
Hepatocellular carcinoma

Pathogenesis · morphology · diagnosis · clinical correlation

Pathology lecture

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Learning objectives

- Relate chronic liver injury and etiologic exposures to tumor development
- Explain β -catenin, TERT and TP53 alterations in HCC
- Recognize major precursors and architectural tumor patterns
- Interpret characteristic imaging and key management constraints

HCC in the spectrum of hepatic malignancy

- HCC is a primary malignant hepatocellular neoplasm
- Intrahepatic cholangiocarcinoma is the other major primary epithelial malignancy
- Metastatic cancers may also produce malignant masses in the liver

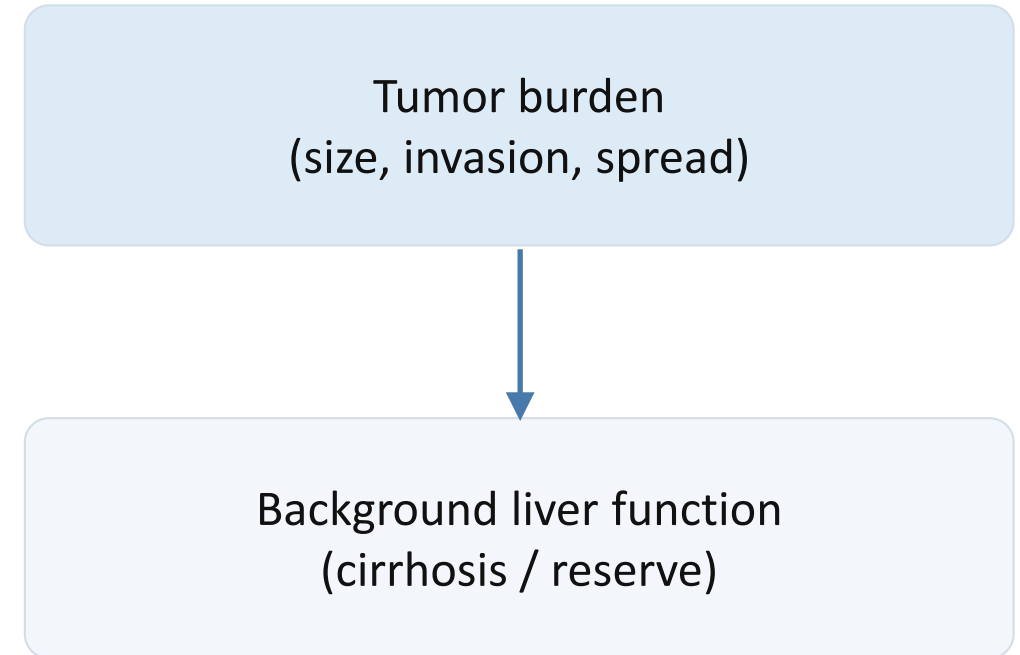
Primary liver cancer

Hepatocellular / biliary

Conceptual comparison

The clinical–pathologic problem

- HCC often arises against a background of chronic liver disease
- Both the neoplasm and the residual liver function influence outcomes
- A minority arise in a liver without cirrhosis



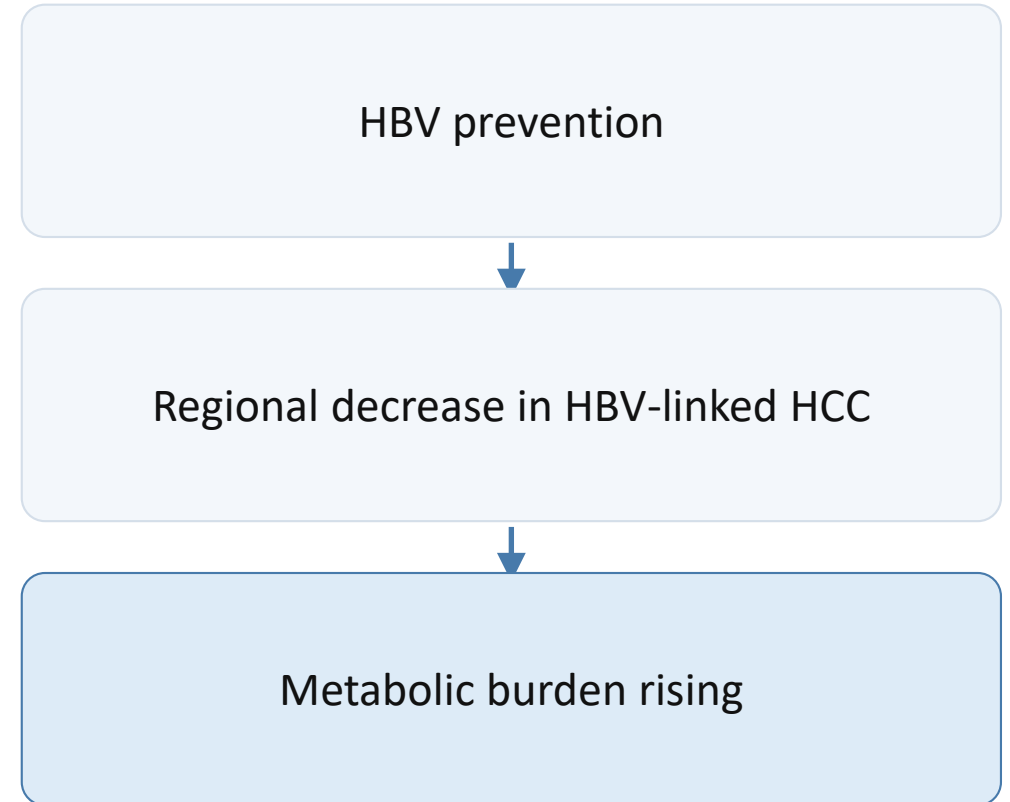
Independent but interacting clinical burdens

Geographic burden

- HCC is particularly frequent where chronic hepatitis B is common
- More than 85% of cases in parts of Asia and sub-Saharan Africa
- These estimates describe the textbook source, not an independently updated 2026 registry

Epidemiologic transition

- HBV vaccination is associated with decreasing HCC incidence in parts of Asia
- Rising metabolic syndrome is contributing to increasing burden in Western countries
- Etiologic patterns vary strongly by population



Schematic / conceptual relations

Demographic clues

- Textbook describes marked male predominance in high-incidence regions
- In perinatally acquired HBV infection, HCC can arise in young adulthood
- Age alone cannot exclude HCC in an appropriate risk context

Cirrhosis is common—but not universal

- Most tumors occur in chronic liver disease with cirrhosis
- Approximately 15%–20% occur in noncirrhotic livers
- Fibrolamellar carcinoma is a prominent noncirrhotic exception

Most HCC

Cirrhotic background

Conceptual comparison

Major etiologic settings

Viral hepatitis

Metabolic / alcohol

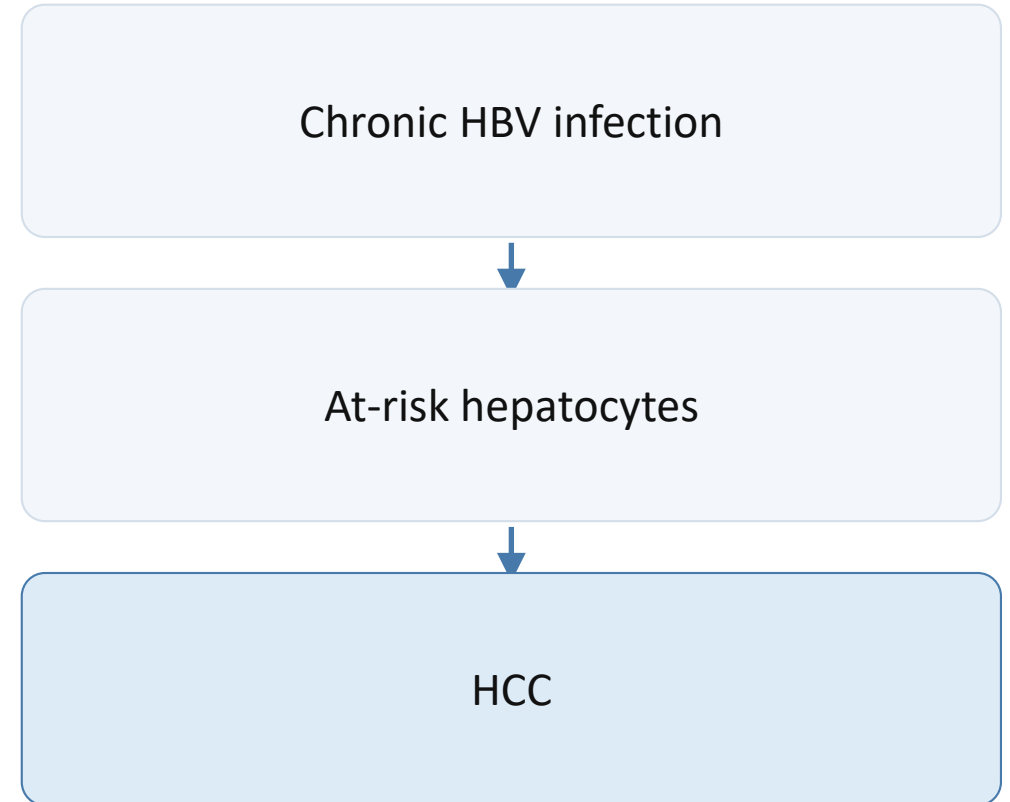
Inherited disease

Aflatoxin

Distinct contributors converge on hepatocarcinogenesis

Hepatitis B: Major carcinogenic context

- Chronic HBV infection is strongly associated with HCC
- Perinatal HBV acquisition underlies early-adult HCC in some endemic populations
- Population prevention through HBV vaccination can reduce future HCC burden



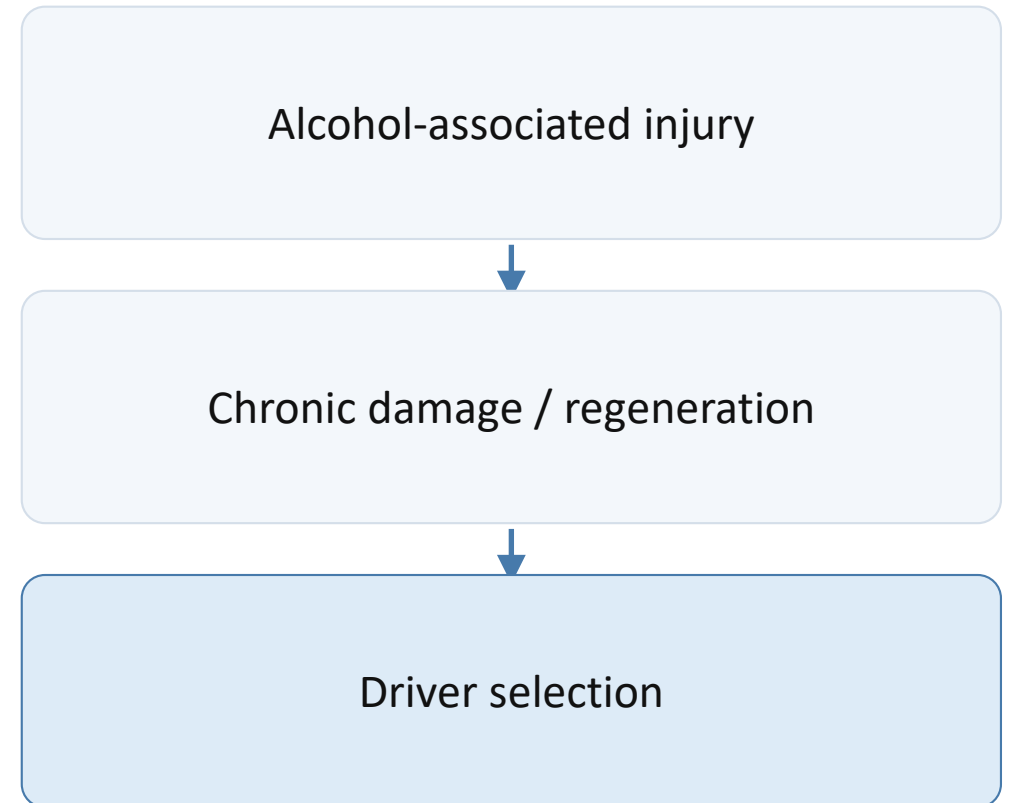
Schematic / conceptual relations

Hepatitis C and long-term hepatic injury

- Chronic hepatitis C is a frequent antecedent condition
- Ongoing inflammation, hepatocyte loss and regeneration support carcinogenesis
- Cirrhotic livers require particular attention to evolving nodules

Alcohol-associated liver disease

- Alcohol-associated chronic liver disease is a recognized HCC risk setting
- Repeated injury and regeneration contribute to accumulation of somatic changes
- Aflatoxin may act synergistically with alcohol in exposed populations



Schematic / conceptual relations

MASLD-related risk

- MASLD is an increasingly important background disease for HCC
- The text explicitly notes HCC can develop without cirrhosis in MASLD
- Therefore, absence of established cirrhosis does not imply zero risk

Inherited metabolic diseases

Hemochromatosis

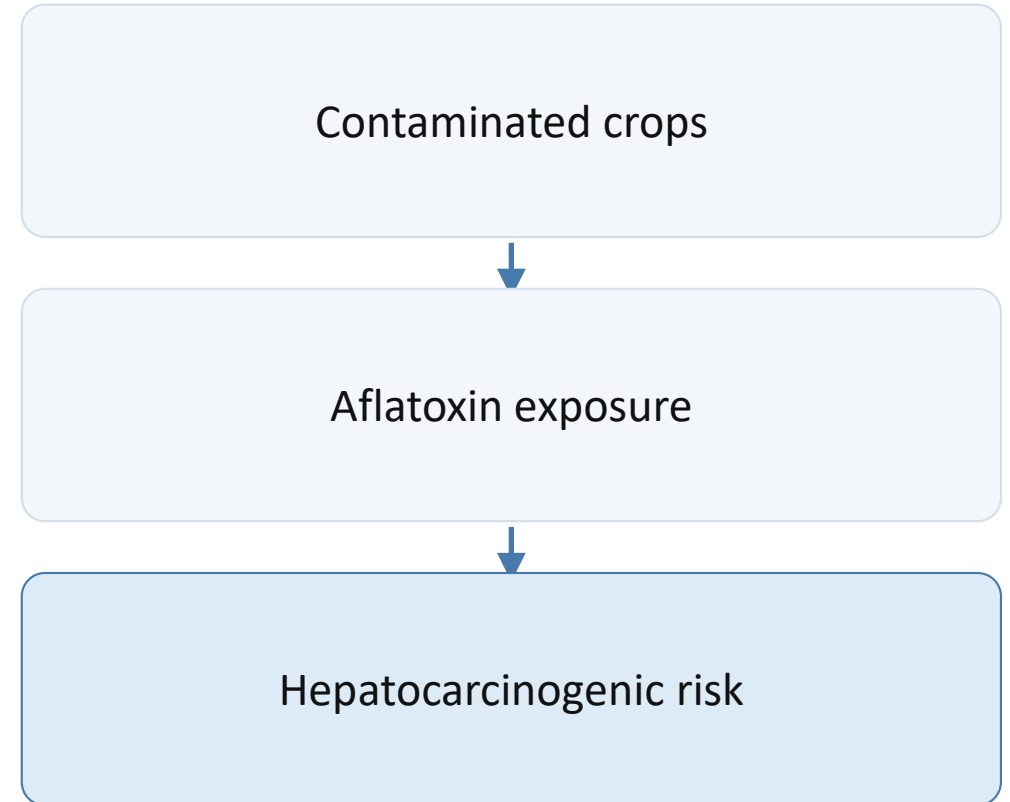
α_1 -antitrypsin deficiency

Other cirrhosis etiologies

- Wilson disease and chronic biliary diseases may increase HCC risk
- Robbins characterizes these risks as lower than those of common etiologies
- These risks remain above the general-population baseline

Aflatoxin exposure

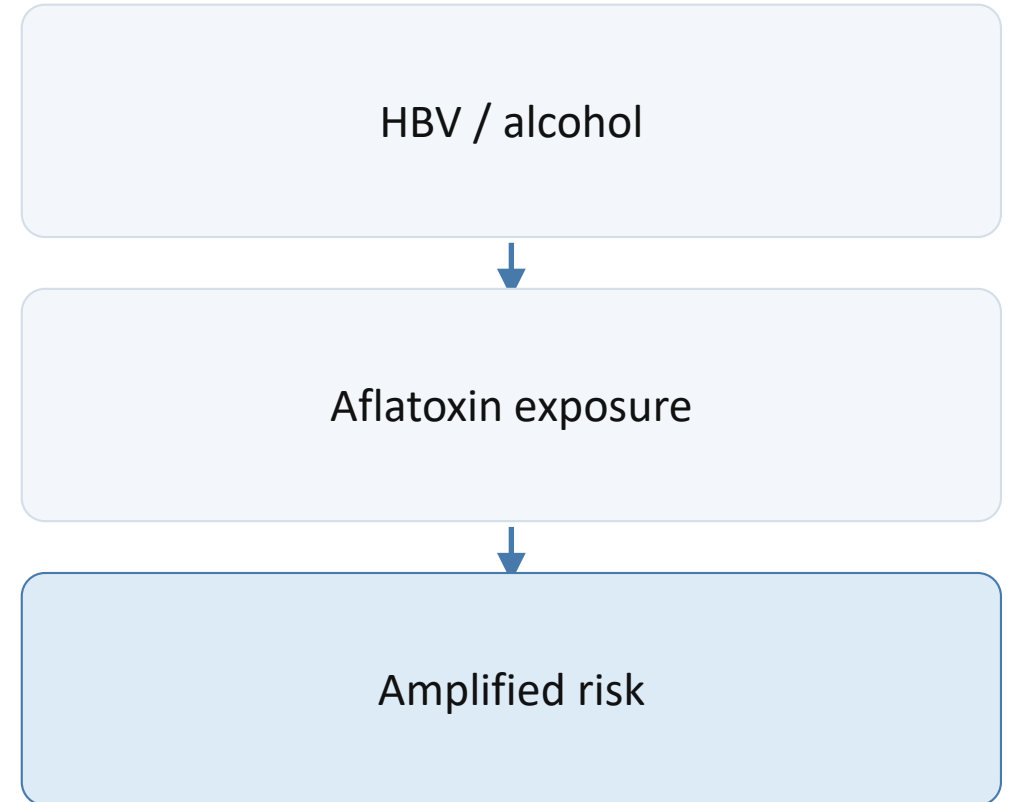
- Aflatoxin is produced by *Aspergillus* species
- Contamination of crops is an exposure pathway in parts of Africa and Asia
- It is a mycotoxin associated with hepatocarcinogenesis



Schematic / conceptual relations

Risk factors can act together

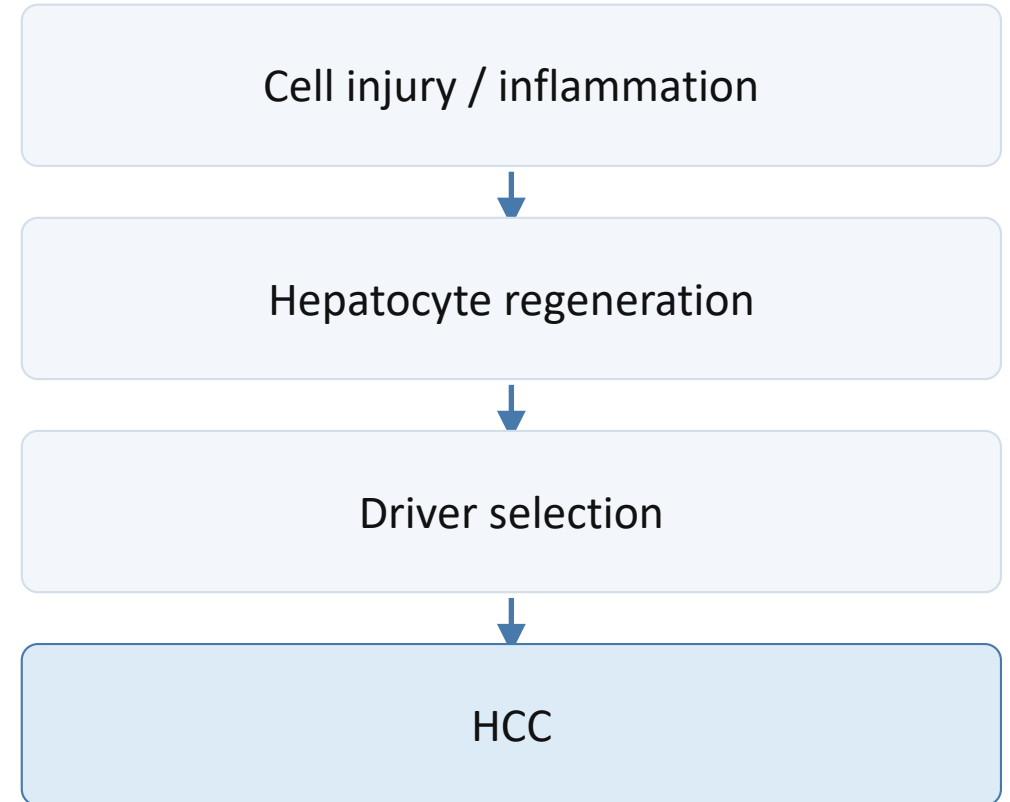
- Synergistic effects between aflatoxin, HBV and alcohol
- Carcinogenesis should not be reduced to a single mutually exclusive exposure
- Regional disease patterns reflect interacting biologic and exposure contexts



Schematic / conceptual relations

A causal framework for HCC

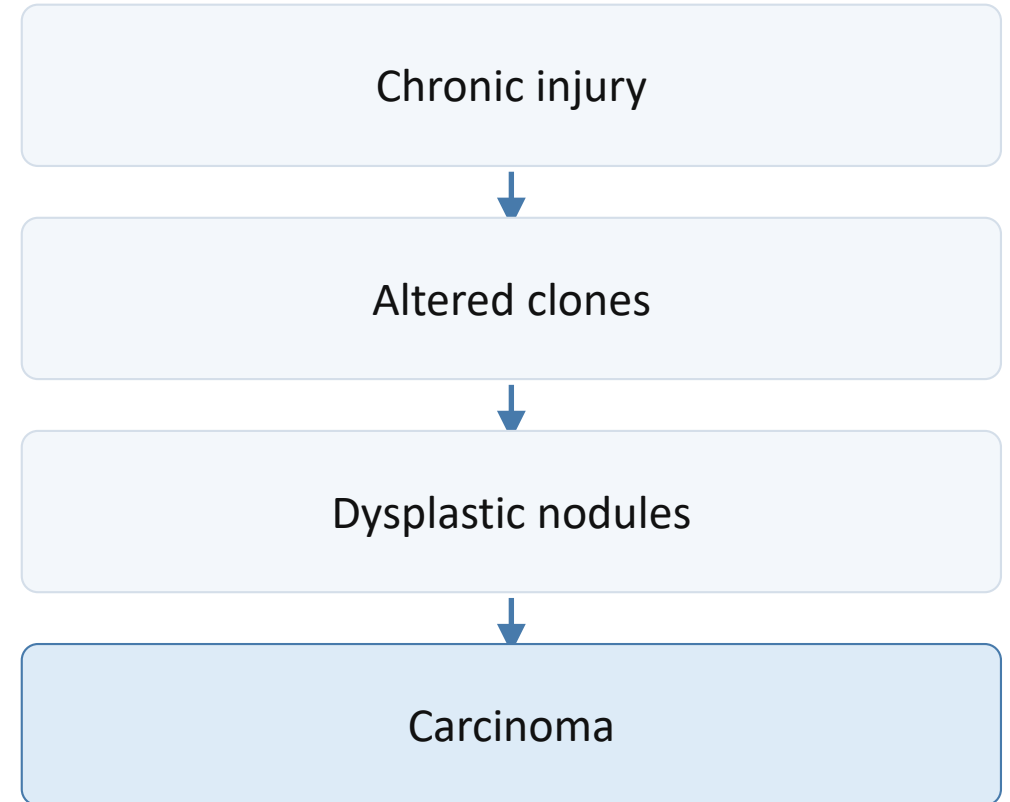
- Repeated hepatocyte damage drives inflammation and regeneration
- Cell proliferation provides opportunities for selection of altered clones
- Driver mutations confer growth or survival advantages
- Progression eventually yields invasive malignant neoplasia



Schematic / conceptual relations

Tumor development is multistep

- Chronic liver disease creates a permissive tissue environment
- Mutated hepatocyte populations may be clonally selected
- Dysplastic lesions can precede overt HCC
- Not every chronically damaged liver develops carcinoma



Schematic / conceptual relations

Three common classes of driver change

β -catenin

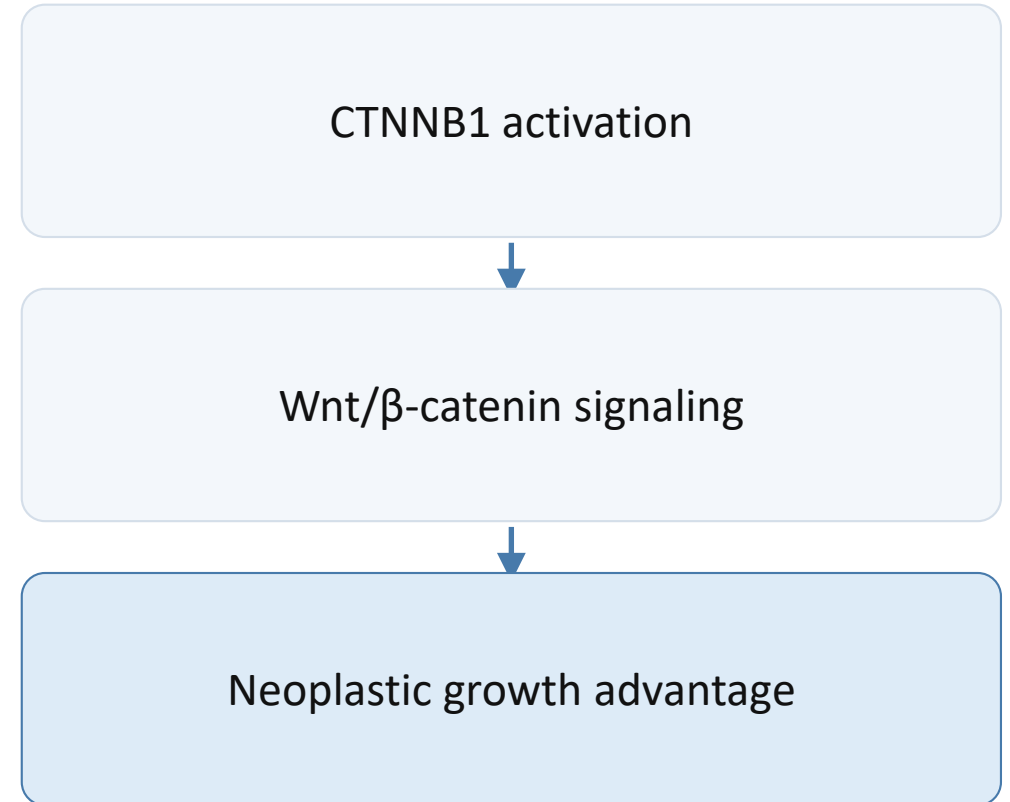
TERT

TP53

Distinct contributors converge on hepatocarcinogenesis

β -catenin pathway activation

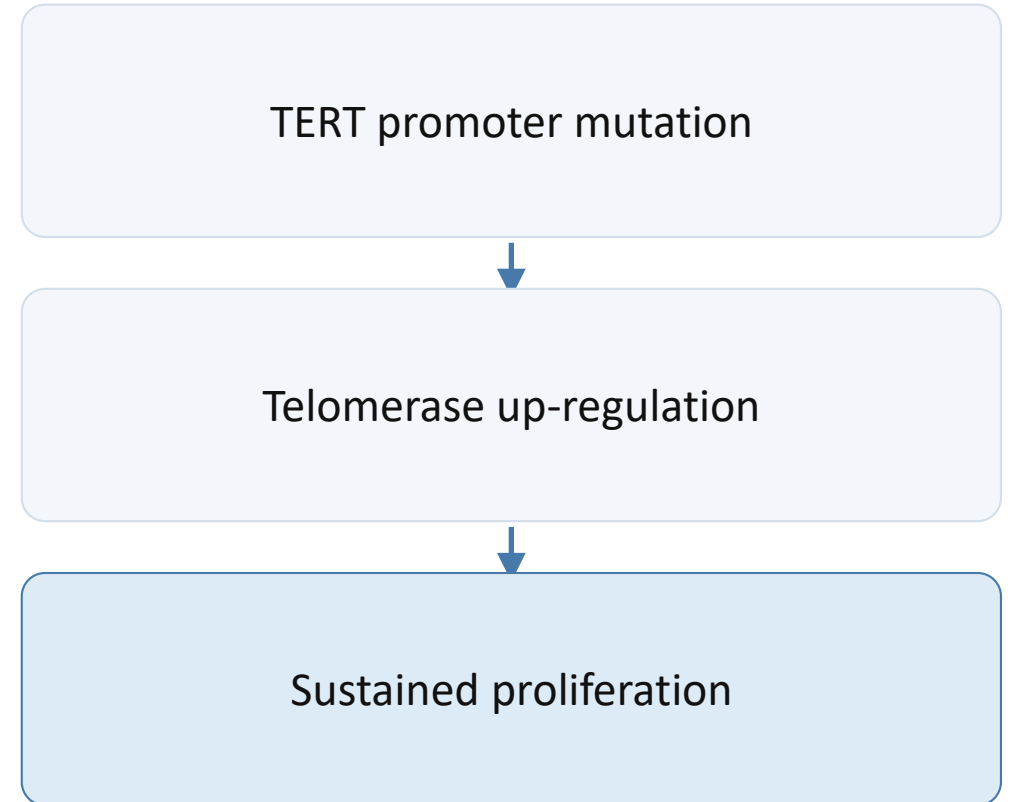
- Activating β -catenin gene mutations in ~40% of HCCs
- Activation of Wnt/ β -catenin signaling supports neoplastic growth
- This pathway also links some hepatocellular adenomas with malignant transformation



Schematic / conceptual relations

TERT promoter alterations

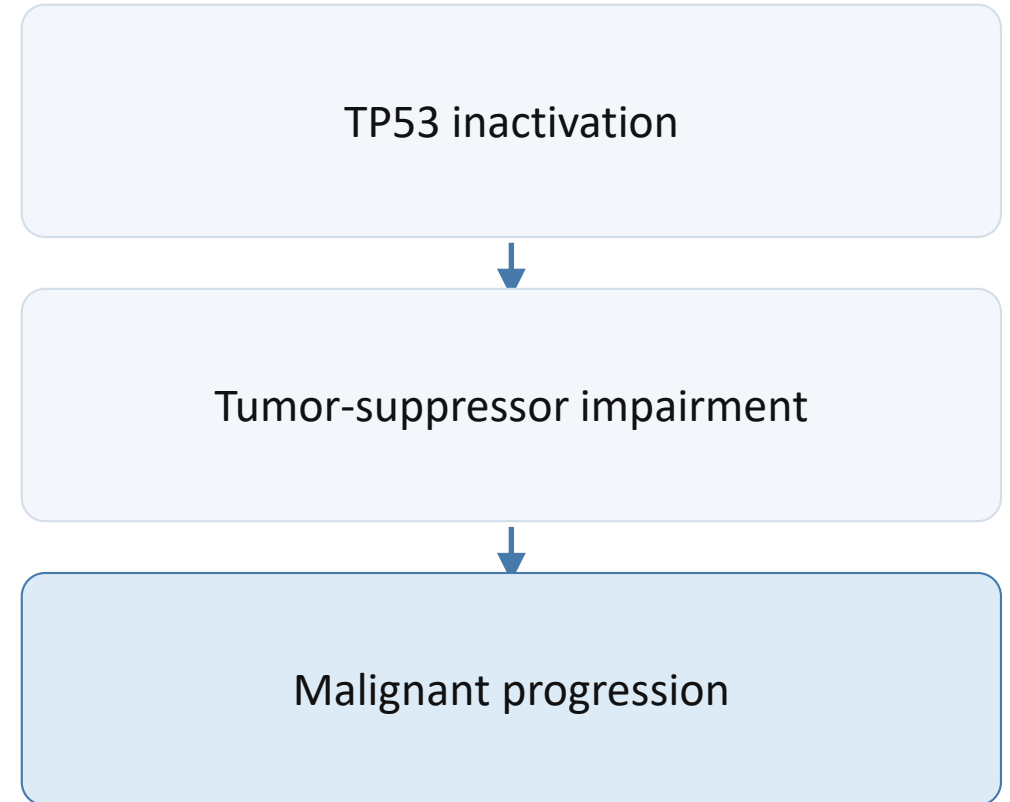
- Promoter mutations in TERT are reported in 50%–60% of HCCs
- Promoter activation increases telomerase activity
- This is a molecular route toward sustained proliferative capacity



Schematic / conceptual relations

TP53 loss of function

- Inactivating TP53 mutations are reported in up to 60% of tumors
- Loss of this tumor-suppressor pathway weakens cellular protection against malignant progression
- This genetic event can cooperate with other driver alterations



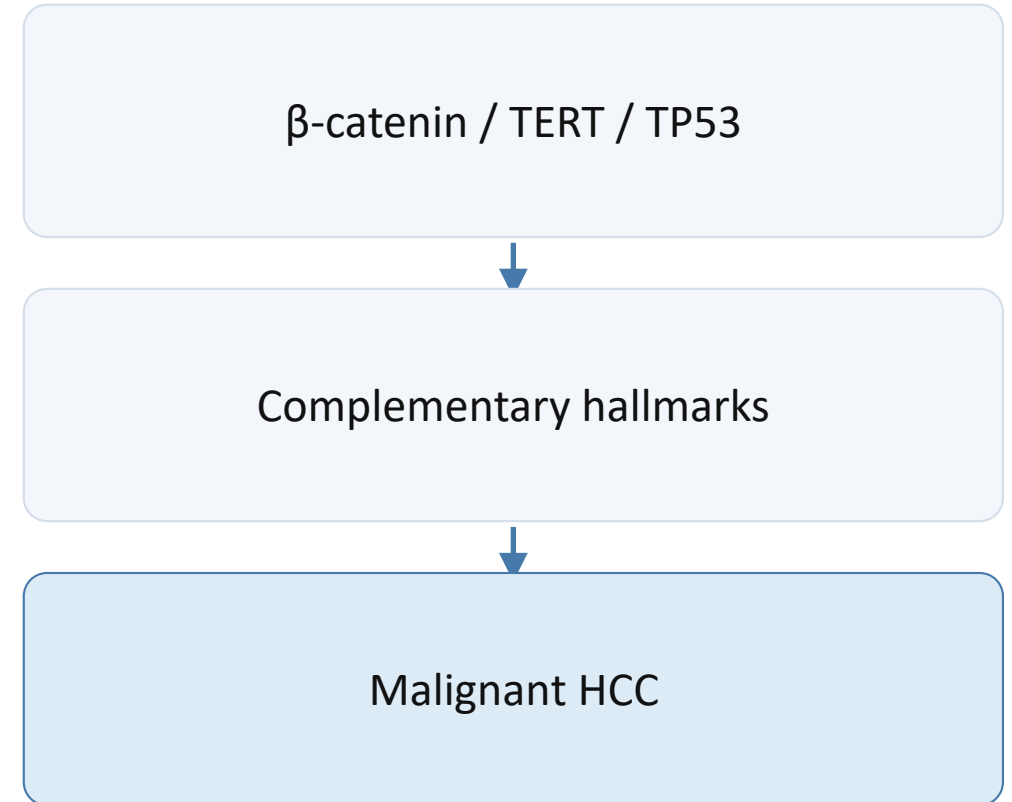
Schematic / conceptual relations

Interpretation of mutation frequencies

- The reported percentages are not exclusive disease subtypes
- Different drivers may coexist in the same malignancy
- Do not add their frequencies to derive the prevalence of HCC
- These are textbook figures; Sequencing cohorts vary

Convergence on cancer hallmarks

- Growth signaling: Activation of β -catenin pathway
- Replicative capacity: Increased telomerase activity
- Tumor suppression: Loss of TP53 function
- Different genomic routes converge on a malignant phenotype



Schematic / conceptual relations

Recognized routes to HCC

- In chronic liver disease: Altered hepatocytes and dysplastic nodules
- In noncirrhotic liver: Malignant progression can occur within an adenoma
- The precursor context depends on the underlying disease

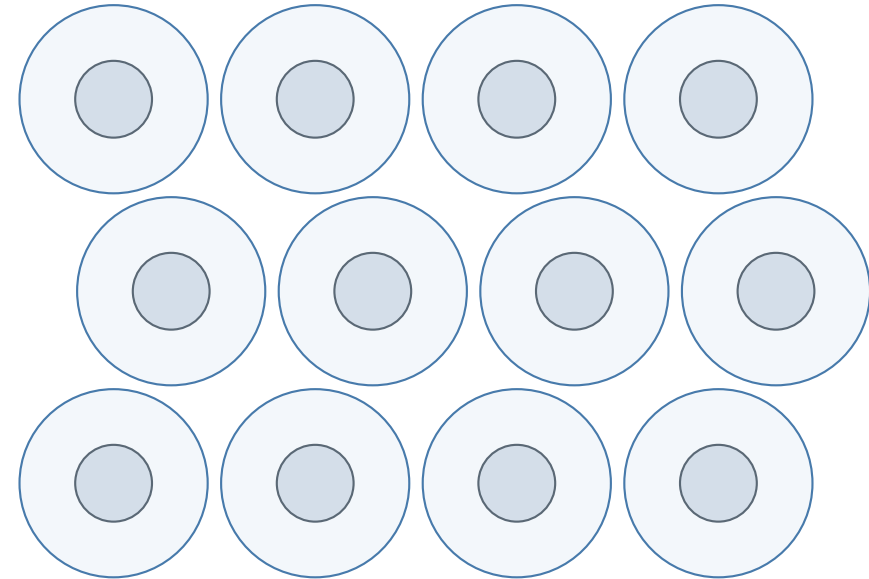
Chronic disease

Dysplastic nodule → HCC

Conceptual comparison

Large cell change

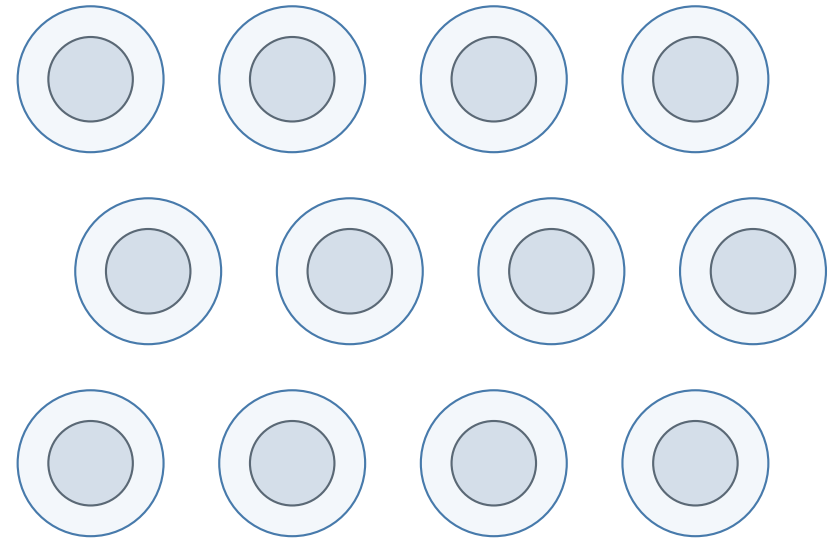
- Hepatocytes are larger than adjacent normal cells
- Nuclei may be enlarged, pleomorphic or multiple
- Nuclear-to-cytoplasmic ratio is not increased
- This is a morphologic alteration in the at-risk liver



Schematic · not a specimen

Small cell change

- Hepatocytes have increased nuclear-to-cytoplasmic ratio
- Mild nuclear hyperchromasia and/or pleomorphism may occur
- The change is particularly relevant in dysplastic nodules



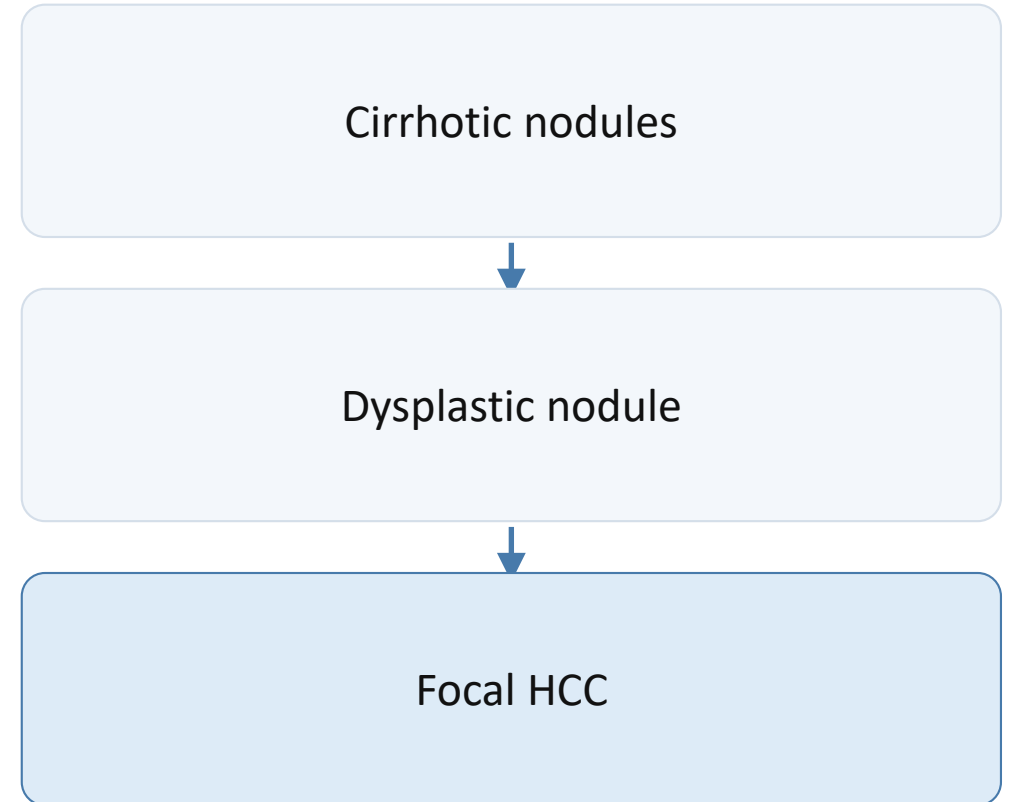
Schematic · not a specimen

Large cell versus small cell change

Feature	Large cell change	Small cell change
Cell size	Enlarged	Relatively small
N:C ratio	Not increased	Increased
Nuclear finding	Enlarged / pleomorphic	Mild hyperchromasia / pleomorphism

Dysplastic nodules in cirrhosis

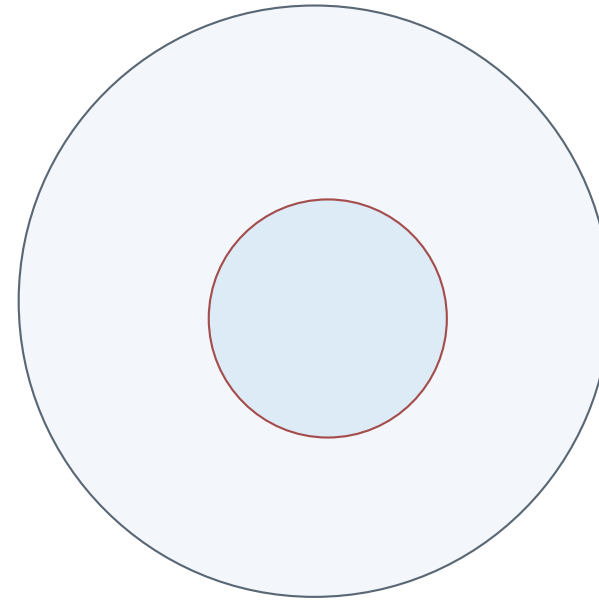
- Nodules differ from neighboring cirrhotic nodules in size or appearance
- Color and vascularization may also differ
- Dysplasia and clonal molecular abnormalities can be present
- Higher-grade lesions may contain early carcinoma



Schematic / conceptual relations

Nodule-in-nodule evolution

- A focus of HCC may develop within a pre-existing dysplastic nodule
- This produces a recognizable nodule-in-nodule configuration
- A distinct subnodule should prompt evaluation for malignant transformation

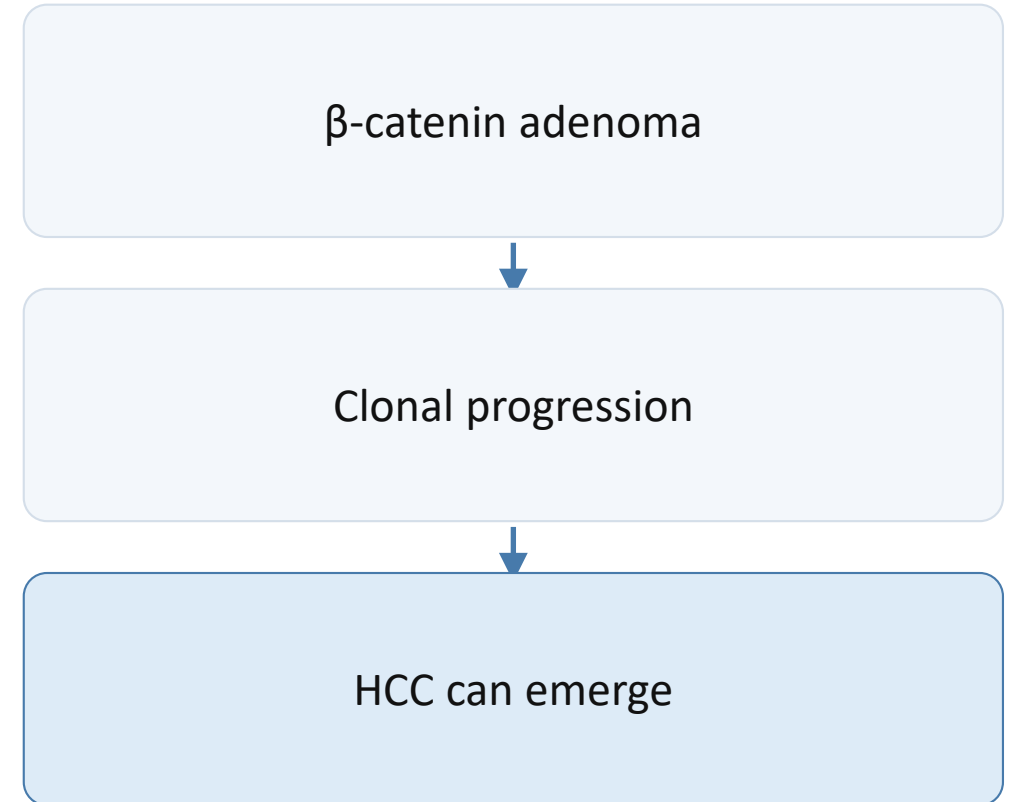


Inner focus within larger nodule

Schematic · not a specimen

Adenoma as a precursor in some settings

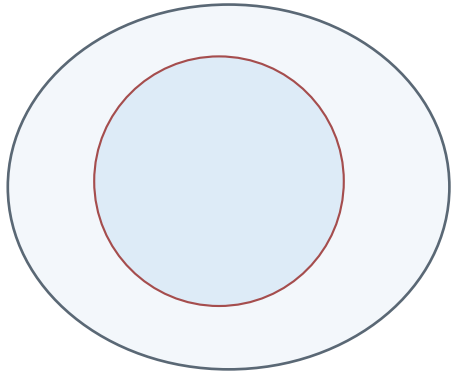
- HCC may arise within hepatocellular adenoma in noncirrhotic liver
- β -catenin–activated adenomas are an important higher-risk subgroup
- Exon 3 CTNNB1 activation is particularly associated with malignant transformation



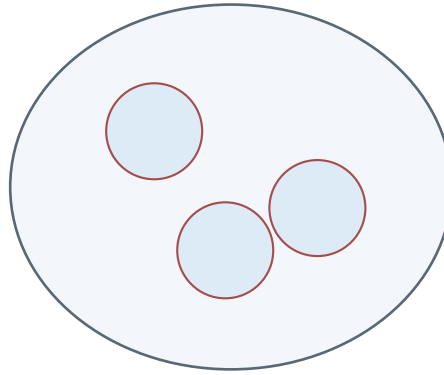
Schematic / conceptual relations

Major patterns of gross growth

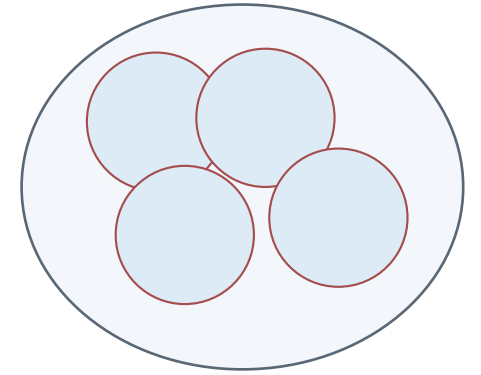
Solitary mass



Multiple nodules



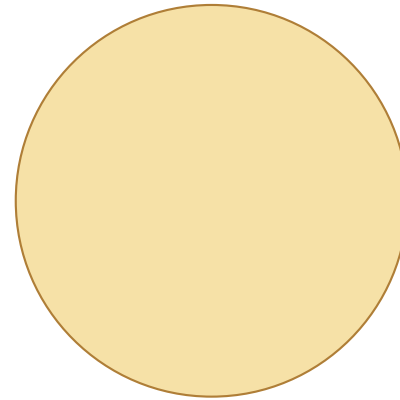
Diffuse infiltration



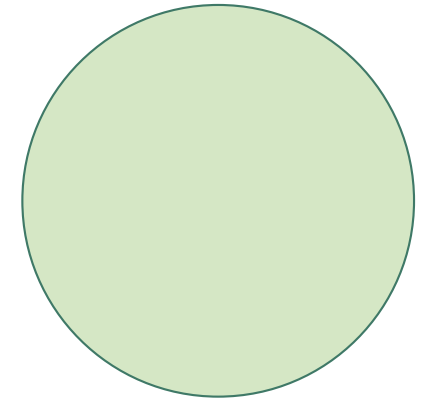
Schematic configurations · not gross specimens

Why HCC masses differ in color

- Yellow coloration may reflect fatty change
- Green coloration may result from cholestasis
- Gross color can suggest tumor composition but is not diagnostic by itself



Fatty change

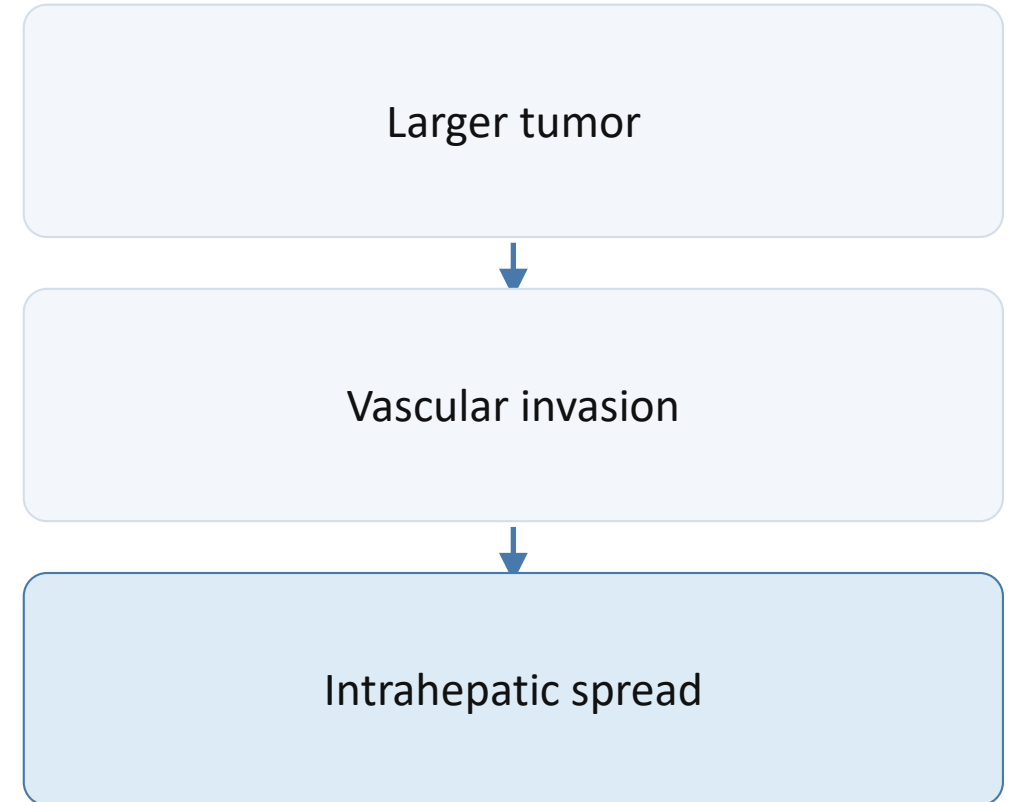


Cholestasis

Schematic · not a specimen

Tumor size and invasive potential

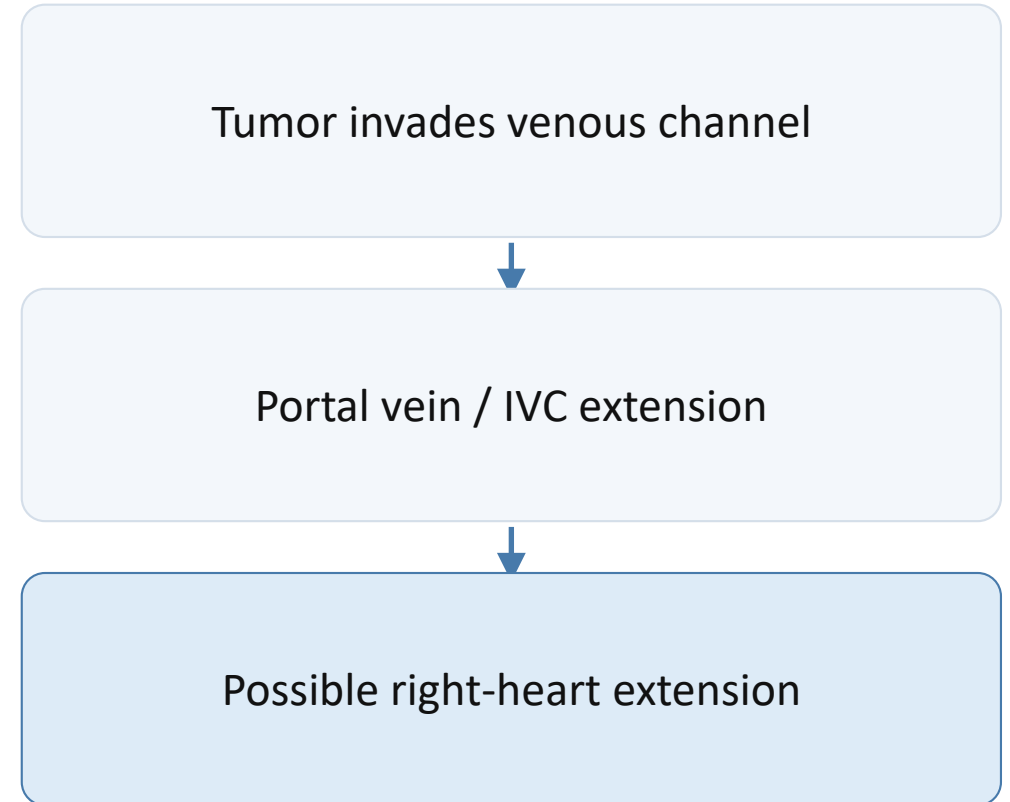
- Tumors larger than 2 cm are more likely to show vascular invasion
- Larger tumors are also more likely to show intrahepatic metastases
- This is a pathologic association, not a stand-alone staging algorithm



Schematic / conceptual relations

Venous invasion is a defining concern

- HCC may invade veins and propagate within vascular channels
- Extension into the portal vein and inferior vena cava can occur
- Rarely, tumor may extend to the right side of the heart



Schematic / conceptual relations

Differentiation modifies cytologic appearance

- Well-differentiated tumors closely resemble hepatocytes
- Moderately differentiated tumors retain partial hepatocellular characteristics
- Poorly differentiated tumors show pronounced atypia

Well differentiated

Poorly differentiated

Conceptual comparison

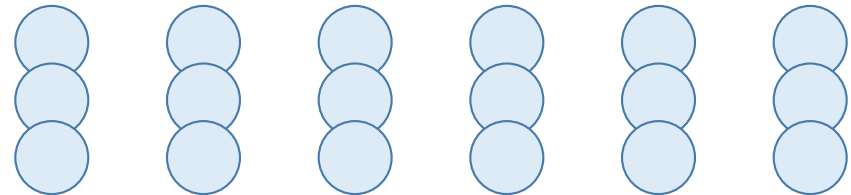
Thickened trabeculae

- Neoplastic hepatocytes may form thick plates or trabeculae
- Normal hepatic cell plates are comparatively thin
- Architectural expansion is an important diagnostic clue

Normal thin plate



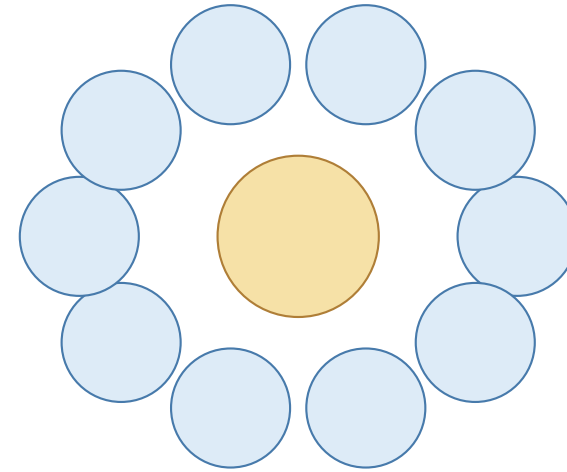
Thickened neoplastic trabecula



Schematic · not a specimen

Pseudoglandular architecture

- HCC may produce pseudoglandular or pseudoacinar spaces
- These are distorted hepatocellular structures, not necessarily true glands
- Bile plugs may be present in these spaces

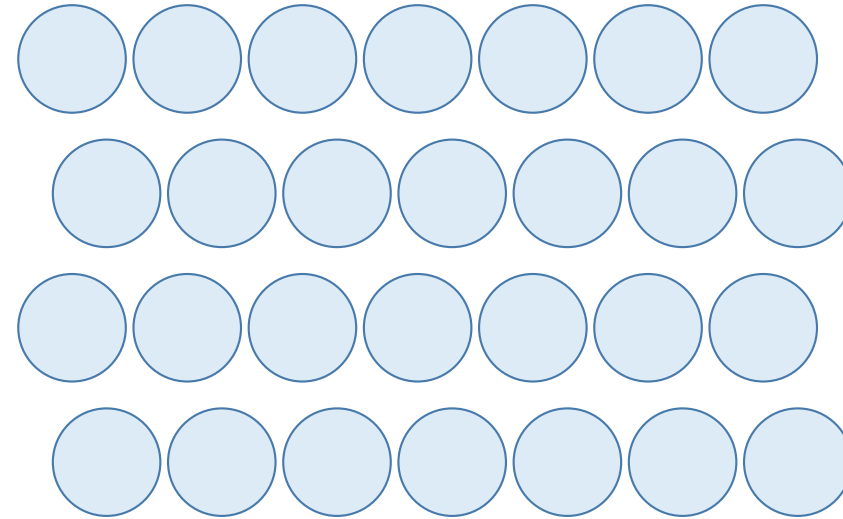


Central lumen / bile plug

Schematic · not a specimen

Solid growth pattern

- HCC may consist of confluent sheets of malignant hepatocytes
- This pattern is one of several microscopic growth architectures
- A single tumor may show architectural variability



Schematic · not a specimen

How the patterns relate

Pattern	Architectural hallmark
Trabecular	Thickened hepatocellular plates
Pseudoglandular	Lumen-like spaces; May contain bile
Solid	Confluent cell sheets

Morphology must be interpreted in context

- Atypia, architecture and the underlying liver all contribute
- Well-differentiated HCC can resemble nonmalignant hepatocellular lesions
- Histologic assessment should not rest on one isolated feature

Fibrolamellar carcinoma is a distinct HCC subtype

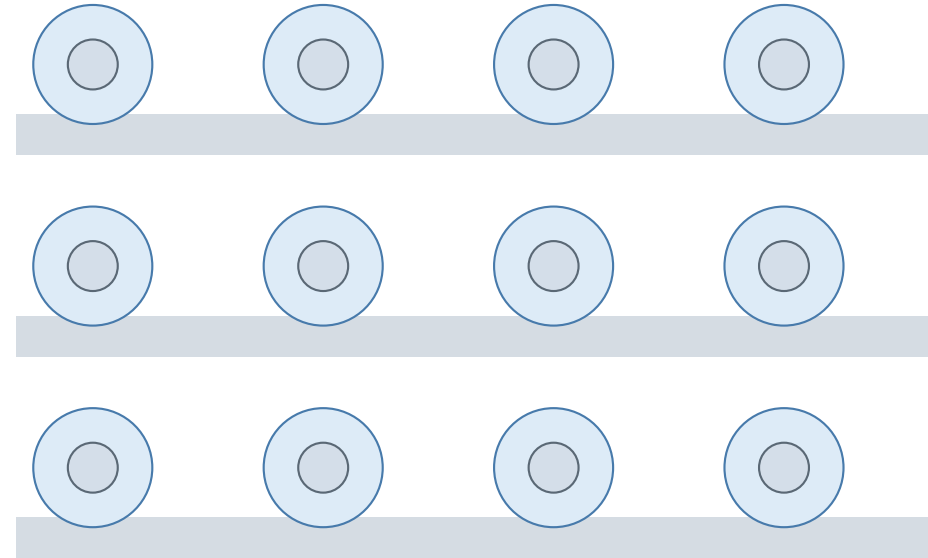
Younger age

Noncirrhotic liver

Characteristic fusion

Fibrolamellar: The diagnostic triad

- Large polygonal tumor cells with granular oncocytic cytoplasm
- Vesicular nuclei bearing conspicuous nucleoli
- Parallel lamellae of dense collagen separating tumor cell groups

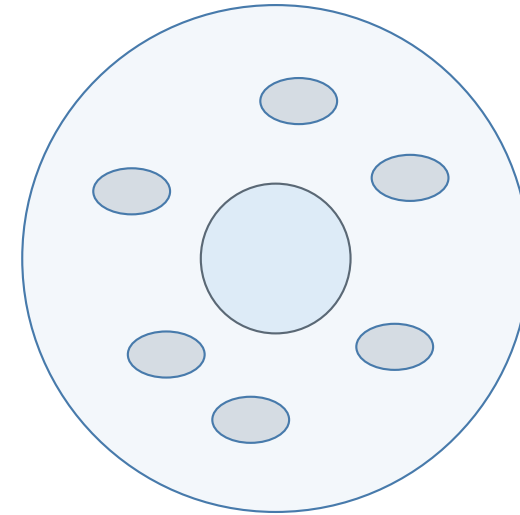


Parallel collagen + large oncocytic cells

Schematic · not a specimen

The oncocytic cytoplasm has a mechanism

- Abundant mitochondria account for granular eosinophilic cytoplasm
- Dense collagen lamellae create a distinctive stromal compartment
- These features explain the term “fibrolamellar”

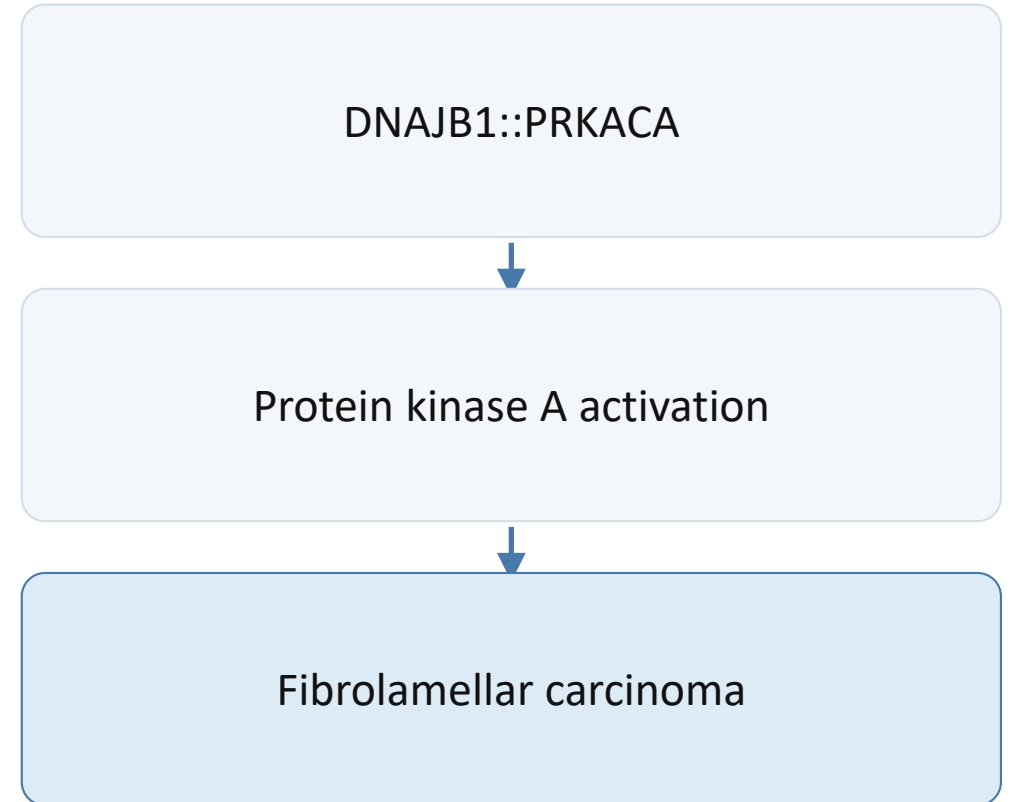


Mitochondria-rich oncocytic cell

Schematic · not a specimen

DNAJB1::PRKACA gene fusion

- Strongly associated with fibrolamellar carcinoma
- The fusion is linked to increased protein kinase A activity
- It distinguishes this subtype from common driver patterns of conventional HCC



Schematic / conceptual relations

Fibrolamellar versus conventional HCC

Feature	Conventional HCC	Fibrolamellar HCC
Background	Often chronic liver disease	Often noncirrhotic
Molecular	β -catenin / TERT / TP53	DNAJB1::PRKACA
Morphology	Varied hepatocellular patterns	Oncocytic cells + collagen

Clinical presentation is nonspecific

Abdominal pain

Systemic symptoms

Hepatomegaly

α -fetoprotein: A limited biomarker

- Serum AFP is frequently elevated in advanced HCC
- Sensitivity is inadequate for screening early-stage HCC by AFP alone
- The fibrolamellar subtype generally lacks AFP elevation

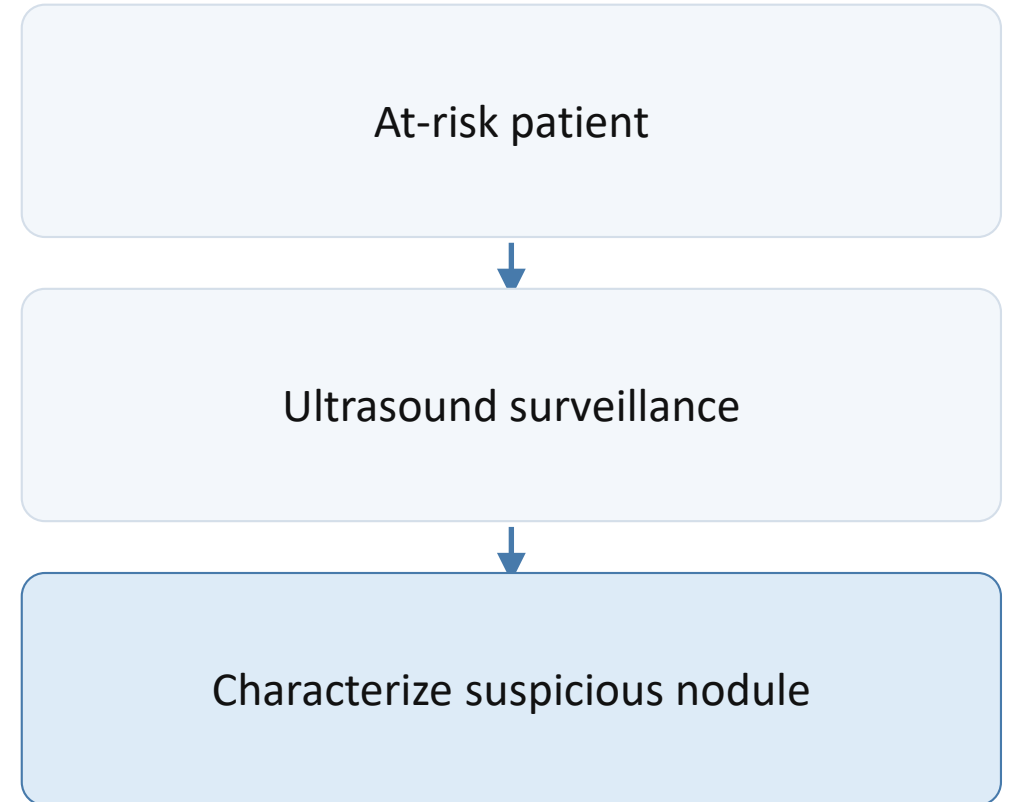
Advanced HCC: Often elevated

Early disease: May be normal

Conceptual comparison

Ultrasound in at-risk livers

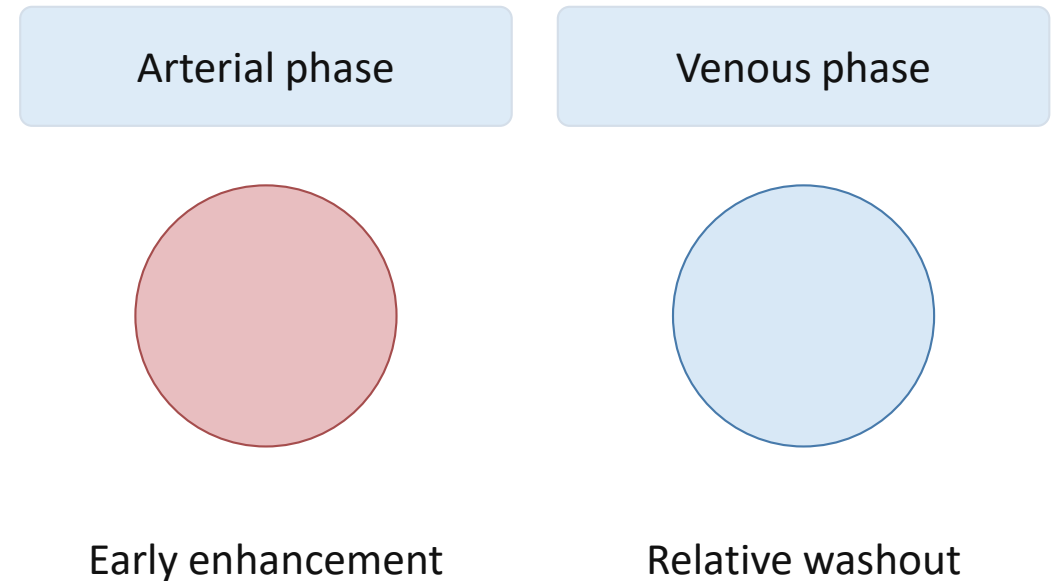
- Ultrasound as a screening method in high-risk patients
- Cirrhosis is a central high-risk setting
- A suspicious observation requires further characterization



Schematic / conceptual relations

Dynamic imaging: Arterial enhancement

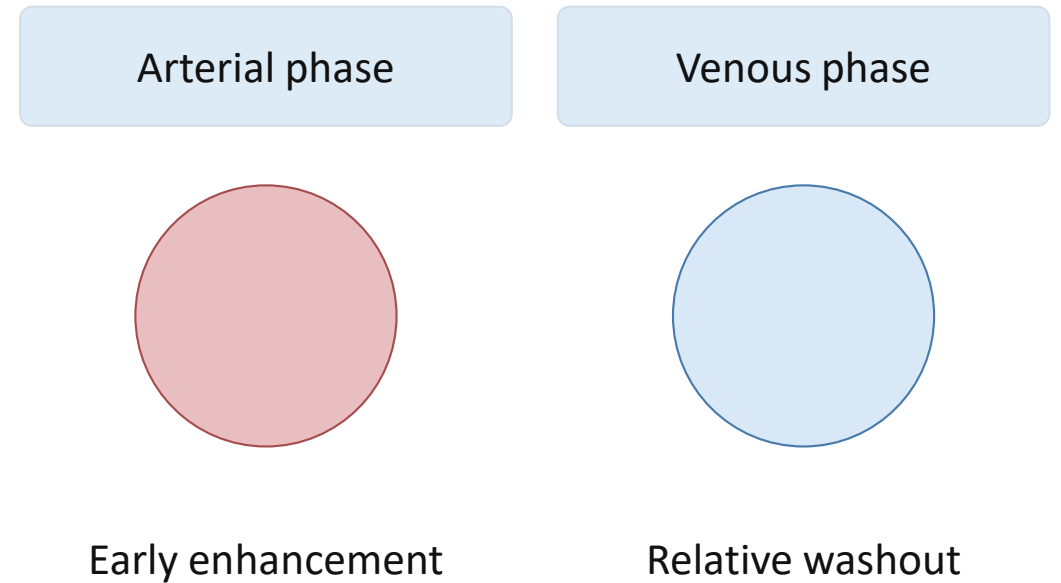
- HCC commonly exhibits early enhancement after contrast delivery
- The arterial-phase behavior reflects the tumor's vascular phenotype
- This is only one phase of a multiphasic examination



Schematic contrast behavior · not a scan

Dynamic imaging: Venous washout

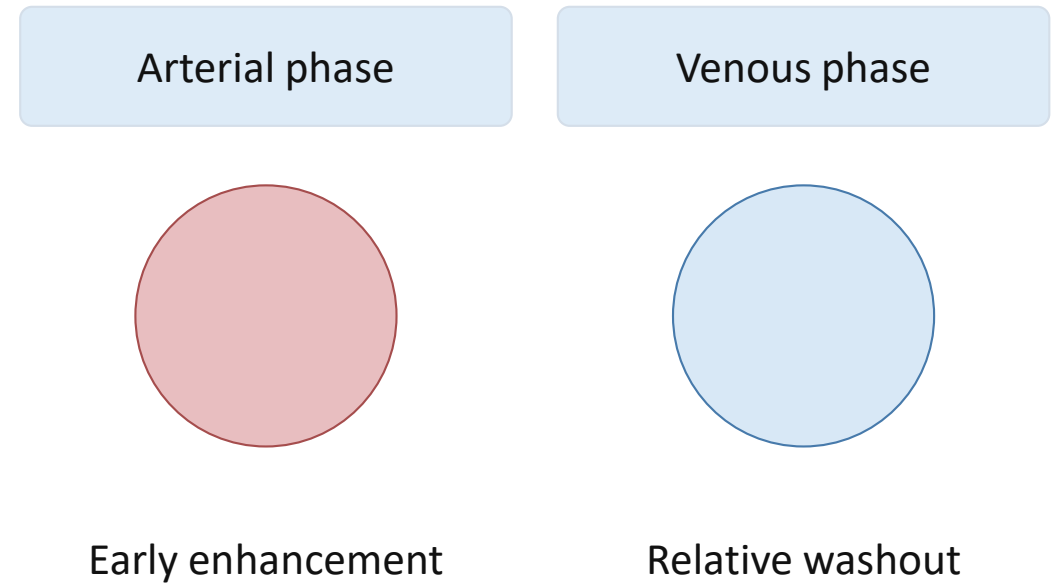
- Rapid washout after arterial enhancement
- Arterial uptake followed by venous washout is strongly characteristic
- Interpretation depends on the entire imaging context



Schematic contrast behavior · not a scan

Imaging pattern as an integrated sequence

- First identify an at-risk patient or a hepatic mass
- Characterize enhancement during arterial phase
- Assess behavior during the venous phase
- Integrate with clinical condition and other findings



Schematic contrast behavior · not a scan

Resection depends on hepatic reserve

- Surgery is favored for resectable HCC in noncirrhotic liver
- Patients with cirrhosis require adequate residual liver function
- Anatomical tumor extent and hepatic function must both be considered

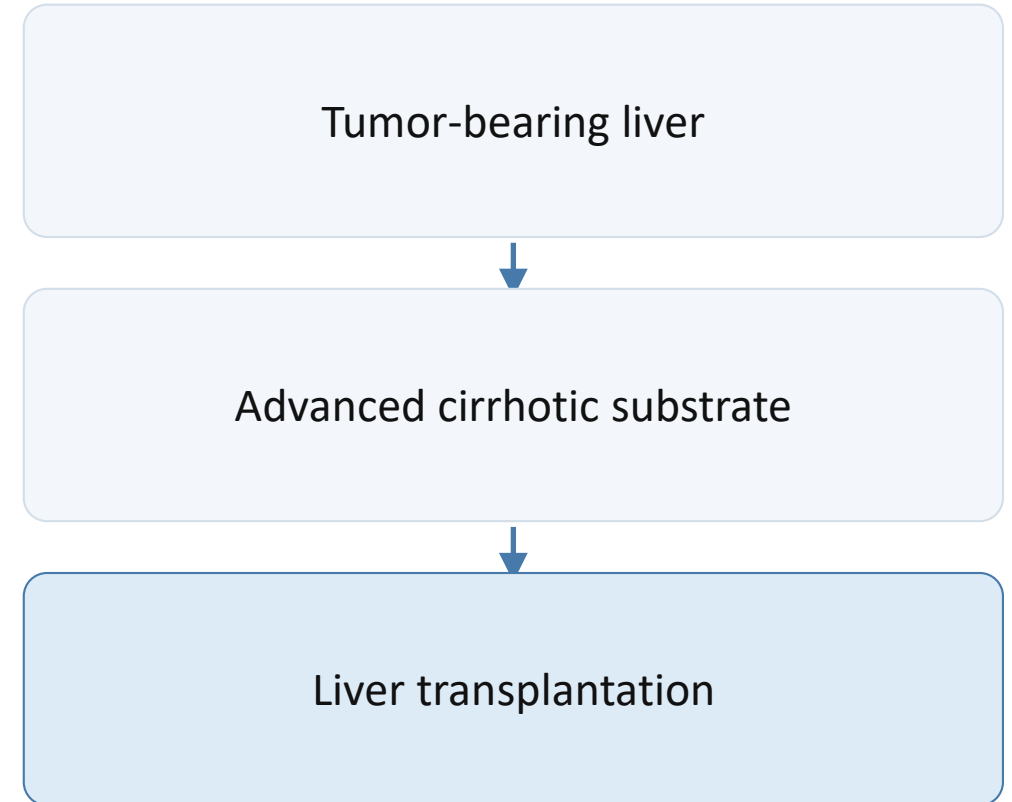
Resectable tumor

Adequate hepatic function

Conceptual comparison

Transplantation addresses two problems

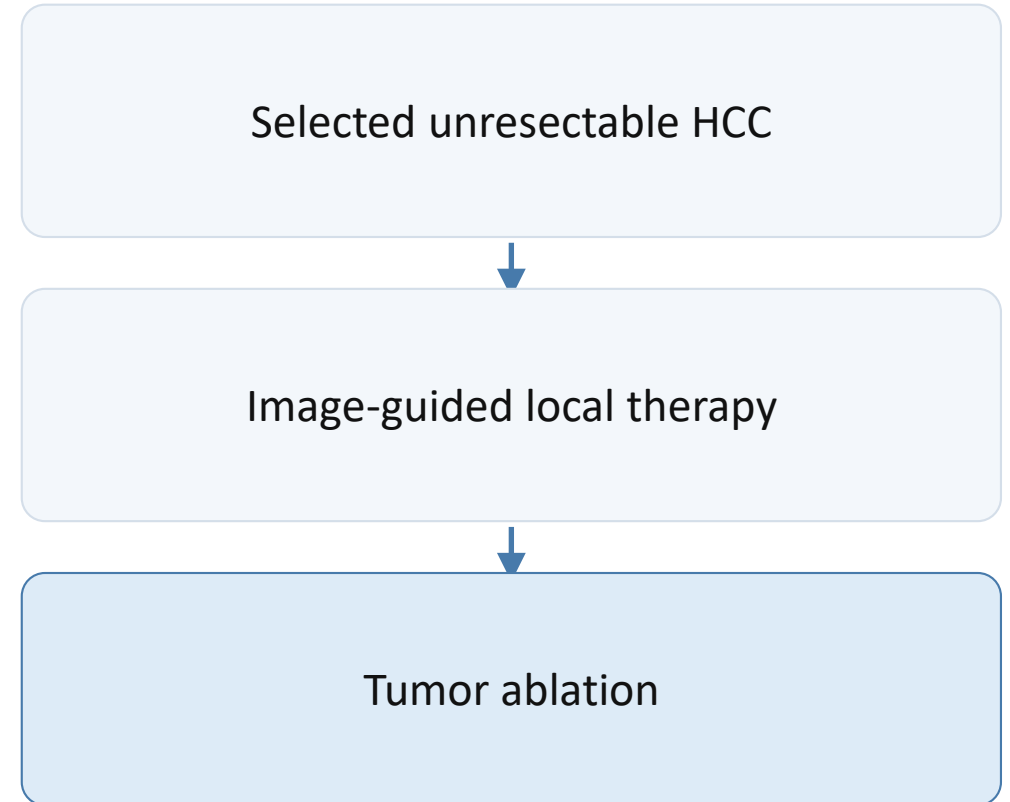
- For HCC associated with advanced cirrhosis, transplantation may be considered
- It removes the tumor-bearing liver together with the diseased parenchyma
- Selection criteria are not specified in this textbook excerpt



Schematic / conceptual relations

Local ablation

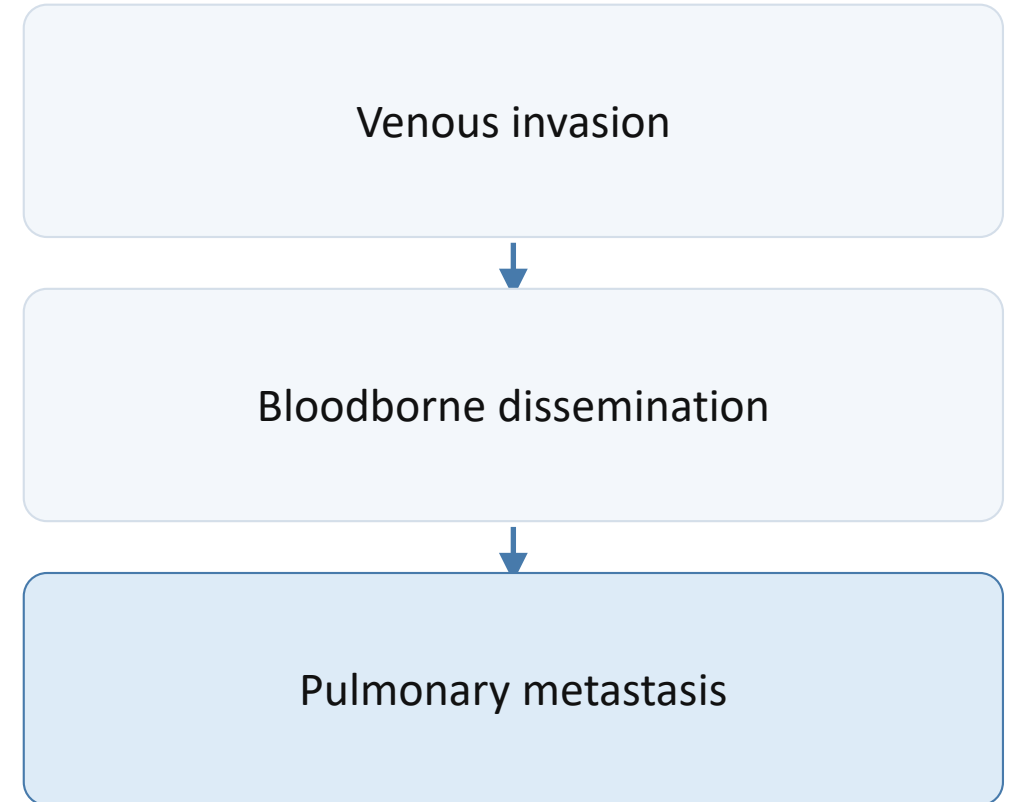
- Image-guided alcohol ablation or radiofrequency ablation may be used
- These for unresectable tumors or non-transplant candidates
- Ablation is a local tumor-directed approach



Schematic / conceptual relations

Hematogenous and regional spread

- Metastases may occur late in the course
- The lung is a particularly important distant hematogenous site
- The excerpt reports lymph-node metastasis in fewer than 5% of cases



Schematic / conceptual relations

Outcome is driven by tumor and host liver

- Underlying cirrhosis can independently worsen prognosis
- Conventional chemotherapy resistance contributes to poor outcomes
- Noncirrhotic patients may tolerate more extensive resection

Tumor extent

Residual hepatic reserve

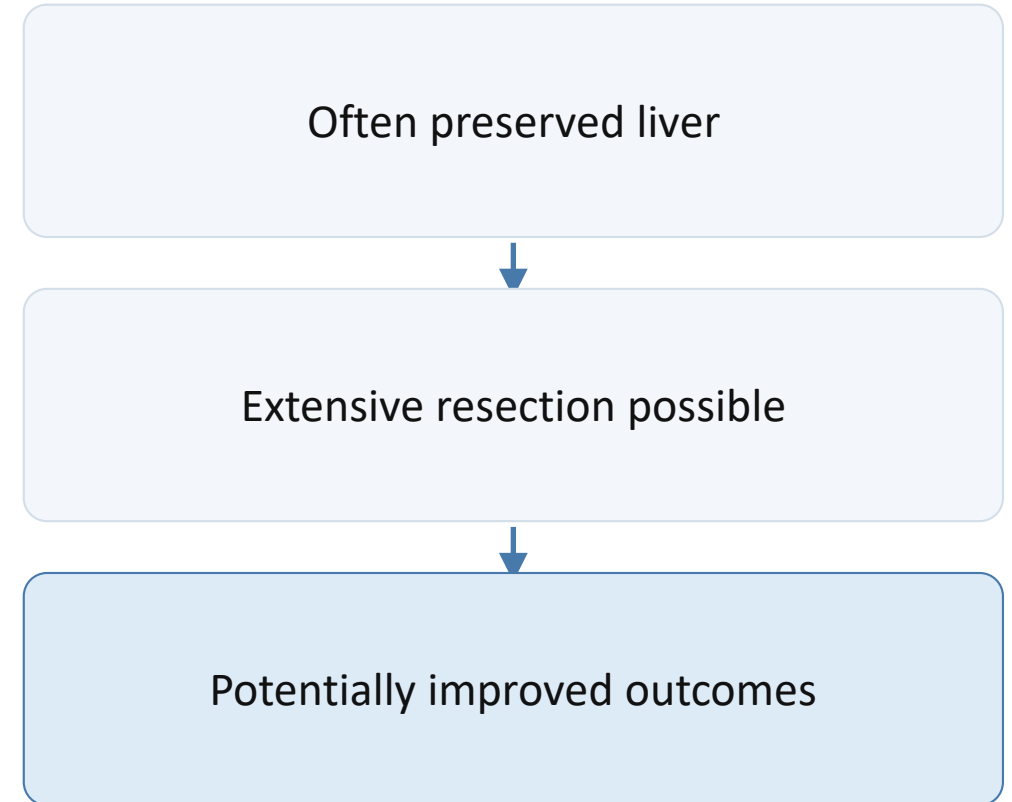
Conceptual comparison

Textbook-reported survival contrasts

Disease extent	Robbins-reported 5-year survival
Confined to liver	~30%
Extrahepatic spread	~5%–10%

Why fibrolamellar outcomes may differ

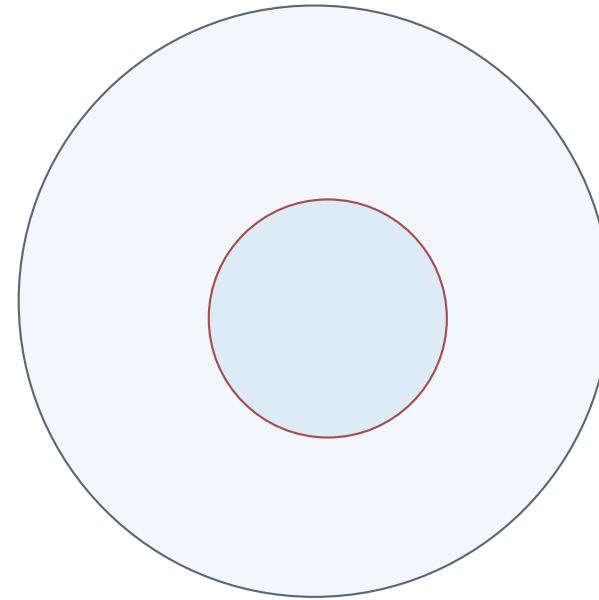
- Absent chronic liver disease often permits larger resections
- Up to 40% with survival of 10 years or longer
- Prognosis is not favorable for every individual patient



Schematic / conceptual relations

Case: A nodule in a cirrhotic liver

- A patient with longstanding chronic hepatitis has a new distinct hepatic nodule
- Its architecture contains an emerging internal subnodule
- Interpretation: Consider dysplastic nodule with evolving HCC

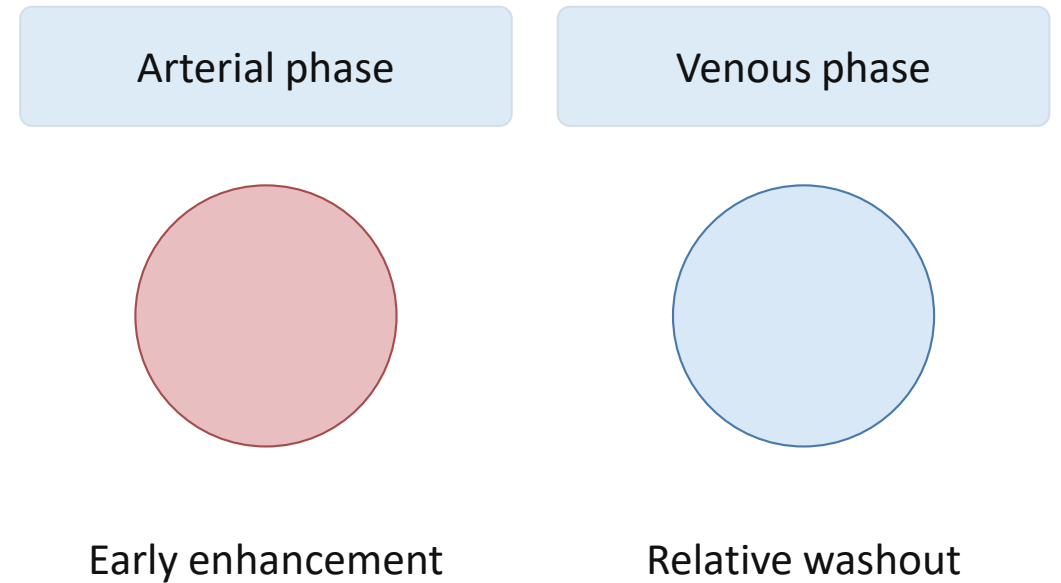


Inner focus within larger nodule

Schematic · not a specimen

Case: Dynamic enhancement of a liver mass

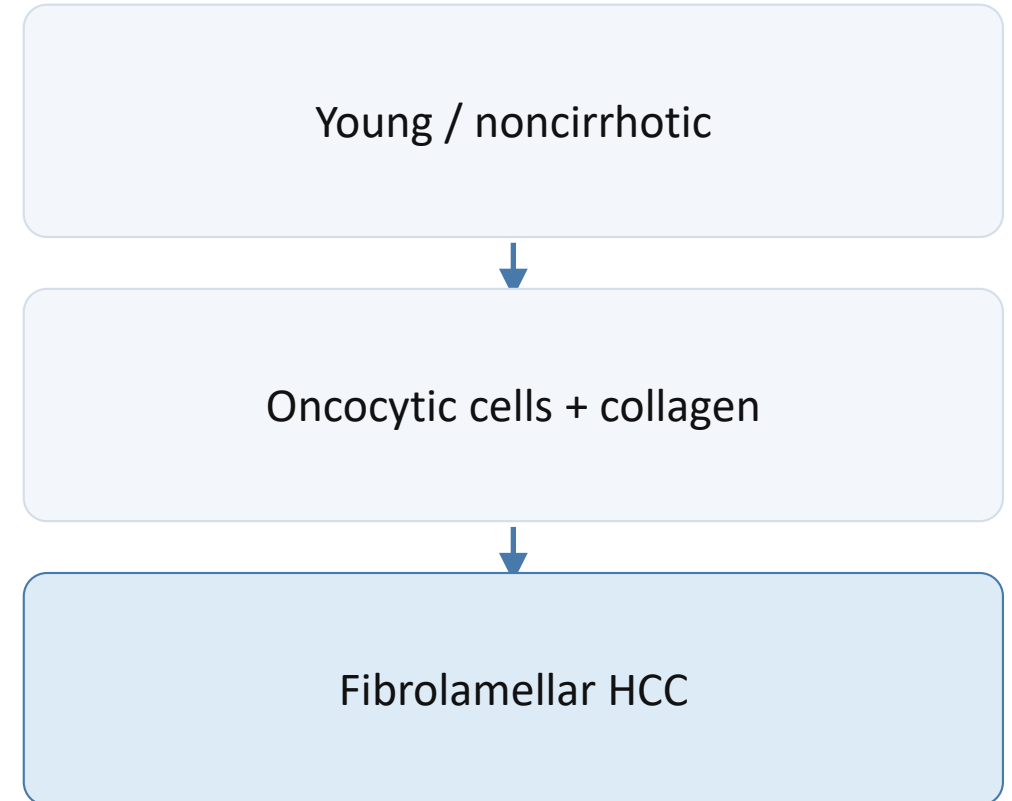
- A high-risk patient has a liver mass with arterial enhancement
- The lesion subsequently becomes relatively hypoenhancing during venous imaging
- Interpretation: Imaging phenotype strongly characteristic of HCC



Schematic contrast behavior · not a scan

Case: Young patient without cirrhosis

- Young adult with a hepatic mass and no chronic liver disease
- Tumor shows oncocytic hepatocytes and dense lamellar collagen
- Interpretation: Fibrolamellar carcinoma;
Consider DNAJB1::PRKACA association



Schematic / conceptual relations

HCC versus hepatocellular adenoma

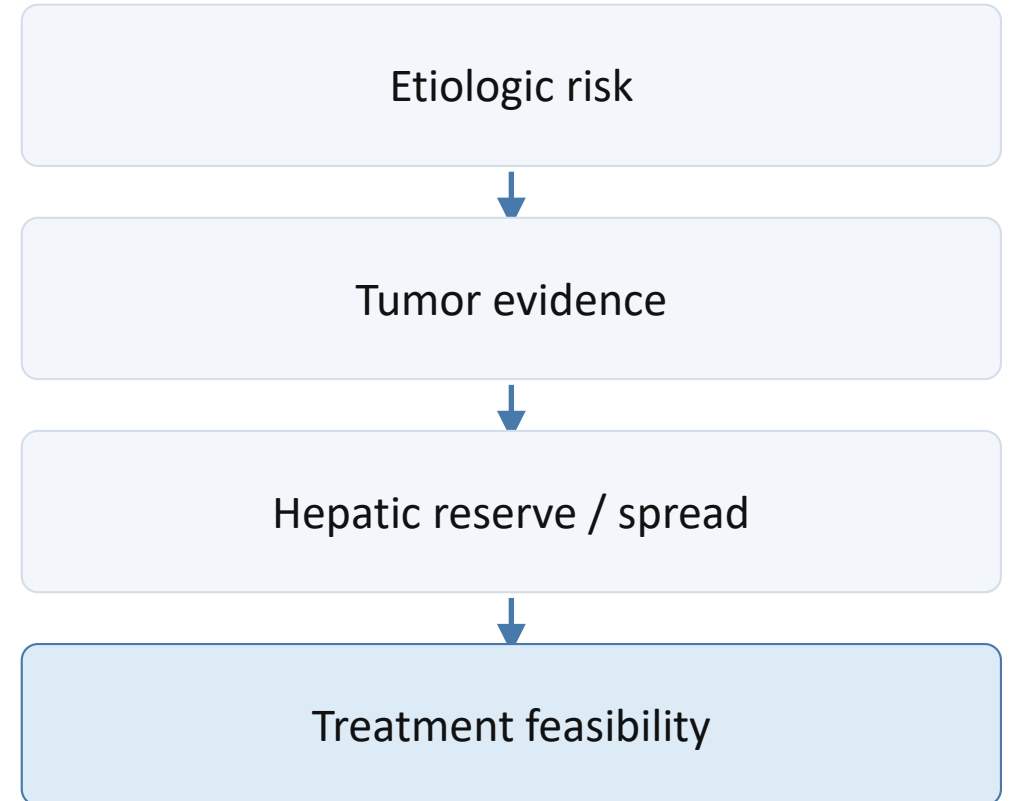
Feature	Hepatocellular adenoma	HCC
Biologic class	Benign neoplasm	Malignant neoplasm
Architecture	Typically thin plates	Often thick plates / pseudoacini
Vascular invasion	Not a benign feature	May be extensive

HCC versus intrahepatic cholangiocarcinoma

Feature	HCC	Intrahepatic cholangiocarcinoma
Cell lineage	Hepatocellular	Biliary epithelial
Primary malignant liver tumor	Major category	Other major category
Primary teaching emphasis	Trabecular / pseudoacinar	Biliary adenocarcinoma

Integrating pathology with clinical decisions

- Risk context identifies patients in whom a new liver nodule is consequential
- Morphology and multiphasic enhancement support diagnostic classification
- Cirrhosis and tumor spread shape management feasibility



Schematic / conceptual relations

Core concepts for recall

Chronic injury



Driver mutations



Morphologic progression



Invasive / metastatic tumor