies, such as intrahepatic (i) cholangiocellular carcinoma (CCC) (Figure 3)\textsuperscript{109,119}.

The term washout describes the temporal reduction of the contrast enhancement after the AP: the lesion shows a hypoenhancement relative to the surrounding liver parenchyma in the PVP and/or the DP (Figure 3)\textsuperscript{109,120}. The washout has two subtypes related to its spatial distribution within the lesion: if more prominent at the periphery of the lesion, it is peripheral; otherwise, it is nonperipheral. Like rim APHE, the peripheral washout can be observed in non-HCC malignancies with the neoplastic cellular component at the periphery, such as iCCC (Figure 3)\textsuperscript{109}. It must be pointed out that the progressive reduction of

\begin{figure}[h]
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\caption{Hepatocellular Carcinoma [HCC, (a-d)], Intrahepatic Cholangiocellular Carcinoma [iCCC, (e-b)], Fibrolamellar HCC on CT (i-l). \textit{a}, Basal acquisition, \textit{b}, late arterial, \textit{c,g,k} portal venous, \textit{d,h,l} late phases. HCC shows the typical \textit{nonrim APHE} [arrow in (b)], with \textit{washout} on the late phase [arrow in d]. iCCC shows the \textit{rim APHE} [arrow in (f)] with a delayed enhancement of the central fibrous component [arrow in (h)], describing a \textit{targetoid appearance}. Fibrolamellar HCC shows calcification at basal acquisition [arrow in (i)], with heterogeneous APHE and washout (j-l).}
\end{figure}
the enhancement resulting in isointensity of the observation with the surrounding liver is not considered wash-out but fade\(^{109}\).

Other contrast behaviors suggestive of benignity are defined in the LI-RADS system\(^{109,121}\). The parallels blood pool enhancement and peripheral discontinuous nodular enhancement are patterns suggestive of Hepatic Hamangioma (HH)\(^{122}\). In the first, the lesion contrast enhancement mirrors the blood pool (i.e., arteries or veins depending on the phase); in the second case, the lesion has peripheral, expanding areas of enhancement mirroring the blood compartment (Figure 2)\(^{122,123}\).

The contrast study involves the assessment of the transitional and hepatobiliary phases after HSCA. While the isointensity or faint hypointensity are suggestive of hepatocellular, benign lesions or pseudolesions, the hypointensity is suggestive of a malignant or non-hepatocellular lesion (Figure 1)\(^{68,124-126}\).

In LI-RADS version 2018, the capsule has a context of use limited to chronic liver disease\(^{102}\). It refers to a smooth, sharp border around an observation that is more conspicuous than the fibrotic tissue surrounding the cirrhotic nodules. The radiological term capsule refers either to a true capsule (i.e., confirmed at pathology) or to a pseudocapsule (i.e., without correspondence at pathology)\(^{109}\). These two entities cannot be distinguished at imaging. The presence of a capsule is mostly associated to HCC; conversely, other malignancies, such as iCCC, have more infiltrative growth. The LI-RADS identifies two subcategories: enhancing and nonenhancing capsule. Specifically, the enhancing capsule is visible as an enhancing rim in the post-arterial phases (except for the hepatobiliary phase) and is a characteristic sign of progressed HCC\(^{109}\).

All the features described with a concentric pattern are globally encompassed within the targetoid appearance. It is defined when at least one of the following features are present: the rim APHE, the peripheral washout, the delayed central enhancement, the targetoid appearance in the transitional or hepatobiliary phase, and the targetoid diffusion restriction. These features are included into the LI-RADS M category (i.e., high probability of malignancy but not specific for HCC)\(^6\). These findings are generally referred to other malignancies than HCC, such as iCCC (Figure 3), where the neoplastic cellular component is in the periphery and the core is fibrotic, ischemic or necrotic\(^{109,127,128}\). However, it must be considered that a small percentage of HCC can show these features. Moreover, other non-neoplastic conditions may have (e.g., abscesses) or may simulate these features (e.g., granulation tissue after locoregional treatments)\(^{109}\).

### Avascular Lesions: an Algorithmic Approach to Hepatic Cystic Lesions

Hepatic cysts (HC) are fluid-filled lesions with or without an epithelial layer and represent a frequent, often incidental finding\(^{8,129,130}\). The assessment of an HC involves four aspects: the number of cysts, the content (biliary, serous, proteinaceous, necrotic, hemorrhagic, or mixed), morphology (wall thickness, septa, solid component, enhancement), and clinical background\(^{131,132}\).

The presence of a solitary or few HC may suggest simple hepatic cysts (SHC), infectious lesions, benign or malignant primary tumors, and metastases\(^{133}\).

The SHC is part of the ductal plate malformations\(^{134}\). SHC comes from a biliary duct that is separated from the remnant biliary system with further cystic dilatation\(^{135}\). It is the most frequent hepatic lesion (~2.5% of the general population), usually asymptomatic\(^{135,136}\). The imaging findings are typical. On CT, it is hypo-attenuating (0-20 HU). On MRI, SHC has a low signal on T1w images and the typical strong hyperintensity on T2w images, with a thin, well-defined wall, without contrast enhancement or mural nodules\(^{133}\). Rarely, complications such as hemorrhage, infection, rupture, or mass effect of larger cysts must be recognized to avoid misdiagnosis\(^{129,137}\).

Infectious lesions rarely appear as a SHC\(^{138}\). The colonization by the infectious agent can be from the bloodstream or contiguity (i.e., biliary tree), eventually on altered or necrotic parenchyma\(^{139,140}\). Radiological findings partially depend on the etiological factor\(^{138}\). Pyogenic abscesses (PA) are the most frequent among the visceral abscesses, and they are often symptomatic (pain and fever are present in up to 75% and 90% of cases)\(^{138}\). Escherichia Coli, Klebsiella Pneumoniae, and Streptococci are the most frequent causes by contiguity or hematogenous spread\(^{141-143}\). After a pre-suppurative phase, the lesion progresses to a cluster of cystic lesions, which coalesce into a single cyst with irregular walls and septations\(^{132,133}\).

The content has a variable aspect on CT and MRI; gas bubbles may be present\(^{144-147}\). The enhancement of perilesional liver parenchyma is also variable: an eventual inner, hyperenhancing layer of granulomatous tissue may be surrounded by an external edematous hypoenhancing layer\(^{139,130}\).
Amoebic abscesses (Entamoeba Histolitica) are relatively rare in the Western world, but their clinical aspect is similar to PA \cite{144,148}; the clinical data are helpful for the differential diagnosis \cite{149}. Hydatid cysts (Echinococcus Granulosus) are frequent in underdeveloped areas and in people who live in contact with animals (e.g., sheep) \cite{150,151}. Most hydatid infections are asymptomatic, and overlooked, unless complications \cite{150,152}. The categories of Gharbi and the World Health Organization (WHO) classifications are based on the reproductive stage of the parasite matched with the correspondent imaging findings: they range from the simple, thin-wall cyst to intralesional membranes or daughter cysts (all fertile stages), and the inactive cysts (solid or calcified) \cite{153,154}.

The presence of solid, enhancing components (complex cysts, i.e., thick wall, septa, nodules) suggests the neoplastic origin of the solitary cyst \cite{150}. Metastases are the most common malignant lesions in the non-cirrhotic liver; less frequently, they may present a cystic aspect \cite{150,155}. The causes may rely on a rapid growth not supported by the vascular supply of the hypervascular metastases (e.g., neuroendocrine tumors, melanomas, or gastrointestinal stromal tumors, GIST) or necrosis after treatment (e.g., GIST) \cite{156-158}. Adenocarcinomas producing mucin (e.g., ovarian or colorectal cancer, Figure 4) may also give cystic liver metastases \cite{157}. The imaging findings are usually non-specific, the differential diagnosis with primary cystic tumors is based on the clinical history of a primary tumor \cite{130,135}. Mucinous cystic tumors (MCT) and intraductal papillary neoplasms of the biliary ducts (IPNB) are rare primary cystic tumors \cite{159}. They have a variable malignant potential (6% for MCT, 40-80% for IPNB), the first can be described as a complex cyst, while the latter has communication with the biliary tree \cite{159}. Imaging findings, such as nodules and wall enhancement, are correlated with malignancy of MCT, but with limited diagnostic yield \cite{160,161}.

The presence of multiple hepatic cysts can be related to congenital abnormalities \cite{132}. Ductal plate malformations can involve intrahepatic or extrahepatic ducts and derive from the insufficient remodeling of the cylindrical ductal plate \cite{134}. The different malformations are related to the stage

\begin{figure}
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\caption{Liver metastases: breast (a-c), and colorectal cancer (d-f) on CT. Basal acquisition (a,d). Contrast study: late arterial (b,e), and portal venous (c,f) phases. Liver metastases from breast adenocarcinoma show heterogeneous hyperenhancement mainly on the periphery with perilesional enhancement (a-c). Colorectal liver metastases (d-f) appear mostly hypovascular with hypodense, non-enhancing areas giving the appearance of complex cyst.}
\end{figure}
An overview of liver metastases: from hypovascular to hypervascular lesions

The term “hypovascular” and “hypervascular” are not standardized in the LI-RADS lexicon. In general, they refer to the relative enhancement of the lesion compared to the liver.

Liver metastases (LM) have a wide spectrum of imaging findings, depending on the primary tumors, differentiation, histologic behavior (e.g., solid or mucinous), eventual complications, and conditions of the surrounding parenchyma.

Many malignancies, mainly from the gastrointestinal tract, preferentially metastasize to the liver, followed by other primary sites. Many factors affect the phenomenon, such as the huge amount of systemic and portal blood flowing to the liver, the sinusoidal fenestration, and the effect of exosomes on the Kupffer cells in the formation of metastatic niche. LMs usually have an arterial supply. Thus they can be classified on the arterial flow. Hypovascular LMs have reduced enhancement than the liver and are better depicted on the portal phase; hypervascular LMs enhance more than the liver with venous washout or fade.

The paradigm of the hypovascular lesion is the LM from adenocarcinomas of the gastrointestinal tract (Figure 4). The typical architecture consists of a central core with variable aspects: desmoplastic, necrotic, or hemorrhagic. The peripheral, growing portion of the metastasis is classified into different categories at pathology: desmoplastic, pushing, and infiltrative, while the sinusoidal and portal are rare. In the desmoplastic pattern, the LM is surrounded by a fibrous band of fibrotic tissue which contributes to the perilesional enhancement due to vascular compression, the opening of arteriportal shunts, and inflammatory infiltrates; it is usually associated with a better prognosis. Some cases, the effects of the LM on the surrounding parenchyma are detected on CT or MRI as perilesional enhancement (which is different from rim APHE). Currently, a hypothetical correlation between the lesion border on CT and MRI and the pushing or infiltrative pattern has not been demonstrated. Globally, the variable aspect of the lesion core (i.e., fibrosis, necrosis, hemorrhage), the concentration of the viable tumor at the periphery, and the effects on the surrounding parenchyma are responsible for the targetoid aspect on T2w images, DWI, and on contrast studies.

Conversely, malignancies such as NET, GIST, melanoma, sarcomas, renal cell carcinomas, thyroid, and breast carcinomas are frequently hypervascular: a known primary malignancy or a chronic liver disease are helpful for the differential diagnosis with HCC. Common characteristics of these lesions is the APHE (rim or nonrim, Figure 4) due to the significant neoangiogenesis. The washout or fade is variable across the different hypervascular metastases and sometimes provides useful information about the primary malignancy. Finally, the signal intensity on T1 and T2 images is variable due to several factors (e.g., melanin, necrosis, or hemorrhage); on DWI a restricted diffusion is usually noticed.
Hypervascular Liver Lesions: Benign and Malignant Entities

A broad variety of liver lesions are hypervascular (i.e., they present APHE), and their differential diagnosis is sometimes challenging. HH is the most frequent hypervascular lesion after HC (Figure 2)\(^{205}\). The structure of HH explains the imaging findings. It is a mesenchymal lesion composed of multiple vascular spaces with hampered blood flow\(^{222}\). At MRI, the typical T2 marked hyperintensity derived to the nearly-still blood within the vascular spaces without any restriction on DWI\(^{216}\). The contrast enhancement, both on CT and MRI, parallels the blood pool. Thus, the attenuation or the signal is comparable to the vascular compartment better depicted in the respective phase\(^{109,208}\). The most common subtype is cavernous hemangioma, where the large vascular spaces are responsible for peripheral nodular enhancement. In larger lesions, the signal can be inhomogeneous and the progressive, centripetal enhancement can be incomplete in late phases\(^{109,208}\). The flash-filling hemangioma is rarer (16% of HH); the difference with cavernous HH is in the rapid enhancement, which parallels the blood pool\(^{222}\). Other rare, atypical findings are related to the evolution of HH or complications\(^{207}\). The centrifugal enhancement of HH can be explained by the peripheral fibrosis of the lesion\(^{222}\). The sclerosing and sclerosed HH are the end-stage of the fibrotic evolution of HH, particularly in the cirrhotic liver\(^{209-211}\). While calcifications are relatively frequent, other aspects like fluid-fluid levels, and multicystic or pedunculated HH are less frequent\(^{207}\).

Focal Nodular Hyperplasia (FNH) has an incidence of 0.9% and is the second most benign lesion after HH (Figure 1)\(^{212}\). Pathologically, FNH is a hyperplastic, regenerative response to the arterial supply and the ductular proliferation without the development of the portal tract\(^{213}\). The potential of malignant transformation is null\(^{213}\). MRI is considered the gold standard for the assessment of FNH\(^{214}\). At basal acquisitions, FNH typically has a mild-moderate T2 hyperintensity and is hypointense on T1w images\(^{215}\). The overlap with the other lesions on DWI-ADC images limits the diagnostic performance of this sequence\(^{216,217}\). In contrast studies, the central scar is visible in 60% (CT) and 80% (MRI) of cases with delayed enhancement. FNH shows the typical APHE with slight hyperintensity on portal venous phase or fade\(^{215,218,219}\). The active uptake of HSCA by the normal hepatocytes reflects the 4 different patterns on the hepatobiliary phase: homogeneous and heterogeneous hyperintensity, isointensity, hypointensity with peripheral uptake\(^{72,218-220}\). Few caveats must be pointed on the hepatobiliary phase. The perilesional HSCA retention from hepatocellular reaction to CCC and metastases must be differentiated from the peripheral ring uptake of FNH; a targetoid aspect with central hyperintensity suggests retention from fibrous tissue (e.g., metastases) rather than the active uptake of FNH\(^{221}\).

Hepatocellular adenoma (HA) is ten times less frequent than FNH\(^{222}\). It is detected mainly in young females and has a correlation with an abnormal exposure or metabolism of sexual hormones, obesity, glucose storage diseases, maturity-onset diabetes and other complex syndromes (Figure 1)\(^{222}\). At pathology, HA is a benign, clonal hepatocellular neoplasm with a potential evolution to malignancy of 5%; this requires a different management than FNH\(^{223-225}\). The HA are classified in molecular subtypes: inactivation of hepatocyte nuclear factor 1 alpha (HNF1α, 15-40%), inflammatory (18-44%), telangiectatic (previously included among FNH, with the expression of serum amyloid protein, SAA, and C-reactive protein, CRP), activation of β-catenin (with the highest potential of malignant transformation), mixed inflammatory and β-catenin, activation of sonic hedgehog (4%), and unclassified (7-23%)\(^{226}\). Typical features of HA are intrallesional fat, detectable at chemical-shift MRI, various hyperintensity on T2w images, APHE with fade or washout, and a reduced uptake of HSCA with hypointensity on the hepatobiliary phase\(^{218,219}\). Some studies\(^{223,227}\) aimed to correlate the imaging findings on MRI with the molecular subtypes, e.g., the presence of intrallesional fat and moderate APHE in HNF1α, or the atoll sign (i.e., peripheral rim hyperintensity) on T2w with the inflammatory subtype. Though the hypointensity on hepatobiliary phase was considered the most important finding for the differential diagnosis with FNH, its accuracy may have been overestimated due to several factors. The small case series, the misclassification of inflammatory HA within FNH, the absence of molecular data, the active uptake of HSCA by some HA, may lead to misclassification of these lesions in the published data; thus, a more integrated assessment of MRI findings is warranted\(^{214,227-230}\). The differential diagnosis may be more complex when...
other hypervascular lesions are involved in the differential diagnosis with FNH and HA\textsuperscript{231}.

An important differential diagnosis of FNH and HA is HCC and its fibrolamellar variant on non-cirrhotic liver (Figure 3)\textsuperscript{232}. HCC on non-cirrhotic liver presents similar imaging findings of HCC on cirrhotic liver but more often at a more advanced stage (satellite nodules, neoplastic portal vein thrombi, metastases) due to the lack of surveillance\textsuperscript{276,232}. Fibrolamellar HCC is rare, with a peak incidence in the 2\textsuperscript{nd}-3\textsuperscript{rd} decade of life, comparable to FNH and HA. Fibrolamellar HCC typically presents heterogeneous APHE with washout or fade with hypointensity on hepatobiliary phase\textsuperscript{232}. Key points for the differential diagnosis are calcifications (rare in FNH and HA), a bigger scar than FNH, the heterogeneous APHE (homogeneous in FNH), and lack of intralesional fat or hemorrhage (more frequent in HA)\textsuperscript{232}.

CCC is the second malignancy on non-cirrhotic liver after LMs and on cirrhotic liver after HCC; the most common risk factor is the chronic inflammation of the biliary system (Figure 3)\textsuperscript{111,233}. CCC is classified as intrahepatic (iCCC, proximal to the 2\textsuperscript{nd} order bile ducts), perihilar (to the confluence of the cystic duct), and distal (to the papilla major)\textsuperscript{234}. CCC has three growth patterns: mass-forming, intraductal, periductal infiltrating type\textsuperscript{111,235}. At pathology, the vast majority of CCC are mass-forming\textsuperscript{234}. They are non-capsulated nodules with peripheral, growing cellular compartment and a central, firm, fibrous component; other non-classical aspects (e.g., mucinous) are more rare\textsuperscript{234,236,237}. On CT, iCCC is typically hypo-attenuating, with peripheral, early enhancement corresponding to the neoplastic cellular component (rim APHE) while the central fibrous compartment enhances progressively in the delayed phases\textsuperscript{234}. On MRI, a targetoid aspect on T2w and DWI can be detected, with similar findings at the contrast study\textsuperscript{111,235,238}. Capsular retraction, parenchymal hypotrophy, satellite nodules and vascular encasement, rarely with tumor thrombi, are the effect of the infiltrative behaviour\textsuperscript{111,235,239}. The use of HSCA may be beneficial for the characterization and intra-hepatic staging of iCCC: a mosaic hypointensity or targeted aspect on hepatobiliary phase is more frequent in iCCC (targetoid aspect of LI-RADS M category) than in HCC\textsuperscript{100,240}.

The differential diagnosis of other rare hypervascular lesions is beyond the aim of this paper and are described elsewhere\textsuperscript{111,114,241}.

### Chronic Liver Disease: Focus on HCC

HCC is the most frequent malignant tumor in chronic liver disease (CLD)\textsuperscript{2}. Several risk factors are responsible of CLD (e.g., viral, metabolic, toxic...); they sustain chronic, inflammatory damage to the liver parenchyma with a wide, progressive spectrum of damage, from steatosis to fibrosis and cirrhosis\textsuperscript{242}. Historically, the role of imaging in the assessment of CLD was limited. In fact, the typical morphological changes such as the relative hypertrophy of the left and caudate lobe, areas of parenchymal atrophy or confluent fibrosis, the expansion of the gallbladder fossa and perihilar space, altered signal or density are typical of advanced stages of CLD\textsuperscript{235,243-246}. The efforts for the noninvasive assessment of CLD at imaging started with Doppler evaluation of portal hypertension and the hepatic vascularization globally as a consequence of cirrhosis, with ongoing studies on advanced US and MRI techniques\textsuperscript{247-252}. Elastography techniques with ultrasound were subsequently introduced to assess parenchyma stiffness, being the management of cirrhosis one of the main applications\textsuperscript{233,234}. MR elastography has shown promising results, but its utilization is less diffuse\textsuperscript{255}. Other advanced techniques based on artificial intelligence are still in the experimental field\textsuperscript{256-260}. The epidemiology of CLD is changing after the introduction of the newer antivirals and with the increase of metabolic diseases: while MRI is considered the gold standard for noninvasive assessment of steatosis, CT and ultrasound are active fields of research\textsuperscript{261-266}.

The progression of the disease leads to the progressive impairment of liver function with multisystemic consequences and the necessity of transplantation\textsuperscript{267-270}. During the progression of CLD, chronic inflammation also leads to hepatocarcinogenesis: the accurate diagnosis of HCC and the tumor burden is fundamental for the eligibility for transplantation or specific treatments\textsuperscript{267,271,272}. At pathology, hepatocarcinogenesis is a continuous process toward de-differentiation with the development of clonal hepatocellular populations leading to HCC\textsuperscript{273,274}. Cirrhotic or regenerative nodules are surrounded by fibrosis and are the result of the remodeling of liver parenchyma: hepatocytes are normal without any clonality\textsuperscript{275}. The dysplastic nodules (DN) are classified in low- and high-grade: the first have clone-like populations and unpaired arteries, while the high-grade DN have cellular atypia,
trabeculae or pseudoglands. Early HCC is the analogous of the carcinoma in situ of other districts; the difference with the high-grade DN is the stromal invasion, although the growth pattern is not properly infiltrative. The progressed HCC has infiltrative or expansive growth pattern and the ability to metastasize.

Several histological changes occur during hepatocarcinogenesis, detectable at imaging. Neoangiogenesis is characterized by unpaired arteries (not matched with the portal triads) and sinusoidal capillarization (basal membranes with loss of fenestrae); both appear in dysplastic nodules and subsequent steps of hepatocarcinogenesis. The venous drainage changes from the hepatic veins (until early HCC) to sinusoids (progressed HCC without fibrous capsule) and portal veins (progressed HCC with fibrous capsule): this contributes to the corona enhancement in progressed HCC and may explain portal vein tumors. The capsule formation is a fibrovascular structure typical of progressed HCC. The metabolic changes involve the OATP and MRP (multi-drug resistance protein) transporters detected with HSCA, the first being reduced in the high-grade DN and subsequent lesions.

Globally, these pathological alterations explain the radiological findings used for the non-invasive diagnosis of HCC (Figure 3). The proportion of unpaired arteries and reduced portal tracts are responsible of the reduced blood supply of the high-grade DN, and of the APHE of HCC; the mechanisms behind washout and corona enhancement are more complex and non-completely understood. Thus, the first radiological finding of hepatocarcinogenesis is the reduced uptake of HSCA; it is followed by washout in the high-grade DN, APHE in HCC, and the capsule appearance and corona enhancement of progressed HCC. The actual guidelines in the Western world rely on these criteria: the European Association for the study of the Liver (EASL) considered the wash-in (non-rim APHE) and the washout (nonperipheral), independently in the use of HSCA; the LI-RADS categories (in particular from 3 to 5, with increasing probability of HCC at pathology) are assigned on lesion diameter, non-rim APHE, nonperipheral washout and growth while other CT and MRI findings are considered as ancillary features. For a more detailed review of pathological and imaging findings in HCC, please refer to the study by Choi et al.

Beyond Imaging: When to Biopsy?

Liver biopsy is an invasive procedure with reduced, but not negligible, risk of complications, and its use should be relegated to specific cases. The ACR proposed an algorithm for the management of incidental liver lesions on CT. The first discriminant is the lesion diameter (<1 cm, 1-1.5 cm; >1.5 cm); then, the patients are classified in low- or high-risk on the presence of chronic liver diseases or known malignancy. The third step is lesion characterization. In case of hypervascular lesions or in the presence of features suggestive for malignancy (e.g., targetoid aspect, MRI, metabolic imaging (e.g., PET/CT), or biopsy are particularly recommended for larger lesions.

Conversely, in CLD, the high pre-test probability of HCC limits the use of biopsy. In the EASL guidelines, the biopsy is suggested after at least two inconclusive radiological examinations. On the other hand, the indications for liver biopsy in the LI-RADS system are different. Liver biopsy is indicated if the histological or molecular characterization is necessary for treatment or clinical trials, in case of LI-RADS M category or diffuse malignancy, in the presence of extrapepatic malignancy, in selected cases of LI-RADS 3 and 4 categories, or LI-RADS 5 observations in subjects not at risk.

Conclusions

The occurrence of a liver lesion in routine clinical imaging is a frequent event. The differential diagnosis may be challenging for the beginner. The comprehensive, organized, and standardized evaluation of imaging findings, explained by their pathological background, together with clinical data and risk factors, allows, in most cases, the accurate diagnosis of liver lesions.
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Focal liver lesions for beginners

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