Recent Advances in Cytogenetics and Molecular Biology of Adult Hepatocellular Tumors: Implications for Imaging and Management[1]

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Focal nodular hyperplasia (FNH), hepatocellular adenoma (HCA), and hepatocellular carcinoma (HCC) compose hepatocellular neoplasms that occur in adults. These tumors demonstrate characteristic epidemiologic and histopathologic features and clinical and imaging manifestations. HCAs are monoclonal neoplasms characterized by increased predilection to hemorrhage or rupture and occasional transformation to HCC. On the other hand, FNH is a polyclonal tumorlike lesion that occurs in response to increased perfusion and has an indolent clinical course. Up to 90% of HCCs occur in the setting of cirrhosis. Chronic viral hepatitis (hepatitis B and hepatitis C) infection and metabolic syndrome are major risk factors that can induce HCCs in nonfibrotic liver. Recent advances in pathology and genetics have led to better understanding of the histogenesis, natural history, and molecular events that determine specific oncologic pathways used by these neoplasms. HCAs are now believed to result from specific genetic mutations involving *TCF1* (transcription factor 1 gene), *IL6ST* (interleukin 6 signal transducer gene), and *CTNNB1* (β catenin–1 gene); FNHs are characterized by an "imbalance" of angiopoietin. While the β catenin signaling pathway is associated with well- and moderately differentiated HCCs, mutations involving *p53* (tumor protein 53 gene), *MMP14* (matrix metalloproteinase 14 gene), and *RhoC* (Ras homolog gene family, member C) are associated with larger tumor size, higher tumor grade with resultant shortened tumor-free survival, and poor prognosis. Fibrolamellar carcinoma (FLC), a unique HCC subtype, exhibits genomic homogeneity that partly explains its better overall prognosis. On the basis of recent study results involving cytogenetics and oncologic pathways of HCCs, novel drugs that act against molecular targets are being developed. Indeed, sorafenib (a multikinase inhibitor) is currently being used in the successful treatment of patients with advanced HCC. Characterization of genetic abnormalities and genotype-phenotype correlations in adult hepatocellular tumors provides better understanding of tumor pathology and biology, imaging findings, prognosis, and response to molecular therapeutics.

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Learning Objectives

After reading the article and taking the test, the reader will be able to:

- Review the current principles of the cytogenetics and molecular biology of adult hepatocellular neoplasms.
- Discuss the implications of cytogenetic alterations on imaging appearances of hepatocellular neoplasms, including genotype-phenotype correlation.
- Describe the implications of cytogenetic and biologic principles on management of hepatic neoplasms.

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Recent advances in cytogenetics and molecular biology have caused paradigm shifts in all aspects of oncology and have helped clarify understanding of histogenesis and tumor morphology and biology. Numerous studies have helped decipher the complex interplay of host and environmental factors in the pathogenesis of adult hepatocellular neoplasms. Based on genotype-phenotype correlation, hepatocellular adenomas (HCAs) are currently categorized into four histogenetic types that show characteristic histomorphology, imaging findings, and biologic behavior (1). HCAs characterized by *TCF1* (transcription factor 1 gene) mutations show diffuse steatosis, association with familial diabetes or adenomatosis, and an indolent clinical course except for a small increase in the risk of bleeding (1,2). Inflammatory HCAs (caused by *IL6ST* [interleukin 6 signal transducer gene] mutations) with inflammatory infiltrates and marked sinusoidal dilatation, display an increased propensity to hemorrhage and a small risk of malignant transformation (1,2). HCAs due to *CTNNB1* (β catenin–1 gene) mutations, and HCAs in glycogen storage disease show an increased risk of transformation to hepatocellular carcinoma (HCC) (1,2). A wide variety of chromosomal alterations, including genetic and epigenetic abnormalities resulting in activation of proto-oncogenes and silencing of tumor suppressor genes, are thought to play a causative role in HCC. HCCs associated with different etiologic factors show distinct genetic "signatures." While chromosomal instability and *AXIN1* (axin-1 gene) mutations characterize HCCs due to chronic hepatitis B infection, aflatoxin B exposure, and metabolic syndrome–induced HCCs show frequent *p53* (tumor protein 53 gene) mutations (3,4). Better understanding of the tumor nosology and the molecular events involved in the origin and progression of hepatocellular tumors permit development of effective targeted therapies; the use of sorafenib in the management of advanced HCC is a testament to this (5). In this review, we will provide a current update on the cytogenetics and molecular biology of adult hepatocellular neoplasms and their implications for imaging and treatment.

Essentials

- On the basis of genetic abnormalities, pathology findings, and clinical features, hepatocellular adenomas (HCAs) are classified into four distinct subtypes, each associated with specific gene mutations, characteristic histomorphology, risk factors, biologic behavior, and natural history (including patterns of complications); select subtypes have distinct imaging findings that permit accurate diagnosis.
- Complete resection is an effective option, with low to negligible recurrence rate, for nonsteatotic HCAs larger than 5 cm, for HCAs that continue to grow despite stopping the offending drugs (oral contraceptives, androgens, steroids, clomiphene, or barbiturates), or HCAs with β catenin activation (based on imaging and/or biopsy findings), for HCAs with malignant changes, and for all HCAs in males.
- Better understanding of tumor nosology and the molecular events involved in the origin and progression of hepatocellular tumors permits development of effective targeted therapies; the use of sorafenib in management of advanced hepatocellular carcinoma (HCC) is a testament to this.
- Metabolic syndrome (dyslipidemia, insulin resistance or type 2 diabetes, hypertension, and obesity) is an important and emerging risk factor for HCC, and up to 25% of cases of nonalcoholic steatohepatitis in the setting of metabolic syndrome progress to cirrhosis.
- There are several "molecular signatures" that help predict tumor biology in human HCC and, hence, influence the imaging appearance and prognosis.

Focal Nodular Hyperplasia

Focal nodular hyperplasia (FNH), the second most common benign liver tumor (after hemangioma), accounts for up to 8% of all liver neoplasms, with an estimated prevalence of 0.9% (6). FNH occurs predominantly in young women in the 3rd and 4th decades of life. In pathologic terms, FNH is characterized by regenerative hepatic nodules with a central scar and radiating fibrous cords that contain dystrophic vessels and reactive ductules. The majority of FNHs are solitary (80%), smaller than 5 cm in diameter, and occur near the surface of the liver (7). In contrast to monoclonal HCAs, which frequently bleed, FNHs are polyclonal tumorlike lesions and do not undergo hemorrhage or malignant transformation. The majority of FNHs are asymptomatic; up to a third of patients may present with abdominal pain or a palpable mass (8). Typically, FNH follows a benign natural course and remains stable or may even decrease in size at follow-up examination (9,10).

FNH does not show *CTNNB, p53,* or *HNF1*α (hepatocyte nuclear factor 1 α gene) mutations. FNHs typically show dysregulation of angiopoietin genes. Angiopoietin genes (*ANGPT1* and *ANGPT2*) are responsible for maturation of blood vessels. An increase in the *ANGPT1/ANGPT2* expression ratio results in uncontrolled maturation and remodeling of vessels, resulting in dystrophic vascular architecture typical of FNH (11,12). In contrast to HCAs, which are true neoplasms, FNHs are thought to occur as a result of hyperplastic response to a vascular anomaly, with disorganized growth of hepatocytes and bile ducts. In a normal liver, the artery within the portal tract supplies the peribiliary vascular plexus,

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Abbreviations:
FNH = focal nodular hyperplasia
HCA = hepatocellular adenoma
HCC = hepatocellular carcinoma

Potential conflicts of interest are listed at the end of this article.

the portal vein wall, and the portal tract interstitium. According to the hypothesis of Wanless et al (13), FNH results from portal tract injury (due either to portal tract inflammation or arterial ischemia) leading to arterioportal or hepatic venous shunts, arterialized sinusoids with hepatocellular hyperplasia, and cholestasis. It is believed that the disappearance of portal vein and bile ducts leads to ductular reaction and fibrosis. Arterial hyperperfusion (and resultant hyperoxemia) leads to increased expression of vascular endothelial and somatic growth factors and activation of hepatic stellate cells (14). Activated stellate cells are thought to be responsible for the formation of the characteristic central scar (15). Although an association with oral contraceptive use has been speculated, owing to increased prevalence of these tumors in young women, studies have shown that FNH is not hormonally dependent and is not affected by oral contraceptives or pregnancy (16). FNHs also occur in association with other vascular abnormalities, such as hereditary hemorrhagic telangiectasia (Rendu-Osler-Weber disease) and congenital absence of the portal vein (17). β-Catenin activation without mutation has also been shown to occur in focal nodular hyperplasia, contributing to hepatocellular hyperplasia and regeneration (18). The major pathogenetic mechanisms involved in the evolution of FNH, with correlative imaging appearances, are summarized in Figure 1.

Figure 1

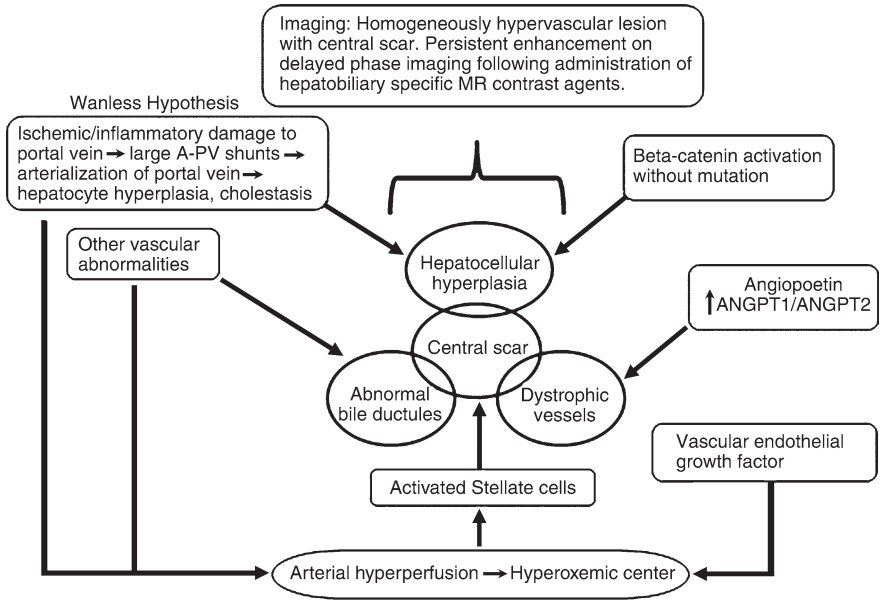


Figure 1: Chart shows pathogenesis of FNH with correlative imaging findings. *A-PV* = arterial–portal venous, MR = magnetic resonance.

At ultrasonography (US), FNH is typically isoechoic to the liver parenchyma and may show a central vascular scar. Classic FNHs demonstrate characteristic findings on dynamic multiphase computed tomographic (CT) and MR images. FNHs enhance homogeneously in the arterial phase and become isointense to the liver on portal venous phase images (Fig 2). FNHs are iso- to slightly hypointense (to liver) on T1-weighted MR images and iso- to slightly hyperintense on T2-weighted images. The central scar, which is seen in 65%–85% of cases, is typically hyperintense on T2-weighted images and shows delayed enhancement (19).

MR imaging with hepatobiliary-specific contrast agents such as gadoxetic acid (Eovist; Bayer Schering Pharma, Berlin, Germany) is increasingly being used to help confirm the diagnosis of FNH and differentiate it from other hypervascular liver masses such as HCA, HCC, and metastases. About 50% of the gadoxetic acid is preferentially excreted through the hepatobiliary system. FNH is characterized by an increased density of functioning hepatocytes and hence shows persistent enhancement (iso- or hyperintense) on delayed phase (20 minutes) gadoxetic acid–enhanced images (20) (Fig 3). Presence of abnormal bile ductules that fail to communicate with the normal biliary system possibly results in defective or delayed excretion with persistent contrast agent retention. In contrast, HCAs and HCCs typically do not show contrast agent retention.

Asymptomatic FNHs are managed conservatively and do not necessitate surgical intervention. Surgical excision is performed if the lesions become symptomatic or if they enlarge.

Hepatocellular Adenoma

HCAs are uncommon benign monoclonal hepatic neoplasms often seen in young women with a prolonged history of oral contraceptive use. The duration of oral contraceptive use (>5 years) and the estrogen content determine the risk of developing HCAs (21,22). HCAs rarely occur in children and men; the male-to-female ratio has been reported to be 1:9 (23). Other documented risk factors for HCA include use of anabolic steroids, glycogen storage disease (types Ia, III, and VI), hemochromatosis, androgen therapy, use of barbiturates, and clomiphene intake (24–26). Because of a markedly increased proclivity to bleed or rupture and a rare potential for malignant change, HCAs are commonly candidates for surgery.

HCA Subtypes

Clinically, up to 50% of HCAs are asymptomatic (27). Common clinical symptoms include right upper quadrant fullness or discomfort and mass. Severe pain may be related to hemorrhage or infarction. Up to 10% of patients may present with severe abdominal pain with hemoperitoneum (25). Based on genetic abnormalities, pathologic examination findings, and clinical features, HCAs are classified into four distinct subtypes

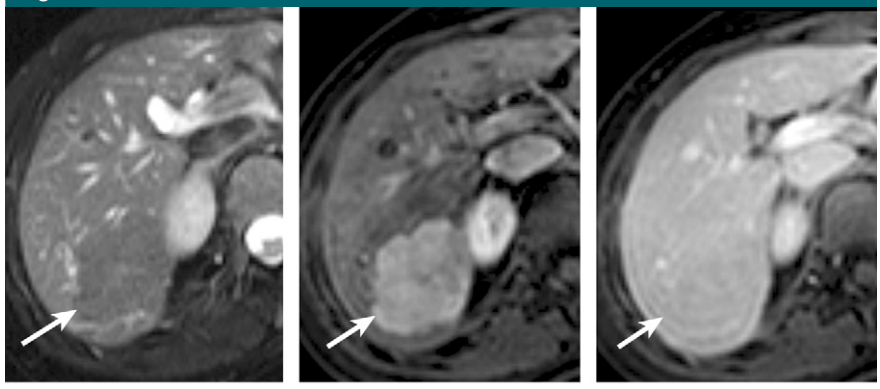
(Table 1) (1,2,25,28). Each HCA subtype is associated with specific gene mutations, characteristic histomorphology, risk factors, biologic behavior, and natural history (including patterns of complications). Furthermore, select subtypes have distinct imaging findings that permit accurate diagnosis.

Inflammatory HCAs, the most common (40%–55%) subtype of HCAs, display characteristic histopathologic features of inflammatory infiltrates, sinusoidal dilatation, and dystrophic vessels without fibrosis. Inflammatory HCAs are associated with obesity, hepatic steatosis, and increased serum and tumor levels of acute inflammatory markers such as γ-glutamyl transferase, serum amyloid–associated protein, and C-reactive protein (29). Previously misclassified as telangiectatic FNH, these tumors tend to bleed frequently (up to 30% of cases) (25). This subtype of HCA can occur in both men and women, with the tumors in men almost always being solitary (2). A small subset (5%–10%) of these tumors with additional β-catenin activation may progress to HCC.

Inflammatory HCAs are characterized by inappropriate and sustained activation of interleukin 6 and STAT3 (signal transducer and activator of transcription 3) signaling pathways. Interleukin 6 is a polyfunctional proinflammatory cytokine that mediates inflammatory response through activation of the JAK-STAT (Janus kinase–signal transducers and activators of transcription) signaling pathway. Sixty percent of inflammatory HCAs demonstrate somatic gain-of-function mutations involving the *IL6ST* gene that encodes the oncogene *gp130* (glycoprotein 130) (30). The remainder of the inflammatory HCAs show *STAT3* activation without mutations in *gp130* (31). At imaging, inflammatory HCAs manifest as hypervascular liver masses with persistent enhancement on portal venous and delayed phase images (Fig 4). On T2-weighted MR images, tumors are markedly hyperintense, correlating with areas of sinusoidal dilatation. Focal areas of microscopic fat may be seen in a small (11%) subset of patients (32). Sensitivity, specificity, and positive and negative predictive values of marked T2 hyperintense signal with delayed persistent enhancement are 85.2%, 87.5%, and 88.5% and 84%, respectively, for the diagnosis of inflammatory HCA (32).

HCAs with *TCF1* gene mutations, the second most common subtype, account for up to 30%–35% of HCAs. *TCF1* encodes the tumor suppressor hepatocyte 1α, *HNF1*α. Biallelic inactivation of *TCF1* may be somatic (90%–95%) or germ line (up to 10%) in origin. *TCF1* gene mutations of somatic origin are almost exclusively seen in young women using oral contraceptives (>90%) and lack cytologic abnormalities and inflammatory infiltrates (17). Up to 50% of female patients develop multiple HCAs. A cause-and-effect relationship between estrogen intake and development of HCAs is still poorly understood. Genotoxic effects of estrogen resulting both in *HNF1*α mutations and in *HNF1*α mutations leading to accumulation of estrogen metabolites that in turn stimulate hepatocyte proliferation, have been implicated (33,34). HCAs with *TCF1* mutations are diffusely steatotic owing to increased fatty acid synthesis and impaired transport of fatty acids resulting in excessive intratumoral lipid accumulation (35). Germ line mutations of the *TCF1* gene result in maturity-onset diabetes of the young type 3 and familial adenomatosis (1,36,37).

Figure 2



a. b. c.

Figure 2: FNH incidentally discovered in an asymptomatic 32-year-old woman. Axial **(a)** T2-weighted (repetition time msec/echo time msec, 1800/85; 6-mm section thickness) and **(b, c)** gadolinium-enhanced T1-weighted (3.62/1.73; 5-mm section thickness) **(b)** hepatic arterial phase and **(c)** portal venous phase MR images show typical imaging features. Lesion (arrow) is homogeneously hypointense with a central hyperintense scar on **a,** shows intense arterial enhancement on **b,** and becomes isointense to liver parenchyma on **c.**

Figure 3

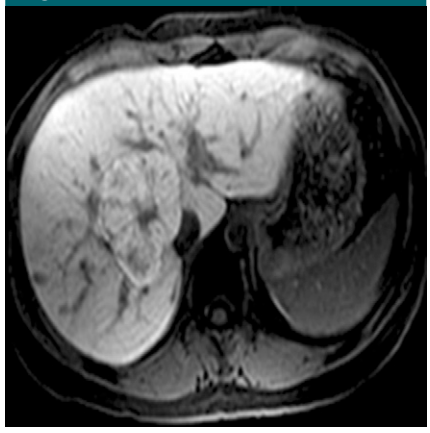


Figure 3: Axial T1-weighed (3.62/1.73; 5-mm section thickness) MR image obtained 20 minutes after administration of gadoxetic acid shows persistent enhancement of lesion with a central scar, characteristic of FNH.

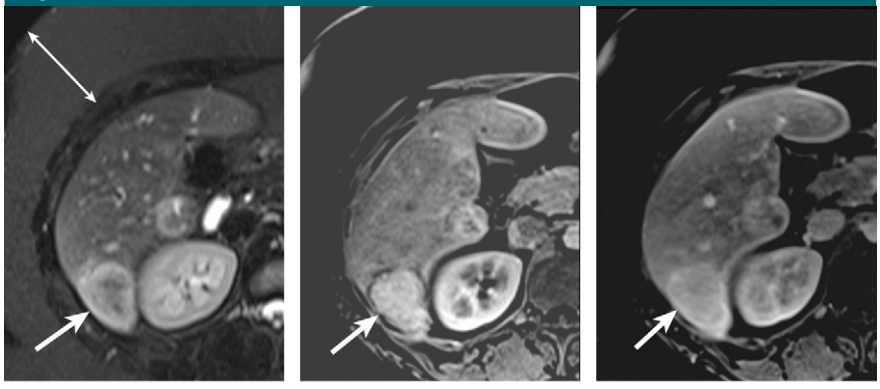
At imaging, *TCF1* gene–associated HCAs appear as heterogeneous lesions with predominant areas of steatosis and variable enhancement. On T1-weighted MR images, these are typically hyperintense owing to the presence of glycogen, fat, and less commonly, hemorrhage. Typically, diffuse signal dropout is seen on T1-weighted chemical shift MR images, indicating intracellular fat (Fig 5). On T2-weighted images, these HCAs are typically homogeneous and can be

Table 1

Summary of Major Subtypes of HCA

Subtype	Sex Distribution	Frequency (%)	Clinical Features	Imaging Features
HCA with *TCF1* gene mutation	Exclusively in women	35–50 Somatic, <5 germ line mutations	Tend to develop adenomatosis; associated with maturity-onset diabetes of the young type 3	Diffuse steatosis within lesion; arterial enhancement that does not persist into venous phase
HCA with β-catenin activation	Men and women	10–18	Associated with male hormone administration and glycogen storage disease; increased risk of progression to HCC.	Not usually steatotic; arterial enhancement with portal venous washout
HCA with inflammatory infiltrates (*IL6ST* mutations)	Most frequent in women, but also found in men	40–55	Associated with obesity, alcohol use and hepatic steatosis. Formerly classified as telengiectatic FNH; Tend to bleed. 10% express beta-catenin and are at risk of malignant transformation.	Marked sinusoidal dilatation; hyperintense on T2-weighted MR images; intense arterial enhancement that persists on venous and delayed phase images
Unclassified		10	...	...

Figure 4



a. b. c.

Figure 4: Inflammatory HCA in a 48-year-old woman who presented with vague upper abdominal discomfort and elevated C-reactive protein and γ-glutamyl transferase levels. Lesion (single-headed arrow) is hyperintense on **(a)** T2-weighted (1800/85; 6-mm section thickness) MR image, shows homogeneous enhancement on **(b)** T1-weighted hepatic arterial phase (3.62/1.73; 5-mm section thickness) MR image, which persists into **(c)** portal venous phase (3.62/1.73; 5-mm section thickness) MR image and delayed phase MR image (not shown) after administration of a gadolinium chelate. Note marked obesity (double-headed arrow on **a**).

iso-, hypo-, or hyperintense to the surrounding liver. After administration of gadolinium chelate, moderate enhancement is seen in the arterial phase without persistent enhancement in the portal venous and delayed phases. Diffusely steatotic adenomas may be difficult to differentiate from benign nodular steatosis and fat-containing HCCs on the basis of imaging findings alone; definitive diagnosis may warrant histopathologic and immunohistochemical analyses (38). The sensitivity, specificity, and positive and negative predictive values of diffuse signal intensity decrease on T1-weighted out-of phase chemical shift images for predicting the *HNF1*α-inactivated tumors are 86.7%, 100%, and 100% and 94.7%, respectively (32). These HCAs may be multiple (up to 50% in some series) and do not have the tendency to undergo malignant transformation (25). HCAs larger than 5 cm may bleed (25).

HCAs with β catenin activation constitute up to 10% of adenomas. Specific risk factors associated with this group of tumors include glycogen storage disease, male hormone administration, and familial polyposis syndrome (2). These subsets of HCA are, therefore, seen in both men and women. The incidence of hepatic adenomas in glycogen storage disease varies from 22%–75% (39). The majority of people with glycogen storage disease develop HCA by the 2nd or 3rd decade. Up to 75% of these patients older than 30 years harbor HCA. Chronic liver inflammation due to glycogen storage disease leads to development of HCAs and HCCs. Major chromosomal and genetic alterations encountered in HCAs in glycogen storage disease include gain of chromosome 6p (possibly involving multiple oncogenes) and loss of chromosome 6q, involving multiple tumor-suppressor genes such as *IGF2R* (insulin-like growth factor 2 receptor) and *LATS1* (large tumor suppressor, homolog 1) (40). Chromosome 6p gains and 6q losses, as well as *IGF2R* mutations, are also frequently described in HCCs and preneoplastic dysplastic nodules, thereby accounting for the high risk of malignant transformation associated with HCAs in patients with glycogen storage disease (41,42). *HNF1*α mutations are not seen in HCAs with glycogen storage disease and *CTNNB1* mutations are less frequently encountered (four of 14 cases reported in the literature at the time of this writing) (1,2,40,43).

On images, HCAs due to *CTNNB1* mutations may appear as homogeneous or heterogeneous hypervascular masses without discernible intratumoral fat (Fig 6). Signal intensity on T2-weighted MR images is heterogeneous and can be iso-, hypo, or hyperintense relative to liver; intense arterial enhancement is seen, which may or may not persist into the delayed phase (32). Tumors occurring in the setting of glycogen storage disease may show diffuse increased attenuation of liver on CT images (Fig 7). HCAs with β catenin activation have an increased risk of transforming to HCC; close-interval imaging follow-up, biopsy, and/or surgical excision may be warranted in this subset of patients. Up to 10% of HCAs do not show *HNF1α*, *CTNNB1,* or *IL6ST* mutations. Predominant molecular pathogenesis of this subset of tumors is still to be elucidated.

Hepatic adenomatosis is defined as the presence of more than 10 adenomas in an otherwise normal liver. Patients with glycogen storage disease are typically excluded from this definition, per the initial description by Flejou et al in 1985 (44). A female preponderance has also been reported, although an association between estrogen or exogenous steroid intake and hepatic adenomatosis is still unclear (45). Steatotic HCAs with *TCF1* gene mutations tend to develop familial hepatic adenomatosis, which accounts for a subset of hepatic adenomatoses. Inflammatory adenomas can also manifest with hepatic adenomatosis (45). Overall, a substantial risk of bleeding (up to 63%) and a small risk of malignant transformation (less than 10%) have been reported with hepatic adenomatosis (46). As noted by Veteläinen et al (47), this is likely due to selection bias when considering only symptomatic patients; the authors in that meta-analysis also concluded that the rate of intrahepatic bleeding and intratumoral bleeding in asymptomatic incidentally discovered adenomatosis are 2% and 13%, respectively, which is not markedly different from that of solitary HCA. The potential risk of complications is, therefore, likely related to the underlying histologic subtype and tumor size rather than to the number of HCAs.

Figure 5

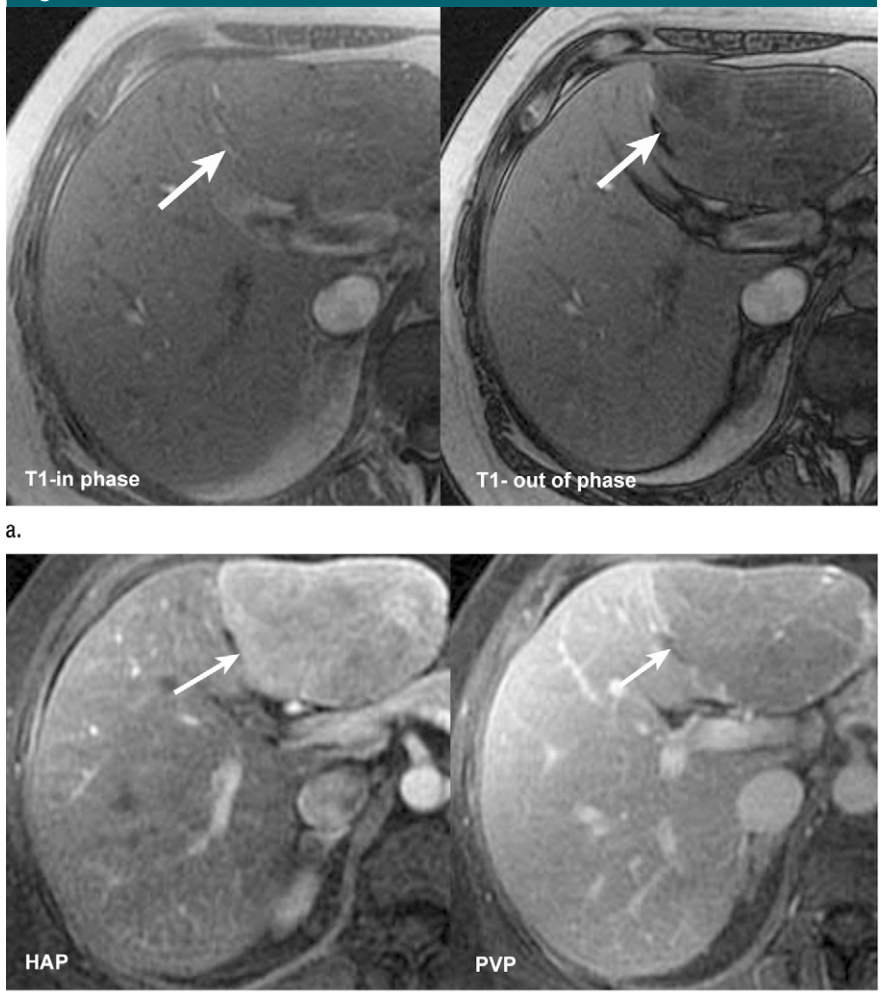


Figure 5: Diffusely steatotic HCA in a 50-year-old woman. Axial 6-mm thick T1-weighted **(a)** in-phase (110/4.5) and out-of phase (110/2.2) MR images show large lesion (arrows) in left hepatic lobe, with diffuse signal intensity decrease evident on out-of-phase image, consistent with presence of microscopic fat. **(b)** After intravenous administration of gadolinium chelate, axial T1-weighted images (3.6/1.5; 4-mm section thickness) show lesion (arrows) with intense arterial enhancement during hepatic arterial phase *(HAP),* which does not persist into portal venous phase *(PVP).*

Management of HCA

Recent insights into the molecular classification of HCA have spawned a new paradigm for its management. Surgical resection was considered the treatment of choice for HCA, with liver transplantation reserved for multiple adenomas. The number of adenomas was previously considered an important independent risk factor for predicting complications such as hemorrhage and malignant transformation. Better understanding of cytogenetics, the different histologic subtypes, and genotype-phenotype correlations obviate aggressive surgical resection with its attendant morbidity in all patients with HCA (25).

It is now clear that the rate of complications depends not on the number of lesions but on the histologic subtype and size of the tumor. HCAs with *HNF1α* mutation and inflammatory HCAs together account for up to 80% of HCAs. The imaging appearances, tumor biology, prognosis, and management of these two major subtypes differ substantially.

Figure 6

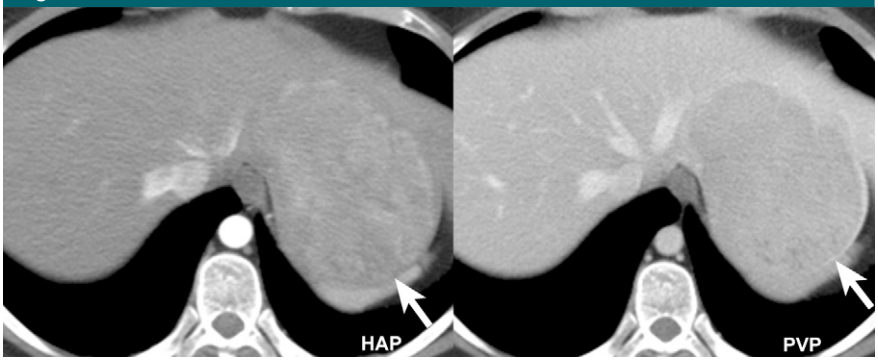


Figure 6: Axial contrast agent–enhanced CT scans show HCC (arrows) against a background of HCA in a 48-year-old woman without cirrhosis or documented risk factors for HCC. Left: Hepatic arterial phase *(HAP)* image shows enhancing mass in left hepatic lobe. Right: Washout is evident in portal venous phase *(PVP)* image. Lesion proved to be HCC arising in an HCA, which was diagnosed at surgical excision.

Figure 7

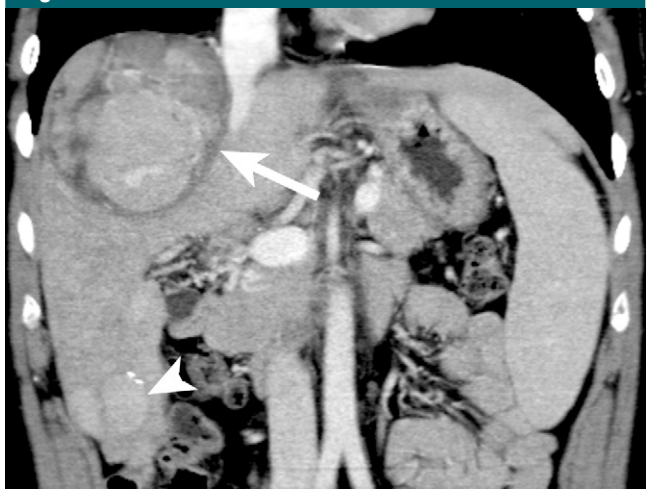


Figure 7: Coronal contrast-enhanced CT scan in 39-year-old man shows multiple HCAs in patient with glycogen storage disease. Foci of intense arterial enhancement intermixed with areas containing fat are seen in largest lesion (arrow) near dome of the liver. Multiple smaller lesions are also seen, some with foci of calcification (arrowhead). Percutaneous biopsy of this large lesion showed HCC against background of HCA.

MR imaging can be used to characterize and differentiate these two major subtypes of HCAs (steatotic and inflammatory) and thus permit optimal management. Management also depends on whether the patient is symptomatic or asymptomatic (Fig 8). Asymptomatic diffusely steatotic HCAs (due to *HNF1*α mutation) are unlikely to undergo malignant transformation (25,27). These adenomas have a lower tendency to bleed, as well; substantial bleeding is seen in up to 9% of tumors (25). Hence, asymptomatic steatotic HCAs do not warrant aggressive surgical resection or biopsy and can be managed with clinical and imaging surveillance (1,35).

In contrast, inflammatory HCAs that occur predominantly in obese patients with background hepatic steatosis harbor a small risk of malignancy. Although peliosis is much more common in inflammatory adenomas than in the *HNF1*α mutated subtype (52% vs 4%), there is no notable difference in risk of clinically manifest bleeding between these two subtypes (16% vs 9%). Risk of malignancy is also higher in males (up to 50%) (27,39). Although *CTNNB* mutations are implicated in malignant transformation of hepatic adenomas, only 20% of malignant HCAs show *CTNNB* mutations, which suggests alternate pathways of malignant transformation (27,39). Overall, up to 20% adenomas manifest with spontaneous bleeding, and up to 10% undergo malignant transformation (25,27). Spontaneous bleeding is seen in tumors larger than 5 cm, and malignant transformation is commonly seen in tumors larger than 8 cm.

Complete surgical resection is, therefore, an effective option for nonsteatotic HCAs larger than 5 cm, HCAs that continue to grow despite stopping use of the offending drugs (oral contraceptives, androgens, steroids, clomiphene, or barbiturates), HCAs with β catenin activation (based on imaging and/or biopsy results), HCAs with malignant changes, and all HCAs in men. Surgical resection is effective, with low rates of recurrence (25,27).

The most common acute manifestation of HCA is intratumoral hemorrhage or rupture causing hemoperitoneum (Fig 9). Hemorrhage secondary to HCA is not always life threatening. Hemodynamic instability is rarely associated with ruptured adenomas, and selective hepatic artery embolization usually stabilizes the patient and reduces tumor size (48–50). Embolization also reduces the risk during elective surgery, and may obviate surgical resection (25,51). Transarterial chemoembolization and radiofrequency ablation are effective, and less aggressive, alternative approaches for tumors smaller than 5 cm in diameter. Radiofrequency ablation has been found to be the most cost-effective approach in the management of small HCAs, as compared with surgery, transarterial embolization, and watchful waiting (52).

Overlapping imaging features between inflammatory HCAs and those with β catenin activation (which may be associated with inflammatory changes) necessitates biopsy in patients with

features of inflammatory adenoma on MR images (32). Biopsy is also recommended for HCAs that continue to grow despite the patient stopping use of the offending drugs (oral contraceptives, steroids, androgens, barbiturates, and clomiphene). Histologically, HCA appears as disorganized cords or plates of hepatocytes with variable degrees of intra- and extracellular fat, telangiectasia, thickened arteries, and lack of bile ductules. Specific findings at immunohistochemical and cytogenetic evaluation help to categorize these tumors into individual subtypes and enable identification of patients at risk. Inflammatory HCAs are characterized by polymorphous inflammatory infiltrates and marked telangiectasia, with tumor cells showing strong expression of serum amyloid–associated protein and C-reactive protein at immunohistochemical examination (31). HCAs with β catenin activation show cytologic abnormalities and pseudoglandular formation at histologic assessment, with strong diffuse overexpression of glutamine synthetase and heterogeneous overexpression of β catenin at immunohistochemical analysis (53). Diffusely steatotic HCAs (those with *HNF1α* mutation) show disorganized cords or plates of hepatocytes containing intra- and extracellular fat. At immunohistochemical evaluation, these adenomas demonstrate lack of staining for liver fatty acid binding protein due to *HNF1α* mutation.

Several potential questions still need to be addressed, however. These include the magnitude of sampling errors associated with needle biopsy, the risk of hemorrhage, and tumor seeding along the needle track, as well as the occasional difficulty in distinguishing HCA from well-differentiated HCC at histopathologic examination of limited core biopsy samples.

Optimal management guidelines for hepatic adenomatosis have not been established. Since the risk of serious complications does not depend on the number of nodules, management of hepatic adenomatosis should depend on the underlying histologic subtype and size of the lesions rather than on their number. Withdrawal of exogenous steroid intake decreases the risk of bleeding but does not affect lesion size or growth (54,55). Symptomatic lesions and asymptomatic lesions larger than 5 cm are preferably managed with surgical resection (54). Liver transplantation should be reserved for cases of progressive liver failure or malignant transformation (56) and is no longer advised for patients with asymptomatic familial adenomatosis. Asymptomatic lesions smaller than 5 cm can, in general, be managed conservatively with close clinical and imaging follow-up (47). In addition, presence of multiple adenomas raises the possibility of coexistent diabetes mellitus (mature-onset diabetes of the young, type 3) (37).

Management of HCA in women of child-bearing age is more complicated, given the increased risk of growth and bleeding during pregnancy. Adenomas that bleed or rupture during pregnancy are frequently found to be large. Up to 59% of large HCAs may rupture, with resultant maternal and fetal mortality rates in the range of 30%–40% (57). However, studies have shown that, contrary to previous belief, pregnancy is not contraindicated in patients with HCA (25). Although there are no consensus guidelines about the management of adenomatosis in young women, aggressive

Figure 8

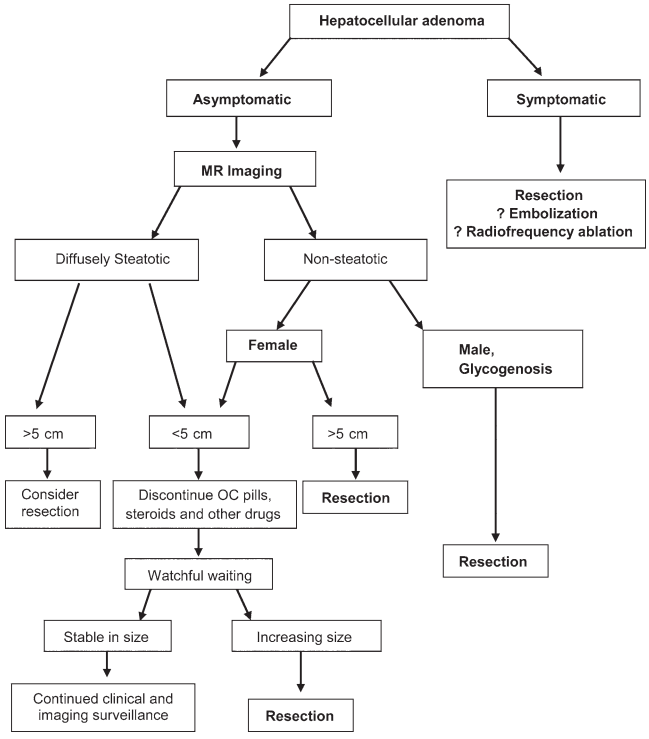


Figure 8: Flowchart depicts management of HCA. The roles of MR imaging and image-guided biopsy are highlighted.

Figure 9

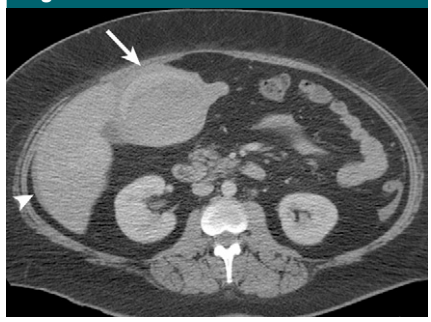


Figure 9: Axial contrast-enhanced CT image in a 45-year-old woman who presented with acute right upper abdominal pain shows large right hepatic mass (arrow) with perilesional and perihepatic hemorrhage (arrowhead), consistent with ruptured HCA with hemoperitoneum.

Figure 10

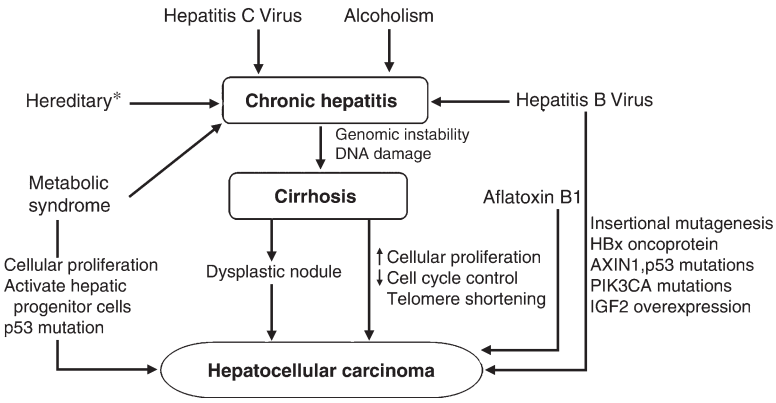


Figure 10: Chart shows major causes of HCC with specific salient molecular mechanisms. * = Includes α1-antitrypsin deficiency, hemochromatosis, acute intermittent porphyria, glycogen storage disease, and autoimmune hepatitis.

management strategies may be warranted for HCAs that are larger than 5 cm or that show interval growth on follow-up images. Asymptomatic HCAs smaller than 5 cm may be managed with close clinical and imaging monitoring. MR imaging seems to be the preferred modality for follow-up in young women, given its inherent advantage of the lack of ionizing radiation. The cost-effectiveness of the various available management strategies, however, still needs to be established with large scale studies.

In general, the majority of small HCAs remain stable, and a small percentage of them tend to have disappeared by the time of follow-up imaging (2). There are no clear-cut data on an optimal interval and duration for follow-up. Annual imaging follow-up of HCAs is recommended for both solitary HCA and hepatic adenomatosis (54), and some authors recommend periodic surveillance until menopause (2).

Hepatocellular Carcinoma

HCC, the most common primary hepatic malignancy (85%–90% of primary liver cancers), is the fastest growing cause of cancer-related deaths in the United States. There has been a two-fold increase in the age-adjusted rates of HCC, from 1.3 per 100 000 per year during 1978–1980 to 3.3 per 100 000 per year during 1999–2001 (58). The current estimated incidence of HCC varies from fewer than 10 cases per 100 000 people per year in North America and Western Europe to 50–150 per 100 000 per year in parts of Africa and Asia (59). HCC is an increasing public health problem because of this increasing incidence and poor survival.

Etiology of HCC

The etiology of HCC is multifactorial, owing to an interplay of potentially preventable environmental factors such as viral infections (hepatitis B and hepatitis C viruses), contaminated food (aflatoxin B1), and industrial chemicals; genetic factors such as hereditary hemochromatosis and α1-antitrypsin deficiency; and lifestyle factors such as alcohol abuse, tobacco use, obesity, and diabetes mellitus (60) (Fig 10). Up to 90% of HCCs occur secondary to underlying chronic liver disease. Chronic hepatitis B infection, metabolic syndrome, and aflatoxin B exposure are emerging etiologic factors of HCC in a nonfibrotic liver.

Chronic hepatitis B virus infection, which is predominantly confined to Asia, is the leading cause of HCC worldwide (53% of HCCs) (61). Hepatitis C virus is the major risk factor for HCC in Japan, North America, and Europe. Around 15%–35% of hepatitis C–infected patients develop cirrhosis after 25–30 years of infection (62). The risk of HCC is estimated to be 1%–3% after 30 years of infection, with an incidence of 2%–8% per year in patients with hepatitis C–related cirrhosis (63,64). The risk of HCC in hepatitis C–induced cirrhosis does not correlate with viral load but depends on a number of host and environmental factors, including advanced age, alcoholism, and tobacco use (65). In contrast, HCC risk in hepatitis B virus–infected individuals depends on the viral load (66). Compared with the healthy population, individuals with chronic hepatitis B viral infection have a 25–37-fold increase in the risk for developing HCC. Aflatoxin B1–contaminated foods also account for a large number of HCC cases in endemic areas (67). Recently, obesity and diabetes mellitus have been implicated as important risk factors for development of HCC (68). Obesity and diabetes mellitus are associated with nonalcoholic steatohepatitis, which progresses to cirrhosis in up to 25% cases (currently included under the rubric of *cryptogenic cirrhosis*), with subsequent increased risk of HCC.

Cytogenetics and Molecular Biology of HCC

Extensive genetic studies on HCC have helped elucidate the pathways of hepatic carcinogenesis that may be etiology specific (integration of hepatitis B viral DNA, *p53, KRAS* mutations) or nonspecific (activation of the Wnt/β-catenin pathway, PI3K/Akt pathway). A vast majority of HCCs arise in the setting of cirrhosis. Molecular mechanisms that induce HCC formation at the cirrhosis stage include telomere shortening with resultant chromosomal instability (fusion, breakage, gains and losses, and translocations); alterations of micro- and macroenvironmental factors (activation of stellate cells with resultant increased production of extracellular matrix proteins, cytokines, and growth factors; immune-mediated and hepatitis-related inflammation), and promotion of cellular proliferation (69–71). Hepatocytes in a cirrhotic liver demonstrate DNA hypermethylation and telomere shortening without other major genetic mutations or chromosomal abnormalities. These events, however, impair the process of regeneration and accelerate the

process of fibrosis. The extent of telomere shortening and telomerase activity in high-grade dysplastic nodules is similar to that of HCC. Telomerase activity is seen in more than 90% of HCCs (64). Deregulation of the DNA methylation process due to DNA damage, hepatitis B virus X protein, and other environmental factors results in global DNA hypomethylation, as well as in specific gene hypermethylation. The former activates the proto-oncogenes and chromosomal alterations, while the latter is responsible for inactivation of tumor suppressor genes. Overall, the major molecular alterations involved in human hepatocarcinogenesis include aneuploidy and chromosomal aberrations (40%) (72), activation of proto-oncogenes (β-catenin, *ras*-MAPK pathway), and inactivation of tumor suppressor genes (*Rb, IGF2R, p53,* and *p16 INK4* mutations or deletions) (64,73). Structural rearrangements are most commonly described in chromosomes 1, 7, and 8 (74). Some HCCs exhibit microsatellite instability associated with a loss of heterozygosity in mismatch repair genes (*hMSH2* and *hMLH1*) (75).

Major oncologic signaling pathways activated in HCCs include Wnt/β-catenin pathway (up to 50%), PI3K/Akt pathway (40%–60% of HCC), the Myc pathway (30%–60%), the hedgehog pathway (50%–60%), and the MET pathway (30%–40%) (64,76–79). The Wnt/β-catenin pathway plays a multitude of roles in liver biology, including regulation of hepatoblast proliferation and differentiation, activation of hepatic stem cells, regulation of liver regeneration, liver zonation, and various metabolic processes in the liver (80–82). Interestingly, a majority of *CTNNB*-mutated HCCs occur independent of cirrhosis, and only 30% of *CTNNB*-mutated HCCs are found with coexistent cirrhosis (83). Although *CTNNB1* mutations are never detected in preneoplastic lesions such as dysplastic or cirrhotic nodules, they have been detected in HCAs and are implicated in progression of HCAs to HCCs (1,29).

Depending on a specific cause, a predominant cytogenetic alteration and molecular pathway plays a crucial role in the causation of HCC. Representative examples include *KRAS* mutations in vinyl chloride–induced HCC (42%) (56), *HRAS* mutations in methylene chloride–induced liver tumors (57), *CTNNB* mutations in hepatitis C–related HCC (45.8%), and hepatitis B–related HCC (22.2%), gain of function at chromosome 10q exclusively associated with hepatitis C–associated HCC, chromosome 11q amplification preferentially seen in hepatitis B–related HCC (58), and *p53* mutations in aflatoxin exposure (30%–60% of aflatoxin-induced HCC) (4). While chronic hepatitis C virus infection increases the risk of HCC exclusively causing fibrosis and cirrhosis, up to 10%–30% of HCCs in hepatitis B virus infection occur in the absence of cirrhosis. Hepatitis B virus primarily acts by integrating the viral DNA into the host genome and inducing genomic instability, genetic aberrations, insertions in the promoter region of tumor suppressor genes such as *p16,* and producing oncoproteins such as hepatitis B virus X protein. Hepatitis B virus–induced HCCs, therefore, have a distinct set of genomic alterations that are remarkably different from other HCCs, including hepatitis C– and alcohol-related ones. *AXIN1* mutations and insulin-like growth factor–2 (IGF2) overexpression are specifically seen in young patients with low viral load and high levels of α-fetoprotein. In contrast, patients with high viral load have *PIK3CA* (the gene encoding phosphatidylinositol 3–kinase) mutations and *p53* inactivation. Both IGF2 overexpression and *PIK3CA* mutations are thought to activate the AKT pathway, which is therefore likely to be the major pathway in hepatitis B–induced carcinogenesis (3). *CTNNB1*/β-catenin activation is typically absent in hepatitis B–related HCCs (84).

Figure 11

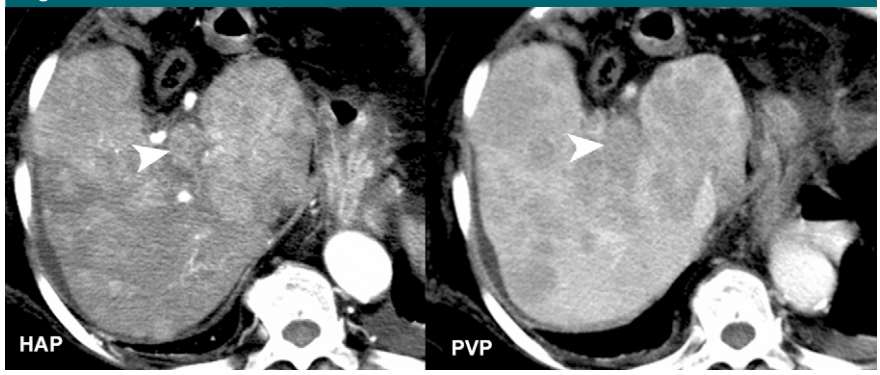
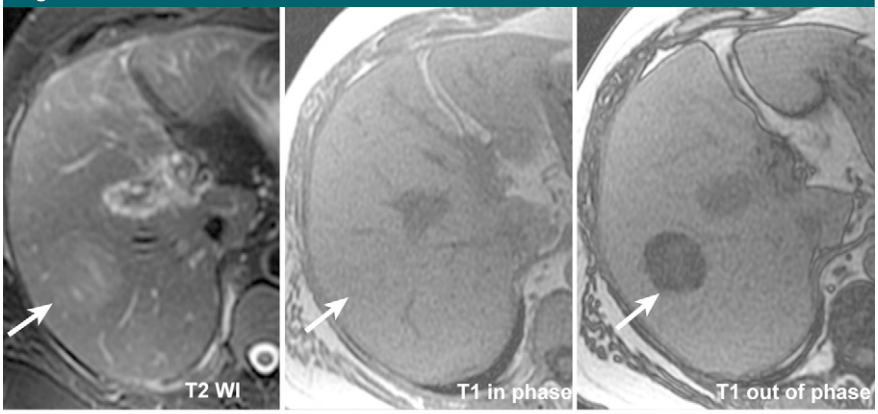


Figure 11: Multifocal HCC with portal vein thrombosis in a 52-year-old man with chronic hepatitis C infection and cirrhosis. Axial contrast-enhanced hepatic arterial phase *(HAP)* and portal venous phase *(PVP)* CT images of liver show multiple arterially enhancing lesions with washout in right and caudate lobes during portal venous phase. Enhancing thrombus is seen in portal vein (arrowheads) is consistent with multifocal HCC with tumoral portal vein thrombus.

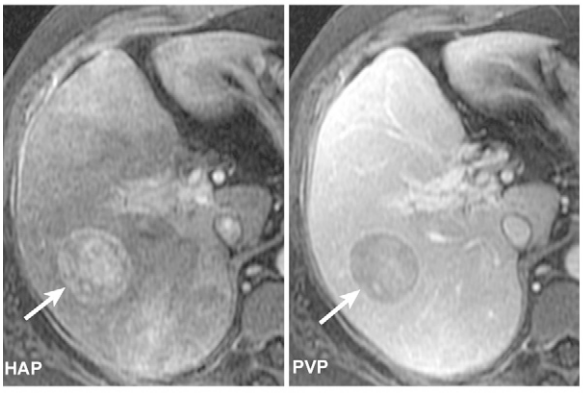
Hepatocarcinogenesis in Metabolic Syndrome

Metabolic syndrome, composed of dyslipidemia, insulin resistance or type 2 diabetes mellitus, hypertension, and obesity, is an important and emerging risk factor for HCC. Up to 25% of cases of nonalcoholic steatohepatitis in the setting of metabolic syndrome progress to cirrhosis (85). Metabolic syndrome can also induce hepatocarcinogenesis independent of the cirrhosis pathway, and studies have shown that most tumors secondary to metabolic syndrome arise in a nonfibrotic liver (68). Pathogenesis and evolution of the tumors in a nonfibrotic, noncirrhotic liver are different from those in a fibrotic or cirrhotic liver. Potential carcinogenic mediators in metabolic syndrome include insulin, lipid peroxidation, and oxidative stress induced by free radicals. These factors are thought to stimulate cellular proliferation, activate hepatic progenitor cells (oval cells), and induce *p53* mutations and epigenetic aberrations (86,87). In

Figure 12



a.



b.

Figure 12: Incidentally discovered HCC in a 42-year-old man without cirrhosis. **(a)** Axial T2-weighted 6-mm-thick (left; 11 250/85) and T1-weighted 5-mm-thick in-phase (middle; 150/4.37) and out-of-phase (right; 150/2.07) MR images demonstrate well-defined T2 hyperintense lesion (arrows) in right lobe with signal intensity decline on out-of-phase image, consistent with presence of microscopic fat. **(b)** Axial gadolinium-enhanced MR images (3.58/1.73, 5-mm section thickness) show lesion (arrows) with intense enhancement on hepatic arterial phase *(HAP)* image (left) with washout and enhancing tumor capsule on portal venous phase *(PVP)* image (right). Surgical resection and histopathologic analysis confirmed diagnosis of well-differentiated HCC.

contrast to viral hepatitis–induced HCC, the β-catenin pathway is not activated in metabolic syndrome–related HCCs. Metabolic syndrome is also associated with an increased risk of HCAs. Indeed, a small subset of HCAs may undergo malignant transformation in this setting.

Interestingly, most tumors that arise in individuals with metabolic syndrome are well differentiated (64.5% vs 28% in patients with chronic liver disease), and tumors in nonfibrotic livers are better differentiated than those in fibrotic livers (68,85). Recent insights into the process of hepatocarcinogenesis in metabolic syndrome and the distinctive molecular biology and evolution of these lesions in fibrotic and nonfibrotic livers may help in the development of strategies for screening patients with metabolic syndrome with or without underlying chronic liver damage.

Management of HCC and the Role of Imaging

The diagnosis of hepatocellular carcinoma is made on the basis of clinical, laboratory (elevated α-fetoprotein level), imaging (US, CT, MR imaging), and pathologic findings. Imaging studies play a vital role in the diagnosis and staging of HCC. Although, α-fetoprotein measurement and US are currently used as screening techniques for detection of HCC in at-risk patients and in those with cirrhosis, the combined sensitivity of these techniques is as low as 50%–60% (88). Serum α-fetoprotein assay has been traditionally used for the diagnosis of HCC and for predicting the prognosis. However, several recent studies have shown very poor sensitivity and specificity for serum α-fetoprotein level in the diagnosis and management of HCC. The sensitivity of serum α-fetoprotein level for detection of HCC is as low as 54% (with a cutoff value of 20 μg/L) and up to 43% of patients with advanced HCC may have α-fetoprotein levels within the normal range. In addition, only approximately 10% of cases of HCC with an α-fetoprotein level higher than 400 μg/L will benefit from currently available forms of therapy (89). Hence, α-fetoprotein level is more a predictor of late-stage disease and poor prognosis than an ideal screening technique for detection of early-stage disease. Newer biomarkers like serum N-glycan profile, serum glycipan 3 levels, and GP73 are being investigated as potential candidates for early detection of HCC (90–92). Of note, are two commercially available alternative biomarkers: des-γ-carboxyprothrombin and the *Lens culinaris* agglutinin reactive fraction of α-fetoprotein (AFP-L3) (93). Although the individual sensitivity for these biomarkers is low at 61% for DCP and 42% for AFP-L3, the combined sensitivity of α-fetoprotein, des-γ-carboxyprothrombin, and AFP-L3 has been reported to be up to 87% (94).

Dynamic contrast-enhanced CT and MR imaging are the most commonly used imaging modalities for the diagnosis and staging of HCC. The pooled sensitivities of MR imaging and CT, respectively, for detection of HCC are reported to be about 81% and 68% (95). Authors of more recent studies on triphasic multidetector CT (16-, 40-, and 64-section scanners) for preoperative detection of HCC, however, have reported a sensitivity of up to 100% for lesions larger than 2 cm and 96% for lesions between 1 and 2 cm (96). The overall accuracy of

MR imaging for detection of HCCs has also markedly improved in recent years with the use of newer contrast agents such as gadobenate dimeglumine (MultiHance; Bracco Diagnostics, Princeton, NJ), ferucarbotran (Resovist; Bayer Schering), and gadoxetic acid (Eovist, Bayer Schering). While the reported accuracy for gadobenate dimeglumine–enhanced MR imaging (dynamic and hepatobiliary phase) is up to 95%, the sensitivity of both ferucarbotran-enhanced and gadoxetic acid–enhanced MR imaging achieves up to 100% for detection of HCCs (97,98).

Typically, HCCs manifest as arterially enhancing lesions that become hypoattenuating in the portal venous phase ("washout"), with delayed enhancement of the tumor capsule (Figs 11, 12). Larger lesions may be more heterogeneous on images. Arterial hypervascularity of HCCs is attributed to the neoangiogenesis. Because tumor cells replace the normal portal triad and portal venous perfusion decreases, the lesions becomes hypoattenuating relative to the liver during portal venous phase imaging. The fibrous tumor capsule, which appears hypointense on T1- and T2-weighted images and shows delayed enhancement, is seen in up to 80% of cases and likely results from activation of stellate cells (99). Presence of a fibrous capsule is also considered to be a favorable prognostic factor, with improved disease-free survival and overall survival rates in patients with encapsulated HCC (100).

The major differential diagnoses of HCC in the setting of cirrhosis are regenerative nodules and dysplastic nodules. Regenerative nodules do not enhance on hepatic arterial phase images because they derive their blood supply largely from the portal vein, with a minimal hepatic arterial contribution (101). However, regenerative nodules can grow up to 5 cm and show arterial enhancement, thereby mimicking HCC (102). On MR images, regenerative nodules are typically isointense to the liver on T1- and T2-weighted images and do not enhance on arterial phase images. Variations include T1 hyperintensity (due to lipid, protein, and copper), T1 hypointensity (due to iron), or arterial enhancement without venous washout (102).

Figure 13

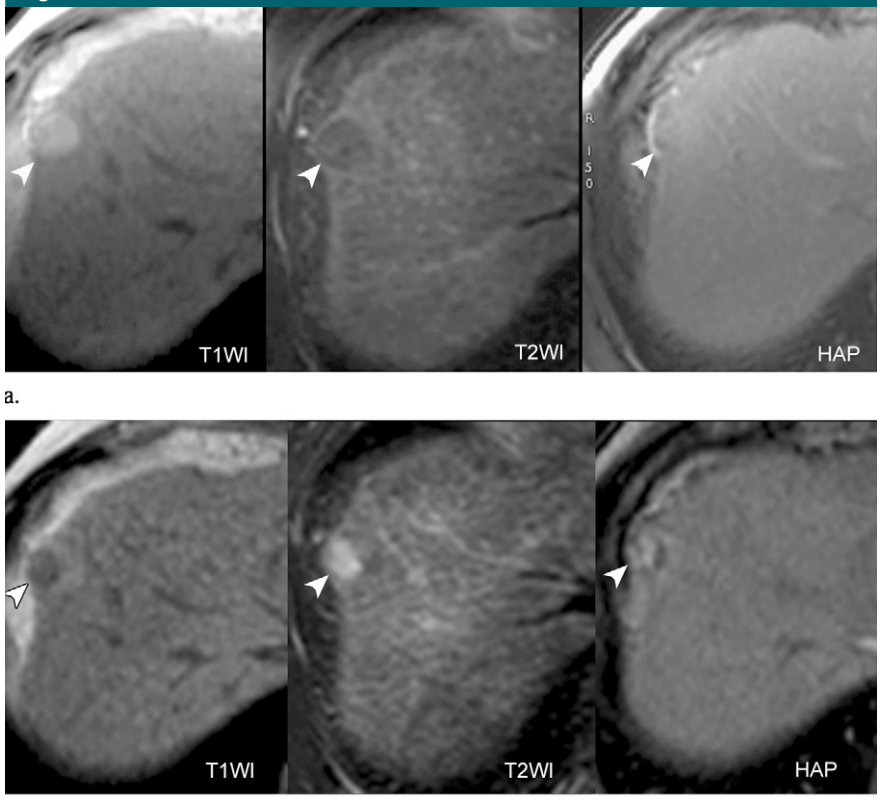


Figure 13: Typical MR imaging features of dysplastic nodule (arrowheads) that progressed to HCC. **(a)** Axial T1-weighted (*T1WI;* 3.62/1.73, 5-mm section thickness), T2-weighted (*T2WI;* 1800/85, 6-mm section thickness), and gadolinium-enhanced hepatic arterial phase (*HAP;* 3.62/1.73, 5-mm section thickness) images show lesion is T1 hyperintense, T2 hypointense, and hypointense without arterial enhancement, respectively, consistent with dysplastic nodule. **(b)** Follow-up images obtained 1 year later show areas low signal intensity on T1-weighted image *(T1WI),* high signal intensity on T2-weighted image *(T2WI),* and heterogeneous arterial enhancement on arterial phase *(HAP)* image, consistent with HCC arising in a dysplastic nodule.

Dysplastic nodules can harbor low-grade or high-grade dysplasia without histologic evidence of malignancy. Low-grade dysplastic nodules typically do not harbor mutations and cannot be definitively categorized as premalignant (103). High-grade dysplastic nodules, in contrast, demonstrate mutations and are premalignant (103,104). On images, dysplastic nodules are typically smaller than 2 cm and appear similar to regenerative nodules (Fig 13). High-grade dysplastic nodules may enhance in the hepatic arterial phase and therefore can simulate HCC (102). In contrast, certain well-differentiated HCCs are primarily fed by the portal vein in their early stages and, hence, may appear hypovascular, mimicking regenerative nodules (105). The development of high-signal-intensity areas on T2-weighted MR images with arterial contrast enhancement in a previously documented dysplastic nodule suggest progression of a dysplastic nodule to HCC (Fig 13; "nodule within a nodule" appearance). Hemodynamic changes in human hepatocarcinogenesis can, therefore, be summarized as decreased arterial flow with preserved portal perfusion in early stages, which then progresses to both arterial and portal hypovascularity followed by a progressive increase in the arterial vascularity (105).

Figure 14

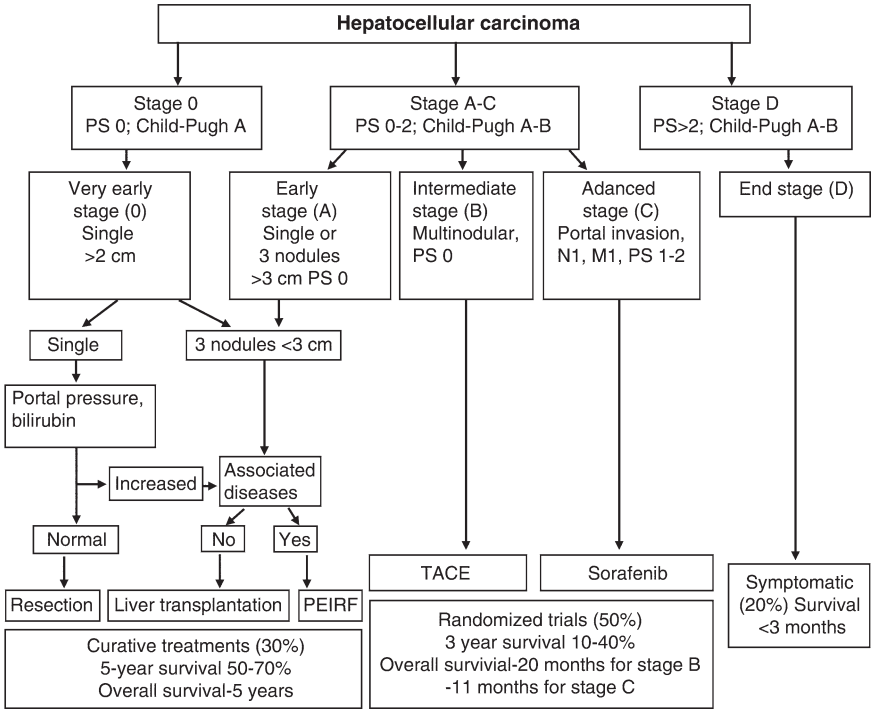


Figure 14: Flowchart depicts Barcelona Clinic Liver Cancer staging and the role of four major approved treatment strategies. Curative resection is optimal for very early HCC (stage 0); radical therapy (resection, orthotopic liver transplantation, percutaneous ethanol injection *[PEI],* and radiofrequency *[RF]* ablation) is reserved for patients with early HCC (stage A). Transcatheter arterial chemoembolization *(TACE)* is beneficial for patients with intermediate HCC (stage B). Sorafenib is effective for patients with advanced HCC with macroscopic vascular invasion and/or extrahepatic metastases. Patients with end-stage disease (stage D) receive symptomatic treatment. *PS* = performance status. (Adapted and reprinted, with permission, from reference 116.)

Gadoxetic acid–enhanced MR imaging has been found to be highly useful for differentiation of a dysplastic nodule from early HCC, with an accuracy of up to 93% for this differentiation (106). The hepatocellular uptake and biliary excretion of this contrast agent depend on hepatocellular expression of the organic anion transporting polypeptide (OATP1) and multidrug resistant protein (MRP2) systems, respectively (107,108). Hepatocytes in dysplastic nodules express both these proteins and hence appear iso- to hyperintense on delayed phase images (hepatocyte phase, 20 minutes after injection). In contrast, the majority of HCCs do not express these transporters and, hence, appear hypointense to the liver on delayed (hepatocyte) phase images. Between 10% and 27% of HCCs may, however, remain iso- to hyperintense on hepatocyte phase images (almost all being well- to moderately differentiated HCCs), which is attributed to the presence of OATP1B3 expression (OATP 1B3 protein) (96,109–111).

The American Association for the Study of Liver Disease guidelines for the diagnosis of HCC concludes that when a lesion is larger than 2 cm, the presence of typical imaging features from any one of three imaging modalities (dynamic contrast-enhanced CT, MR imaging, or contrast agent–enhanced US) is sufficient to establish a diagnosis. However, when the lesions are between 1 and 2 cm in size, two dynamic imaging modalities have to demonstrate the typical imaging features (88). This guideline allows noninvasive categorization of most lesions larger 2 cm and up to 33% of lesions smaller than 2 cm (112). Needle biopsy is recommended for lesions 1–2 cm in diameter that do not have typical imaging characteristics (88). Alternatively, these lesions can be monitored with serial surveillance imaging studies at 3–6 month intervals without adversely affecting management (113). This approach is preferred by some, given the inherent limitations of needle biopsy, such as potential sampling error in small lesions and difficulty in distinguishing a well-differentiated HCC from a dysplastic nodule and normal hepatocytes in a limited biopsy specimen (88,113). Differentiation of HCC from normal liver at histologic examination relies on architectural features of the lesion in addition to the cytologic features. The risk of tumor seeding along the needle track is thought to be negligible (88); however, some investigators (114) raise concern for increased risk of posttransplantation extrahepatic recurrences with needle biopsies.

The prognosis of HCC depends on the stage of the disease at the time of diagnosis. Several scoring systems have been developed for staging HCC. The Barcelona Clinic Liver Cancer classification is the most widely used and generally accepted staging system at present. The role of four approved categories of treatment for HCCs—surgical intervention (resection, liver transplantation), percutaneous intervention (radiofrequency ablation, ethanol injection), transarterial intervention (embolization, chemoembolization, internal radiation therapy), and pharmacologic intervention (sorafenib)—are summarized in Figure 14 (115,116). Patients with very early stage disease (tumor size, <2 cm) are optimal candidates for surgical resection. The radical therapeutic option (liver transplantation, radiofrequency ablation, or percutaneous ethanol injection) is offered to patients with early-stage HCC (up to three nodules < 3 cm in size). While transarterial chemoembolization is reserved for patients with intermediate-stage HCC without portal vein invasion or extrahepatic metastases, sorafenib is the only currently available therapeutic option for candidates with advanced-stage HCC (performance status: 0–2, Child-Pugh A). Patients with

end-stage disease (stage D) receive only symptomatic treatment. Overall, with the currently available diagnostic techniques, curative treatment is possible only in up to 40% of patients with HCC (115,117).

Prognostic Implications of Cytogenetic Alterations in HCC

There have been several attempts at a molecular classification of HCC in recent years. A widely accepted molecular pathogenesis may facilitate better understanding of the pathogenesis, imaging findings, prognosis, and use of molecular targeted therapies. There are several "molecular signatures" that predict tumor biology in HCC and, hence, influence the imaging appearance and the prognosis. Accumulation of β-catenin and activation of Wnt pathway have been associated with well or moderately differentiated tumors with small tumor size and good overall prognosis (118,119), However, the nuclear expression of β-catenin has been associated with an increased incidence of microvascular and macrovascular invasion (78% in mutated HCC vs 38% in HCC without mutations), larger tumor size (greater than twice the size of nonmutated tumors), and multiplicity of nodules (120,121).

Other mutations seen in poorly differentiated tumors involve the *p53, MMP14,* and *RhoC* genes. In contrast to *Rb1* mutations, which are seen in early-stage disease, *p53* mutations are typically seen in advanced-stage tumors (up to 27% of cases) (122,123). Mutations in *p53* have been consistently associated with large tumor size, high tumor grade, and/or poorly differentiated tumors, with resultant shortened tumor-free survival and poor prognosis (124,125). Since the tumor prognosis depends on these factors (mainly vascular invasion), presence of these mutations reflects an aggressive phenotype. A mutation in *MMP14* imparts an increase in matrix metalloproteinase activity with resultant accelerated extracellular matrix degradation. Mutations in *RhoC* result in increased cellular motility. Both the *MMP14* and the *RhoC* genetic events have been consistently associated with poorly differentiated phenotype and an increased tendency for vascular invasion and metastasis (126–128). Up-regulation of other matrix metalloproteinase enzymes like MMP2 and MMP9 is also associated with an increased tendency for invasion and metastases. The phosphatidylinositol 3-kinase (PI3K/AKT) pathway up regulates MMP9 activity and thereby promotes invasion and metastases (129). Increased vascularity of these tumors is mediated by activation and overexpression of angiogenic factors such as vascular endothelial growth factor receptor, platelet-derived growth factor, and angiopoietin-2 (130). This process of neoangiogenesis determines the imaging appearance of HCCs. Regenerative nodules are not hypervascular because of lack of these mutations. Dysplastic nodules may have a variable degree of arterialization and may, therefore, appear as arterially enhancing nodules, thereby mimicking HCC (131–133). Stepwise progression of hepatocarcinogenesis in a cirrhotic liver with salient genetic and imaging features is highlighted in Figure 15.

Sorafenib, a multikinase inhibitor with antiproliferative and antiangiogenic activity is the first systemic medical treatment approved by Food and Drug Administration. It has proved to be effective in all patients with HCC by lowering the tumor progression rate and increased survival (5). Sorafenib primarily inhibits vascular endothelial growth factor (VEGF); this effect is independent of the underlying cause of HCC and highlights the role of the common molecular pathogenesis of HCC. The efficacy of VEGF is, however, still limited, and its indication is therefore restricted to patients with Child-Pugh score A and Eastern Cooperative Oncology Group performance status 0–2, in whom a potentially curative treatment is contraindicated (134). VEGF is also one of the growth factors that is released in excess from the hypoxic residual tumor after local therapy (eg, transarterial chemoembolization). Given, the pivotal role of the growth factor–induced angiogenesis in tumor recurrence, the addition of systemic therapy such as sorafenib may have a notable effect on tumor recurrence and overall prognosis. *IGF2* is another tumor suppressor gene that is inactivated in up to 20%–30% of HCCs. Given the pivotal role of *IGF2* in tumor

Figure 15

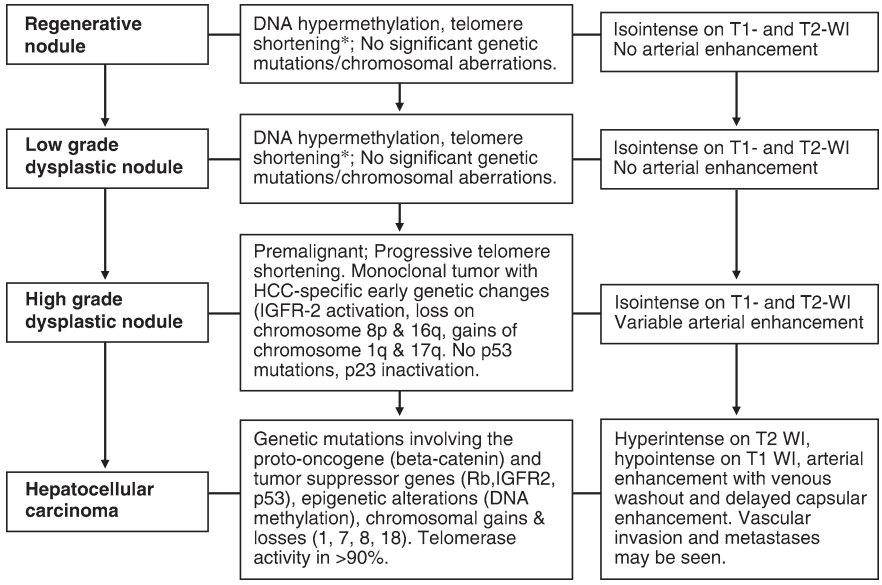


Figure 15: Flowchart depicts stepwise progression of genetic abnormalities and the imaging features in multistep hepatocarcinogenesis in patients with cirrhosis. * = Telomere shortening in low-grade dysplastic nodules is similar to that in background cirrhotic liver, *IGFR-2* = insulin-like growth factor receptor 2, *T1 WI* = T1-weighted MR images, *T2 WI* = T2-weighted MR images.

Table 2

Selected Molecular-targeted Therapies for HCC

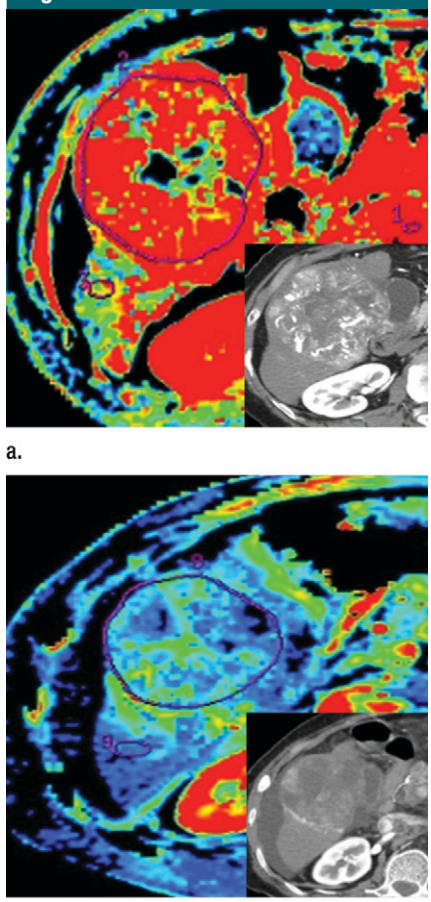
Class and Target*	Drug	Current Development Status†
Antiangiogenic		
VEGFR	Sorafenib‡	FDA approved
VEGFR	Sunitinib	Phase III
VEGFR	Brivanib	Phase III
VEGF	Bevacizumab	Phase III
PDGFR	Sorafenib	FDA approved
PDGFR	Sunitinib	Phase III
PDGFR	Imatinib	Phase II
Growth factor inhibitors		
Anti-EGFR	Erlotinib, gefitinib, lapatinib, cetuximab	Phase II
Anti-IGF1R	Monoclonal antibody A12	Phase II
c-kit	Sorafenib	FDA approved
c-kit	Dasatinib	Phase II
PDGFR	Sorafenib	FDA approved
PDGFR	Sunitinib	Phase III
PDGFR	Imatinib	Phase II
Signal transduction inhibitors		
Raf	Sorafenib	FDA approved
MEK	Vandetanib, AZD6244	Phase II
mTOR	Rapamycin	Phase II-III
mTOR	Everolimus	Phase I-II
Pro-apoptotic agents		
Bcl-2	Oblimersen	Phase II
Cell cycle		
CDK	Flavopiridol	Phase II

* Bcl-2 = B-cell lymphoma 2, CDK = cyclin-dependent kinase, EGFR = epidermal growth factor receptor, IGF1R = insulin-like growth factor 1 receptor, mTOR = mammalian target of rapamycin, PDGFR = platelet-derived growth factor receptor, VEGFR = vascular endothelial growth factor receptor.

† FDA = Food and Drug Administration.

‡ Sorafenib is a multikinase inhibitor with activity against Raf-1, B-Raf, VEGFR2, PDGFR, and c-kit receptors.

Figure 16



a.

b.

Figure 16: Axial functional perfusion CT color maps of blood flow **(a)** before and **(b)** 2 weeks after bevacizumab therapy in 62-year-old man with large HCC in right lobe of liver. Insets show corresponding axial contrast-enhanced CT images. Functional color maps for tissue blood flow are displayed according to color scale, and average perfusion values for each region of interest (outlined) present a distinct range of colors in tumor compared with background liver parenchyma. Avidly enhancing HCC (inset in **a**) in right lobe shows high blood flow (403 mL/100 gm/min at baseline. After 2 weeks of therapy, tumor shows visible reduction in enhancement (inset in **b**) and drastic reduction in blood flow to 26 mL/100 gm/min.

progression, it is being explored as an important target for molecular therapy with the potential to prevent malignant transformation in a small subset of glycogen storage disease–associated HCAs (40,135). These, as well as other novel molecular agents, constitute potential important adjuvant therapies to surgery, ablation, and chemoembolization in the future (Table 2) (115,136). The advent of molecular therapeutics necessitates robust and reliable functional imaging techniques. Perfusion CT is an emerging modality that can be used to monitor response to antiangiogenic therapy by assessing the tumor vascularity (Fig 16).

Fibrolamellar HCC

First described by Edmondson (137) in 1956, fibrolamellar HCC is a distinct type of HCC that accounts for fewer than 5% of HCCs. Fibrolamellar HCC predominantly affects young patients without background cirrhosis or other clinical risk factors (138).

The average age at presentation of fibrolamellar HCC is 25 years (compared with 65 years for conventional HCC); more than 85% of patients are younger than 35 years at the time of presentation (138,139). Equal sex distribution has been noted (140). The clinical manifestation is usually nonspecific and includes a palpable mass, pain, abdominal discomfort, nausea, and weight loss. Jaundice may be seen in up to 40% cases (141). The serum α-fetoprotein level is usually normal. Histologically, fibrolamellar HCCs are characterized by large, polygonal tumor cells (with large nuclei, prominent nucleoli, and abundant eosinophilic cytoplasm) that are enveloped by lamellar bands of abundant fibrous stroma.

In contrast to conventional HCC, fibrolamellar HCC does not show *CTNNB* or *p53* mutations. However, fibrolamellar HCC shows high levels of Y654-β-catenin levels, representing increased receptor

tyrosine kinase signaling in this tumor type. This makes fibrolamellar HCC susceptible to receptor tyrosine kinase targeting (83). Sorafenib, a multikinase inhibitor, may therefore have a strong therapeutic effect in fibrolamellar HCC (116). More than 75% of fibrolamellar HCCs show overexpression of *anterior gradient-2,* an oncogene that is often overexpressed in solid tumors (142). Several other potential chromosomal, genetic, and epigenetic aberrations have been reported, most frequently involving chromosome 1 (143). These genomic alterations are more commonly seen with recurrent and metastatic fibrolamellar HCC. In addition, an overexpression of transforming growth factor–β has been reported and is attributed to the development of typical lamellar fibrosis in these tumors (144). Other potential molecular mechanisms likely to be involved in the pathogenesis of fibrolamellar HCC include activation of the nuclear factor–κ B signaling pathway (145), and involvement of cancer stem cells (possibly arising from dedifferentiation of benign hepatocytes) with markedly reduced cell cycle progression (146). The slow proliferative rate of stem cells might explain the relative resistance to chemotherapy and radiation therapy exhibited by fibrolamellar HCC (146).

On images, fibrolamellar HCCs are usually larger at the time of presentation and manifest as hypervascular heterogeneous hepatic masses without background cirrhosis or chronic liver disease (Fig 17). A disproportionately large central scar is seen in up to 75% cases and calcification is found in up to 68% cases of fibrolamellar HCC (147). In contrast to FNH, the scar in fibrolamellar HCC is hypointense on T2-weighted MR images.

Compared with conventional HCCs, fibrolamellar HCCs demonstrate an increased propensity to metastasize to the lymph nodes and peritoneum (148,149). Metastatic lymphadenopathy can be seen in up to 70% cases (149). Surgical resection is the treatment of choice, with a 5-year survival rate of 37%–76% after complete surgical resection (150). A high relapse rate of 36%–100% has, however, been reported, especially in patients presenting with advanced-stage disease with large primary tumors and lymphatic metastases (151). Despite the tendency toward a high rate of recurrence, this tumor behaves in an indolent fashion, with a high 5-year survival rate of up to 45%–76%, even after relapse (151). Genomic homogeneity with absence of clonal evolution and lack of important genomic alterations likely explain this relatively indolent behavior (152,153). In contrast, other histologic variants of HCC show marked genomic heterogeneity and thus portend a poor prognosis (154). Young age at the time of presentation, high resectability rate, and absence of background liver disease also seem to play a role in determining the prognosis in fibrolamellar HCC. Median survival declines from 112 months after complete surgical resection to 12 months in cases of unresectable disease (150). The 5-year survival rate for fibrolamellar HCC decreases from 86% in patients without metastasis to 39% in patients with metastasis (155). Presence of lymphadenopathy also plays a part in the prognosis; the 5-year survival rate decreases from 100% in patients without lymphadenopathy to 45% in patients with lymphadenopathy (150). Whereas earlier reports suggested a poor prognosis for conventional HCC compared with that for fibrolamellar HCC (respective 5-year survival rates of 6.8% for conventional and 32% for fibrolamellar HCC), authors of more recent studies have reported a 5-year survival rate of up to 56% in noncirrhotic HCC, similar to that for fibrolamellar HCC. Overall, therefore, it is now accepted that the prognosis of fibrolamellar HCC is comparable to that of HCC in patients without cirrhosis but is better than that in patients with cirrhosis-associated HCC (155).

Figure 17

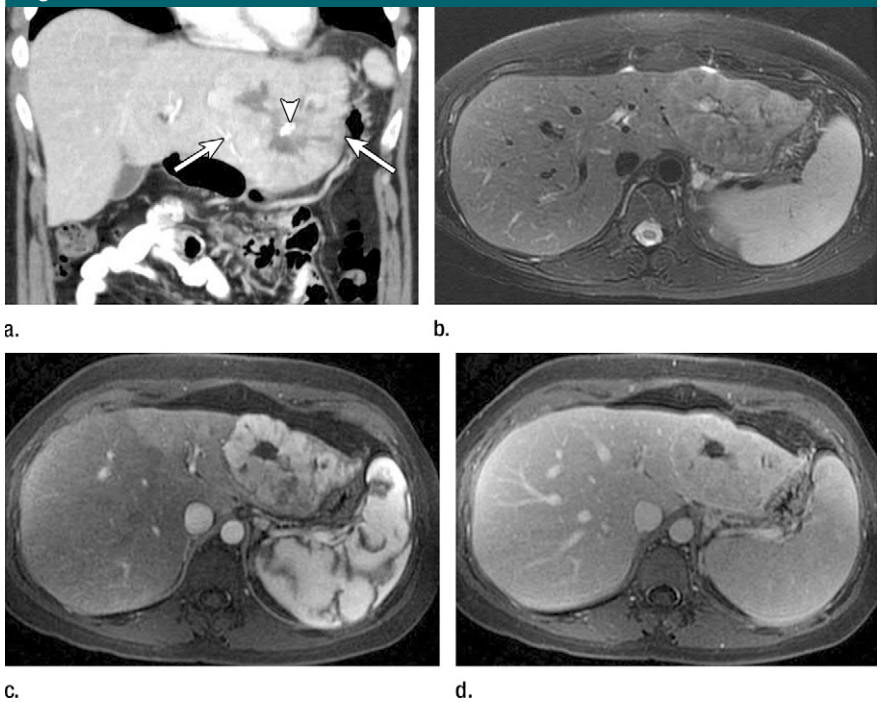


Figure 17: Fibrolamellar HCC in 28-year-old woman. **(a)** Coronal contrast-enhanced CT scan shows homogeneous enhancement of mass (arrows) with central scar and focus of calcification (arrowhead). **(b)** Axial T2-weighted (9473/94, 5-mm section thickness) MR image shows large mass with prominent central scar. **(c, d)** Axial T1-weighted (3.4/1.6, 3.4-mm section thickness) images show **(c)** intense enhancement in hepatic arterial phase and **(d)** isointensity in portal venous phase.

Conclusion

Recent clarification of the molecular mechanisms and the genotype-phenotype

correlations of hepatocellular neoplasms have enabled better classification of tumors on the basis of tumor genetics and biology. Tumors with specific genetic abnormalities demonstrate characteristic clinical and biologic behavior, natural history, response to treatment, and prognosis. HCAs with *HNF1*α mutation are diffusely steatotic, do not tend to undergo malignant transformation, and are associated with familial diabetes or adenomatosis. Inflammatory HCAs are hypervascular with marked peliosis and tendency to bleed. They are associated with obesity, alcohol, and hepatic steatosis. HCAs with *CTNNB* mutation are associated with male hormone administration and glycogen storage disease, frequently undergo malignant transformation, and may simulate HCC on images. Although up to 90% of HCCs arise in the setting of cirrhosis, metabolic syndrome is an emerging cause of HCC in noncirrhotic livers. A wide array of genomic alterations and molecular pathways are involved in hepatocarcinogenesis. Some of these are cause specific (*KRAS, HRAS, AXIN1,* and *p53* mutations), while others determine the tumor biology and prognosis (*CTNNB1, p53, MMP14,* and *RhoC* mutations). Genomic homogeneity, young age at presentation, high resectability rate, and absence of background liver disease in fibrolamellar HCC explain its better prognosis compared with that of cirrhosis-associated HCC. Improved understanding of oncologic pathways has paved the way for the development of new molecular therapeutics aimed at treating advanced disease. The role of multiphase multidetector CT and MR imaging in the detection, characterization, and staging of liver tumors, as well as in surveillance following a wide gamut of targeted treatments, continues to expand and evolve.

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