

Hepatoblastoma

Developmental pathology • molecular mechanisms • clinicopathologic interpretation

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Learning objectives

- Recognize the defining clinical and pathologic features of hepatoblastoma.
- Link Wnt/ β -catenin activation and inherited risk syndromes to tumor development.
- Distinguish epithelial, mixed epithelial–mesenchymal, and important small-cell patterns.
- Interpret diagnosis, PRETEXT extent, response markers, and treatment in context.

A primary childhood liver malignancy

- Hepatoblastoma is the characteristic hepatocellular malignancy of early childhood.
- It resembles immature stages of hepatic differentiation rather than adult liver tissue.
- Hepatocellular carcinoma is a distinct entity and must not be conflated with it.

Primary pediatric liver tumor



Hepatoblastoma

**Other tumors ≠
hepatoblastoma**

A distinct malignant epithelial entity

Age is a major diagnostic clue

- Most children present before 3 years of age; Occurrence beyond this age is uncommon.
- Tumors with overlapping hepatoblastoma and hepatocellular carcinoma morphology may occur in older children.
- “hepatocellular neoplasm, not otherwise specified” for this overlapping category.

Conceptual age distribution

Infancy–3 y

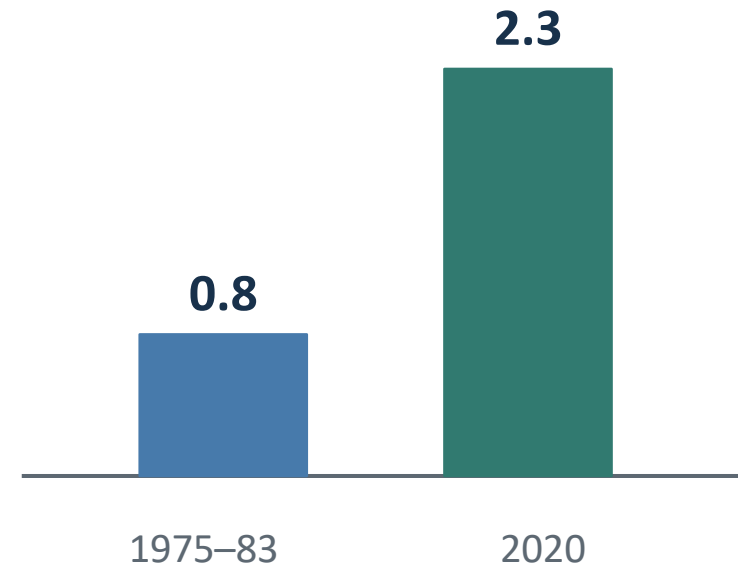
**Older children:
Uncommon**

No numerical curve is implied

Incidence has increased

- An increasing incidence of hepatoblastoma.
- NCI PDQ reports U.S. Incidence rising from 0.8 to 2.3 cases per million children aged ≤ 19 years across the periods shown.
- The cause of the increase is not established; Associations should not be interpreted as proven causation.

U.S. Incidence, children ≤ 19 y

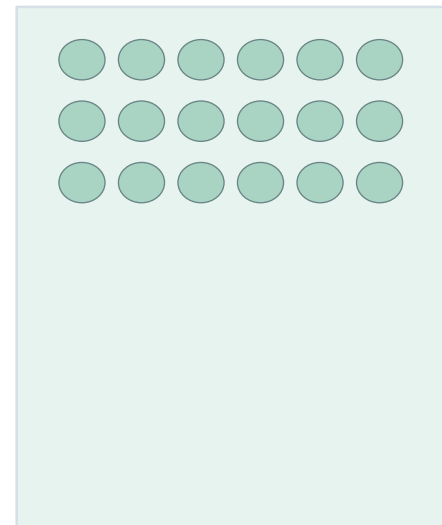


Cases per 1 million (NCI PDQ)

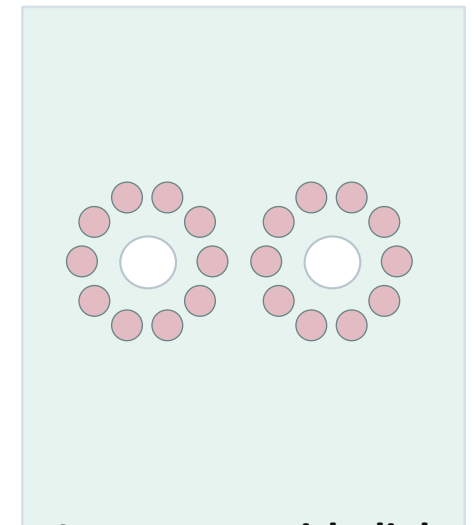
Hepatic developmental identity

- The tumor contains cells with fetal or embryonal hepatocytic morphology.
- Growth patterns evoke liver development but do not recreate normal liver architecture.
- The developmental appearance underlies the names of the principal epithelial patterns.

Original morphology schematic — not a photomicrograph



Hepatic-like plates

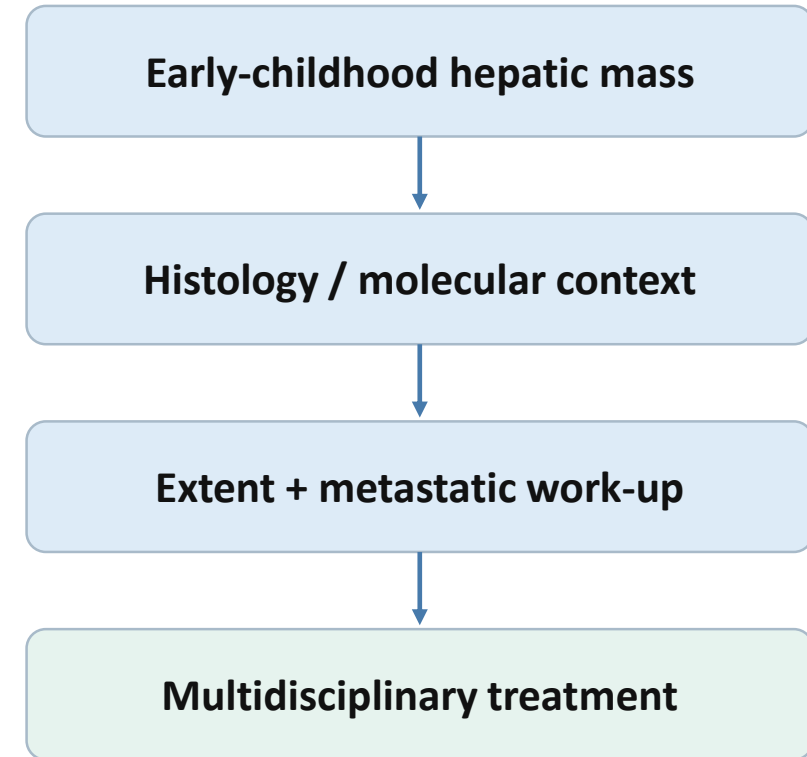


Immature epithelial tubules

Simplified architecture only; No stain or scale is represented

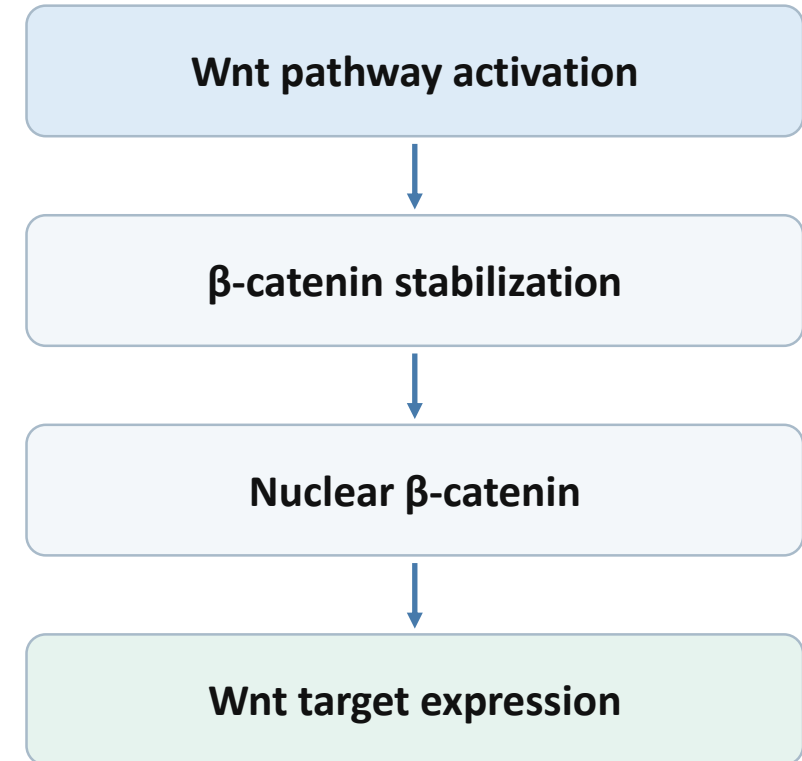
The clinical–pathologic model

- An early-childhood hepatic mass suggests a developmental liver tumor.
- Histology determines the pattern of differentiation and alerts to divergent components.
- Anatomic extent, dissemination, and response influence management beyond morphology alone.



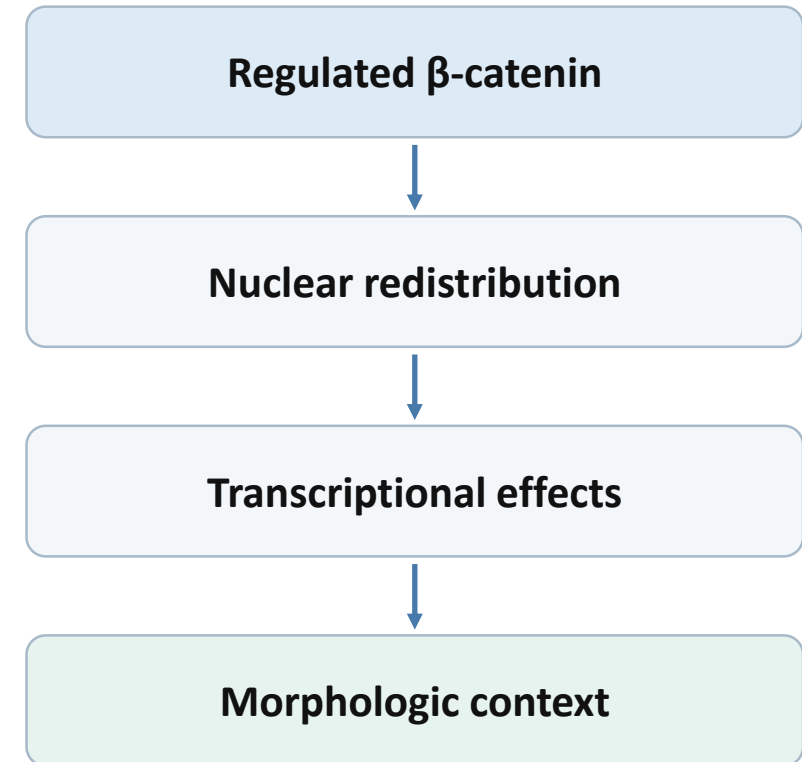
Wnt/ β -catenin signaling is central

- Activation of Wnt signaling is characteristic of hepatoblastoma.
- Nuclear accumulation of β -catenin is an important pathway consequence.
- Expression of Wnt-regulated genes, including glutamine synthetase, is increased in nearly all cases.



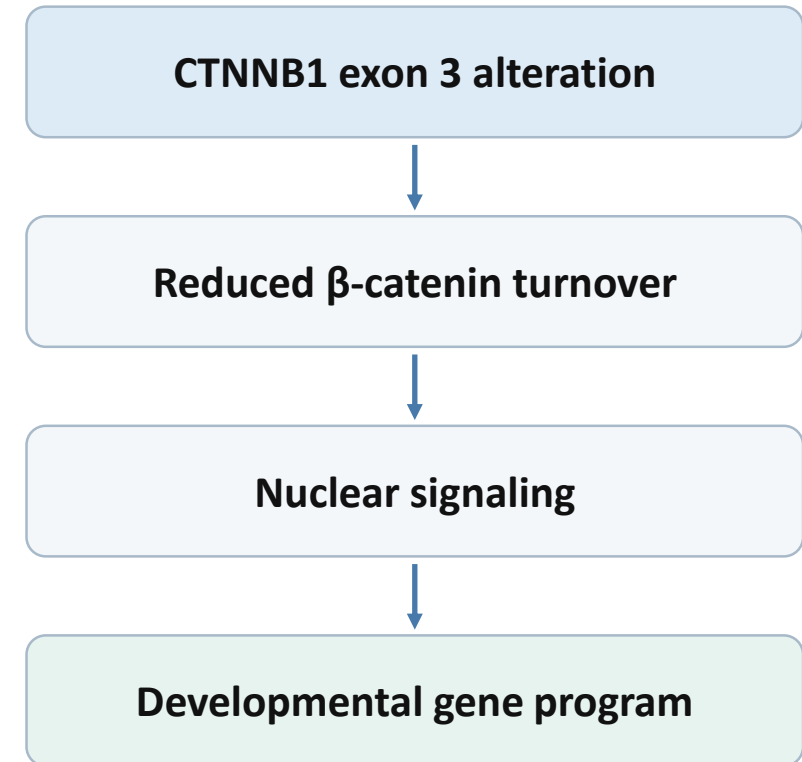
What β -catenin redistribution means

- Membranous β -catenin participates in cell adhesion; Nuclear accumulation indicates transcriptional signaling.
- Nuclear β -catenin is mechanistically relevant, but interpretation requires morphologic context.
- A pathway marker alone does not substitute for a diagnosis.



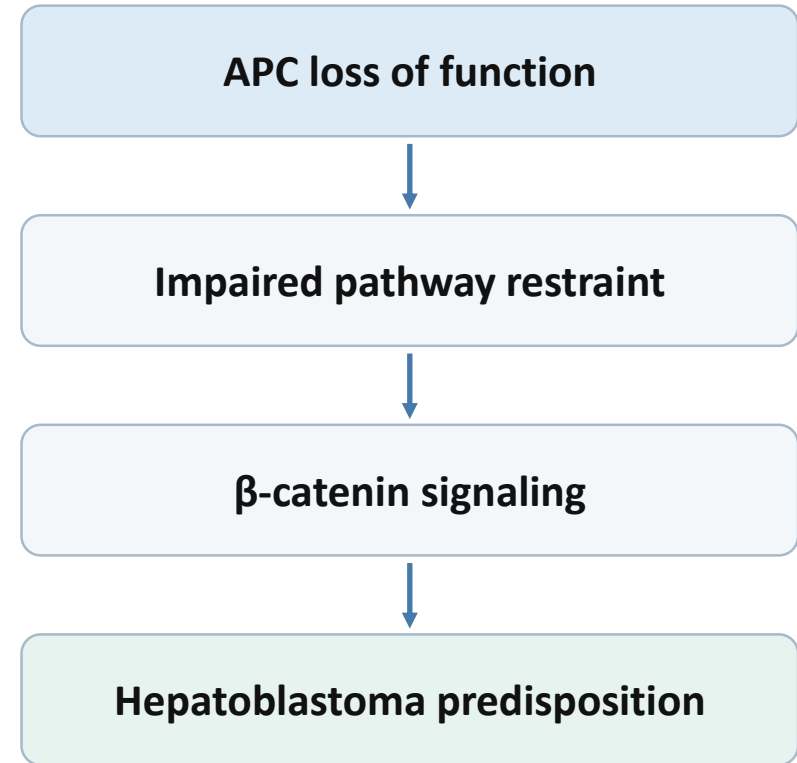
The CTNNB1 molecular route

- NCI genomics PDQ identifies activating variants/deletions involving CTNNB1 exon 3 as a major mechanism.
- Such alterations can stabilize β -catenin and favor nuclear signaling.
- Molecular findings complement, rather than replace, histopathologic interpretation.



APC: A second route to Wnt activation

- APC normally restrains β -catenin signaling.
- Germline APC loss-of-function causes familial adenomatous polyposis (FAP).
- FAP is a recognized predisposition syndrome for hepatoblastoma.



Hereditary predisposition is not universal

- Most presentations are not explained by an identified inherited syndrome.
- Risk associations warrant family and congenital-feature assessment.
- A tumor risk factor is neither diagnostic proof nor evidence of inevitability.

APC / FAP

Beckwith–Wiedemann

Other predispositions

Beckwith–Wiedemann syndrome

- Beckwith–Wiedemann syndrome is associated with congenital overgrowth and hepatoblastoma risk.
- The underlying abnormality concerns imprinting at chromosome 11p15.
- The precise alteration can vary; Syndromic risk is not uniform across molecular subgroups.

11p15 imprinting disruption

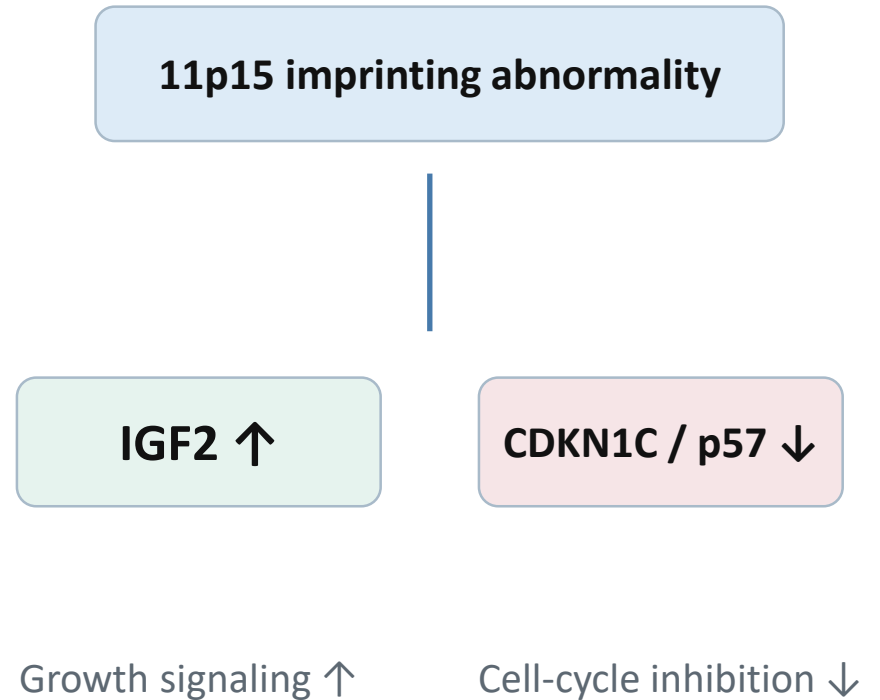


Abnormal fetal growth regulation

Predisposition ≠ diagnosis

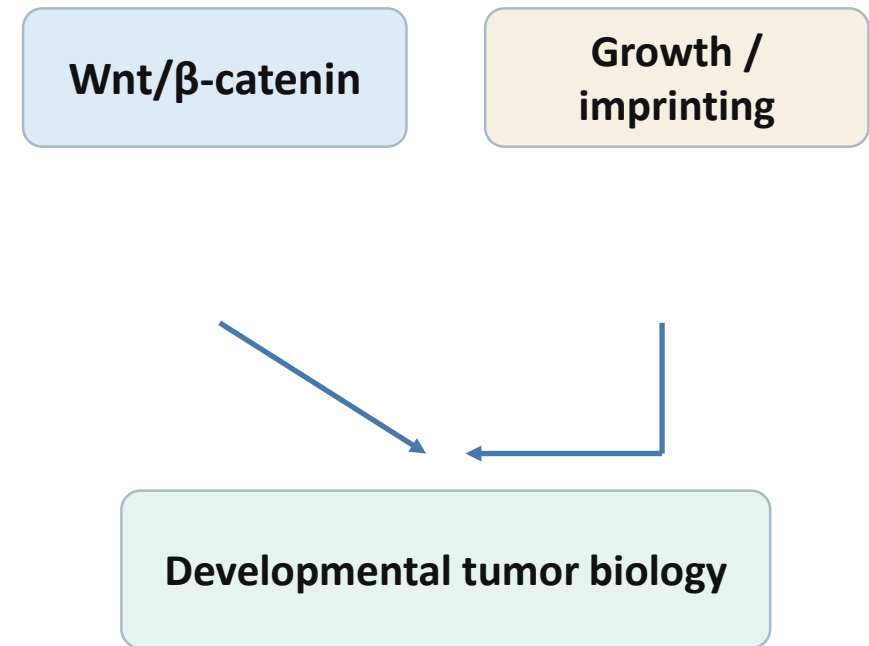
Imprinting and growth regulation

- Altered 11p15 imprinting can drive insulin-like growth factor 2 (IGF2) overexpression.
- Associated loss of CDKN1C expression removes a cell-cycle restraint.
- CDKN1C encodes the cyclin-dependent kinase inhibitor p57.



Two mechanisms, one developmental tumor

- Wnt signaling promotes transcriptional programs associated with growth and differentiation.
- Altered imprinting can increase growth-factor activity and impair cell-cycle regulation.
- These are associated routes; A single linear pathway must not be assumed for every tumor.



Other recognized risk contexts

- NCI lists prematurity with very low birth weight among the epidemiologic associations.
- Other listed conditions include isolated hemihyperplasia and additional overgrowth syndromes.
- Association strength and appropriate surveillance depend on the specific patient context.

Very low birth weight

Isolated hemihyperplasia

Selected congenital syndromes

Prematurity and causation

- Very low birth weight correlates with increased hepatoblastoma risk.
- Better survival of very premature infants may contribute to observed incidence trends.
- A specific causal factor from neonatal intensive care has not been demonstrated.

Observed association

Biologic explanation uncertain

No proved ICU exposure cause

Screening in predisposed children

- Selected predisposition syndromes prompt pediatric tumor-surveillance consideration.
- Abdominal ultrasonography and serum AFP appear in published syndrome-specific strategies.
- Age, genotype, regional guideline, and specialist assessment determine screening decisions.

Genotype + clinical assessment

Ultrasound ± AFP in protocols

Specialist surveillance plan

The two broad Robbins morphologic groups

- Epithelial hepatoblastoma contains fetal and/or embryonal hepatocyte-like cells.
- Mixed epithelial and mesenchymal tumors add divergent stromal differentiation.
- The groups describe observed tissue components, not clinical stage.

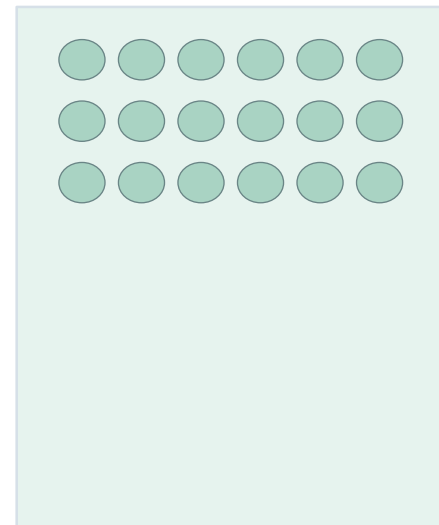
Epithelial

Mixed epithelial + mesenchymal

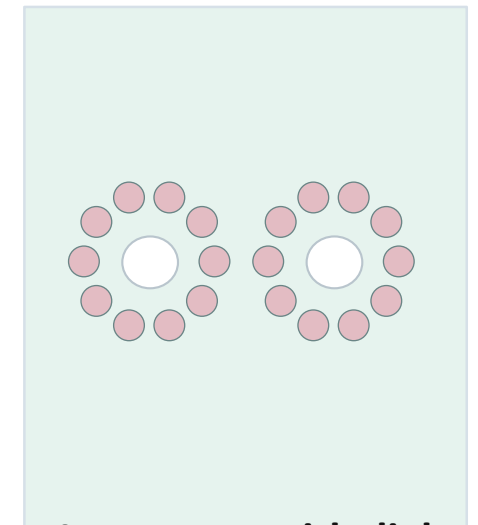
Epithelial hepatoblastoma

- Small polygonal fetal cells and smaller embryonal cells may coexist.
- Cellular architecture includes trabeculae, acini, tubules, or papillary formations.
- The relationship to normal hepatic developmental stages is approximate.

Original morphology schematic — not a photomicrograph



Hepatic-like plates



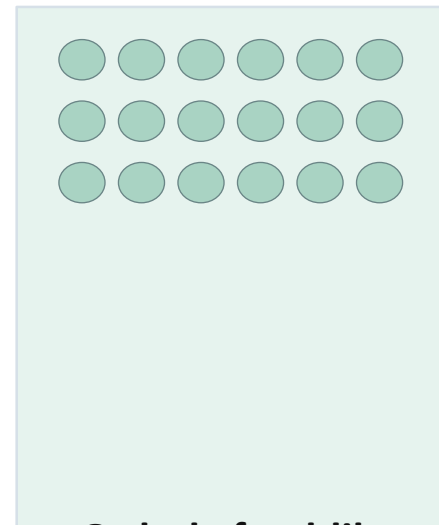
Immature epithelial tubules

Simplified architecture only; No stain or scale is represented

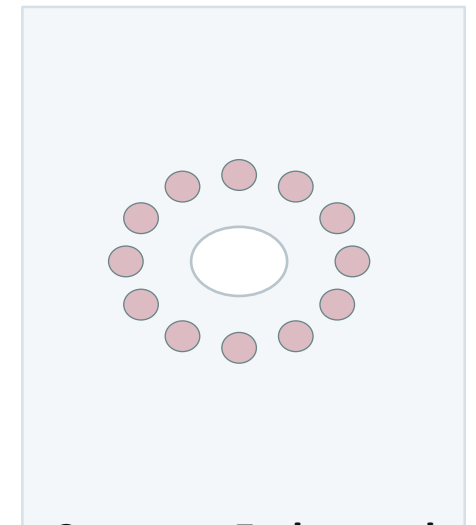
Fetal-pattern differentiation

- A more mature epithelial component resembles fetal hepatocytes.
- Relatively orderly hepatocytic plates may be present.
- The term “fetal” is a histologic descriptor, not an indication that the lesion is benign.

Original morphology schematic — not a photomicrograph



**Orderly fetal-like
plates**



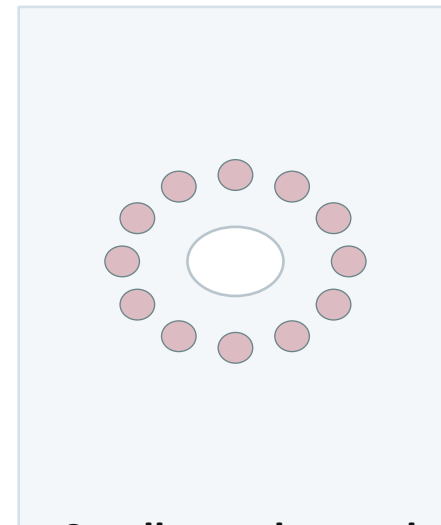
**Contrast: Embryonal
forms**

Simplified architecture only; No stain or scale is represented

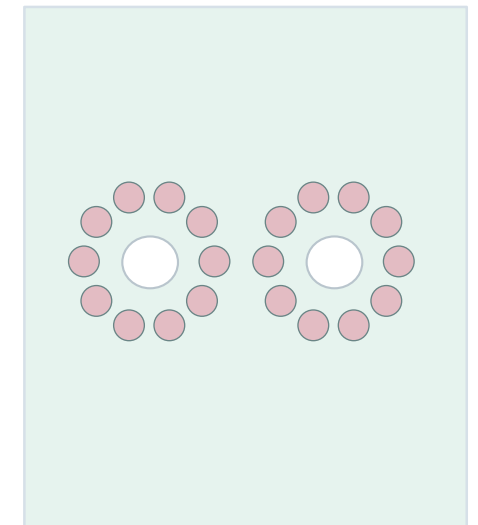
Embryonal-pattern differentiation

- Embryonal cells are smaller and less differentiated than fetal cells.
- Tubular and acinar structures may be prominent in immature epithelial areas.
- Mixed fetal–embryonal morphology is common in clinically encountered tumors.

Original morphology schematic — not a photomicrograph



**Smaller embryonal
cells**



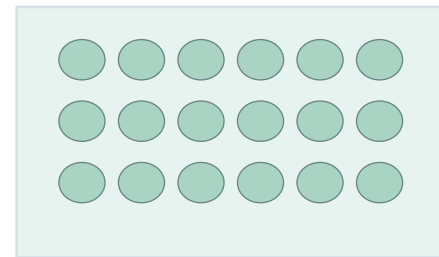
Tubular organization

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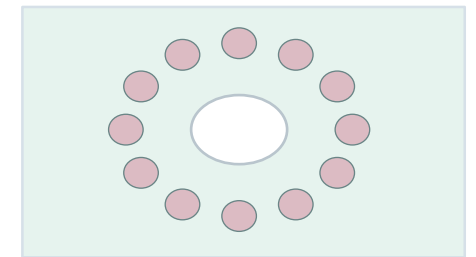
Trabeculae, acini, tubules, papillae

- Each term denotes an architectural configuration of the neoplastic epithelium.
- A single neoplasm may display several patterns in different areas.
- Architecture must be assessed with nuclear and cytoplasmic features.

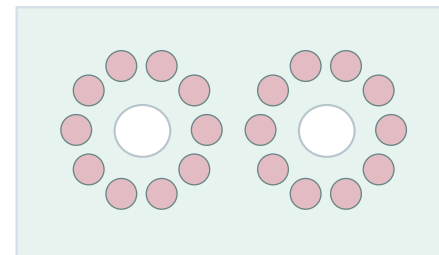
Original morphology schematic — not a photomicrograph



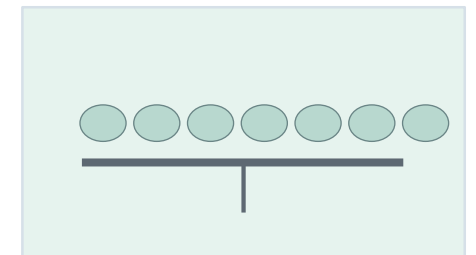
Trabeculae



Acini



Tubules



Papillae

Simplified architecture only; No stain or scale is represented

Mixed epithelial–mesenchymal tumors

- An epithelial hepatoblastoma component coexists with mesenchymal differentiation.
- The mesenchymal element may be primitive or demonstrate tissue formation.
- A small biopsy can underrepresent heterogeneity across the mass.

Hepatocytic epithelium

Primitive stroma

Heterologous tissues

Mesenchymal differentiation

- Robbins specifically describes primitive mesenchyme, osteoid, cartilage, and striated muscle.
- The mesenchymal component broadens the histologic appearance.
- Unexpected heterologous tissue should trigger careful tumor-wide sampling.

Primitive mesenchyme

Osteoid

Cartilage

Striated muscle

Why histologic sampling matters

- A focal component may be absent from limited biopsy material.
- Sampling should account for regions of distinct gross texture and microscopic pattern.
- Post-treatment specimens may show therapy-related changes that complicate subtype assignment.

Conceptual pathology model

Modern subtype language adds resolution

- Contemporary pediatric tumor classification recognizes clinically relevant epithelial patterns.
- Important categories include well-differentiated fetal, mixed fetal/embryonal, and small-cell patterns.
- Robbins' two broad groups remain useful for introductory morphology.

Well-differentiated fetal

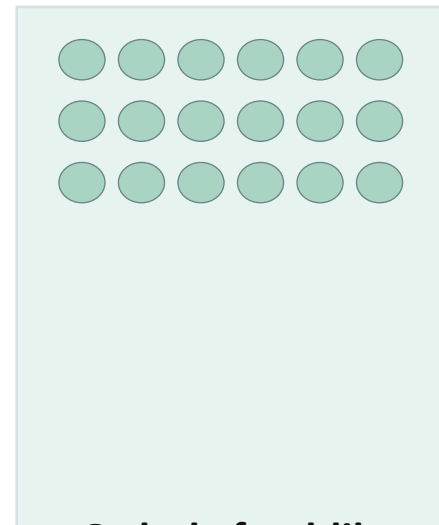
Mixed fetal / embryonal

Small-cell component

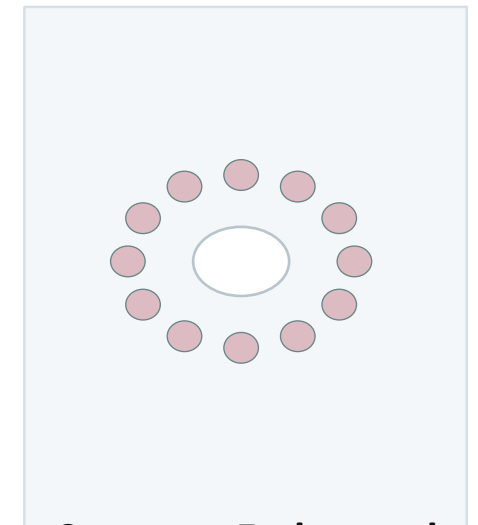
Well-differentiated fetal histology

- This pattern is associated with favorable outcomes in specific, completely resected cohorts.
- Use the complete pathologic criteria and treatment context, not “fetal” appearance alone.
- Do not generalize outcomes from selected resected cases to all hepatoblastomas.

Original morphology schematic — not a photomicrograph



**Orderly fetal-like
plates**



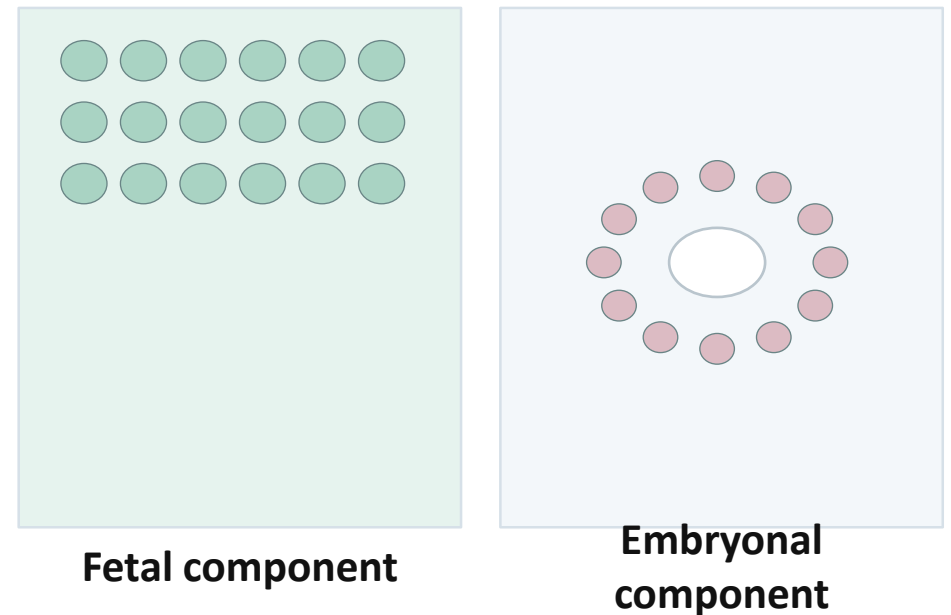
**Contrast: Embryonal
forms**

Simplified architecture only; No stain or scale is represented

Mixed fetal and embryonal histology

- Both epithelial differentiation states may coexist in one tumor.
- The relative distribution may vary between sampled blocks.
- A designation based on limited tissue should communicate uncertainty when appropriate.

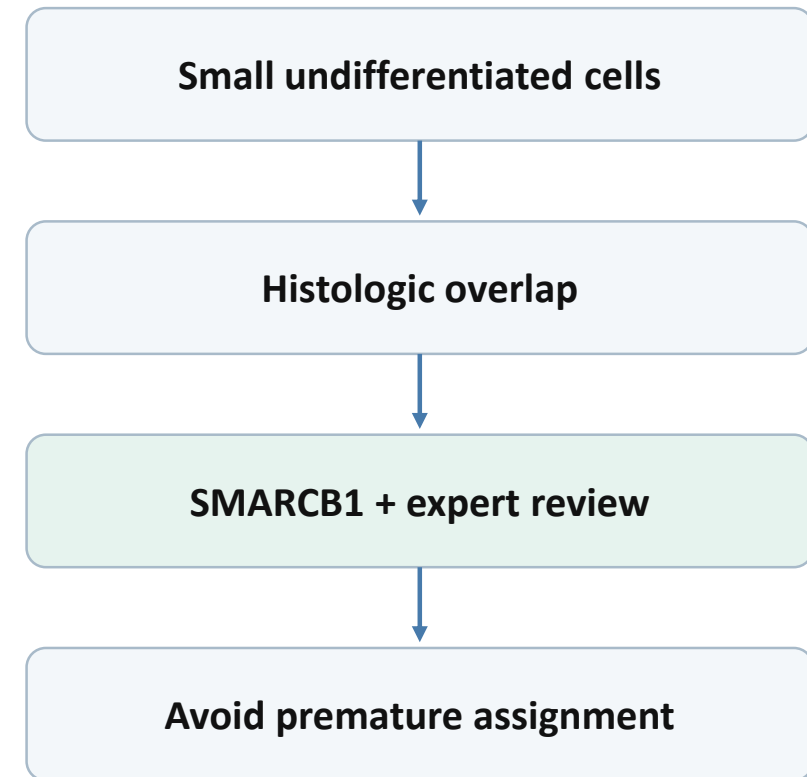
Original morphology schematic — not a photomicrograph



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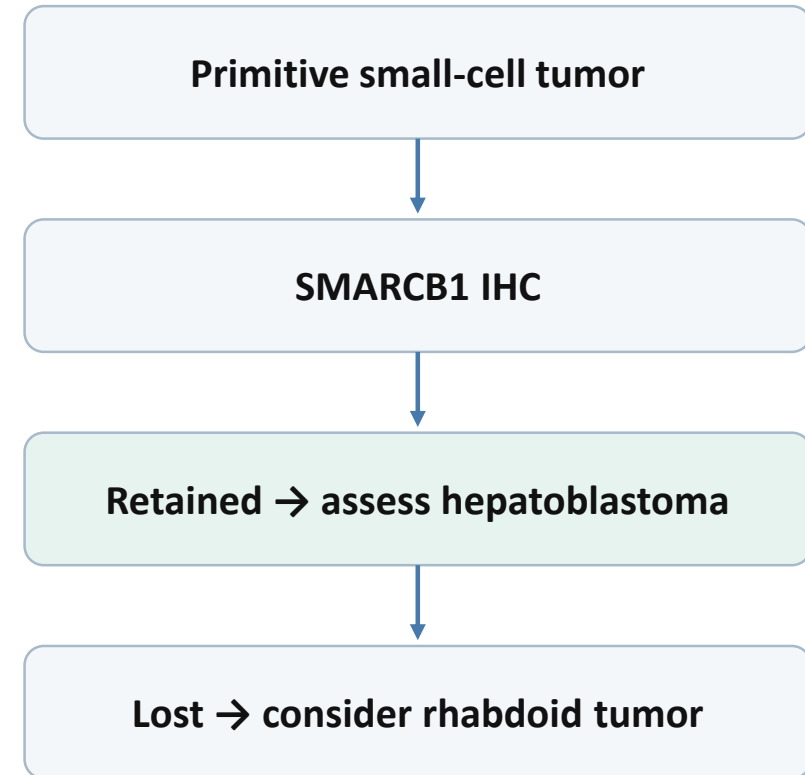
Small-cell components need scrutiny

- Primitive small cells can resemble other pediatric small-round-cell neoplasms.
- Current diagnostic evaluation particularly considers malignant rhabdoid tumor of the liver.
- Morphology alone can be insufficient for this distinction.



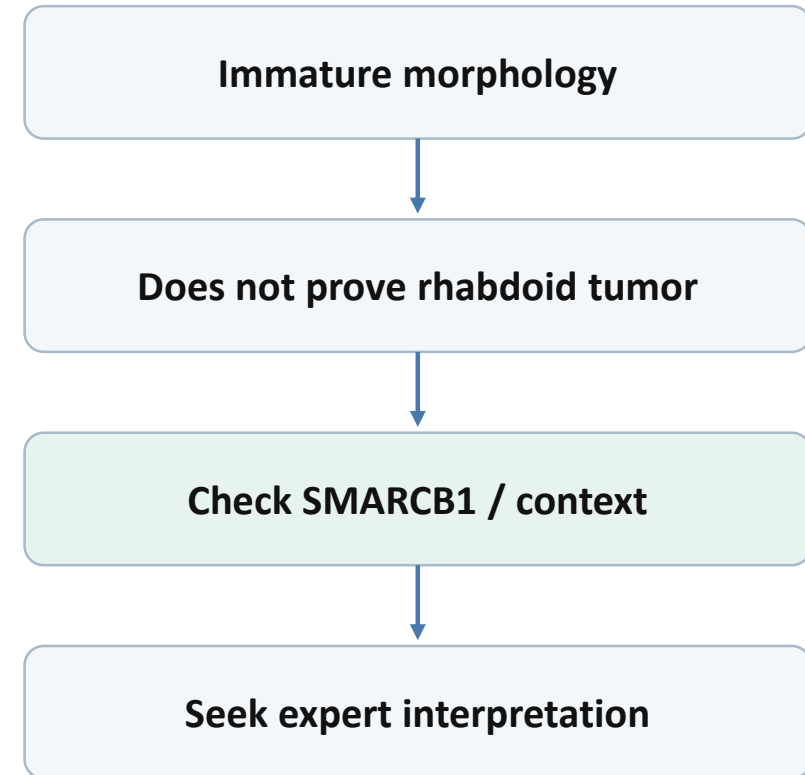
SMARCB1 in the small-cell differential

- Loss of SMARCB1 (INI1) staining is characteristic of malignant rhabdoid tumor.
- Small-cell undifferentiated hepatoblastoma may retain SMARCB1 expression.
- NCI recommends testing small-cell undifferentiated cases to inform classification and care.



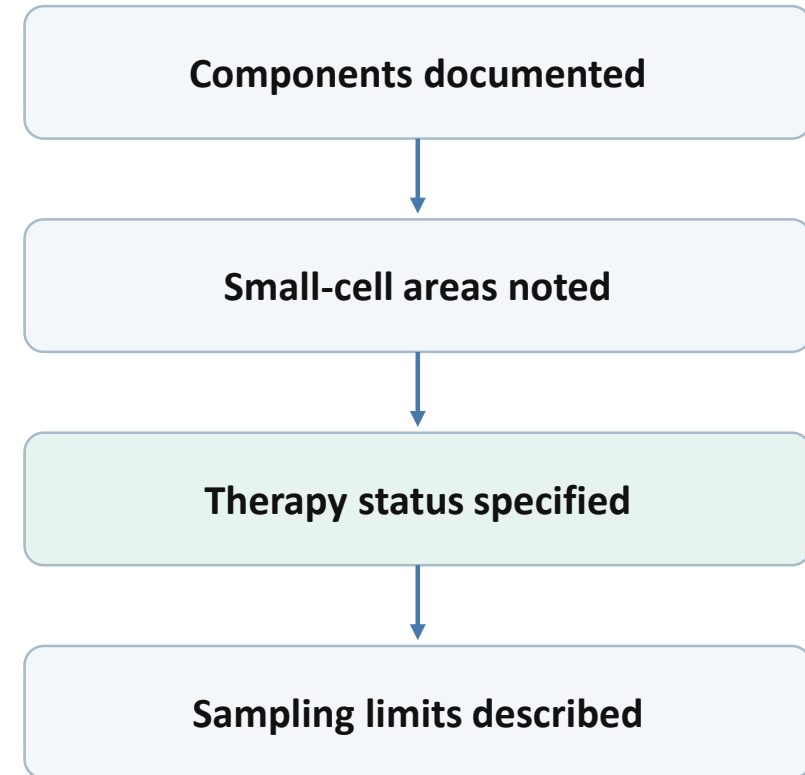
Avoid the “primitive = rhabdoid” shortcut

- Not every small-cell area is a rhabdoid tumor.
- Integrate cytomorphology, other epithelial components, and SMARCB1 immunostaining.
- Ambiguous lesions warrant expert pediatric pathology review.



How to describe a specimen

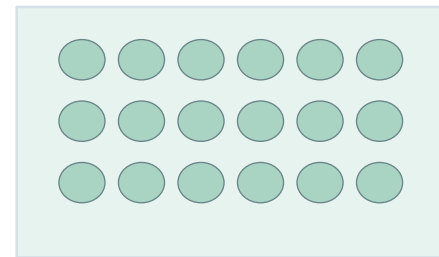
- Specify epithelial patterns and any mesenchymal differentiation actually identified.
- Identify unusual primitive, small-cell, or rhabdoid-appearing areas.
- Record sampling limitations and prior chemotherapy when present.



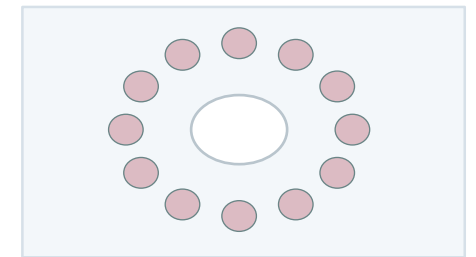
The microscopic architecture is heterogeneous

- Cell size, maturation, and tissue pattern may differ within the same mass.
- Classification should not rely on a single picturesque focus.
- The combined assessment is more defensible than an isolated marker result.

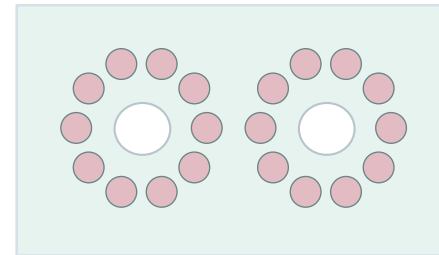
Original morphology schematic — not a photomicrograph



Fetal-like



Embryonal-like



Additional epithelium

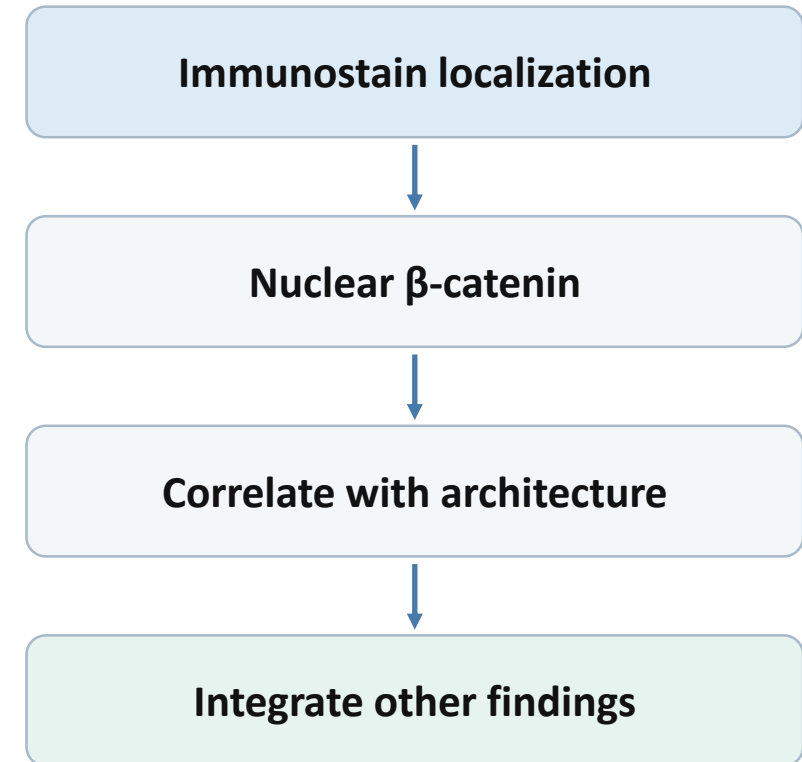


Mesenchymal stroma

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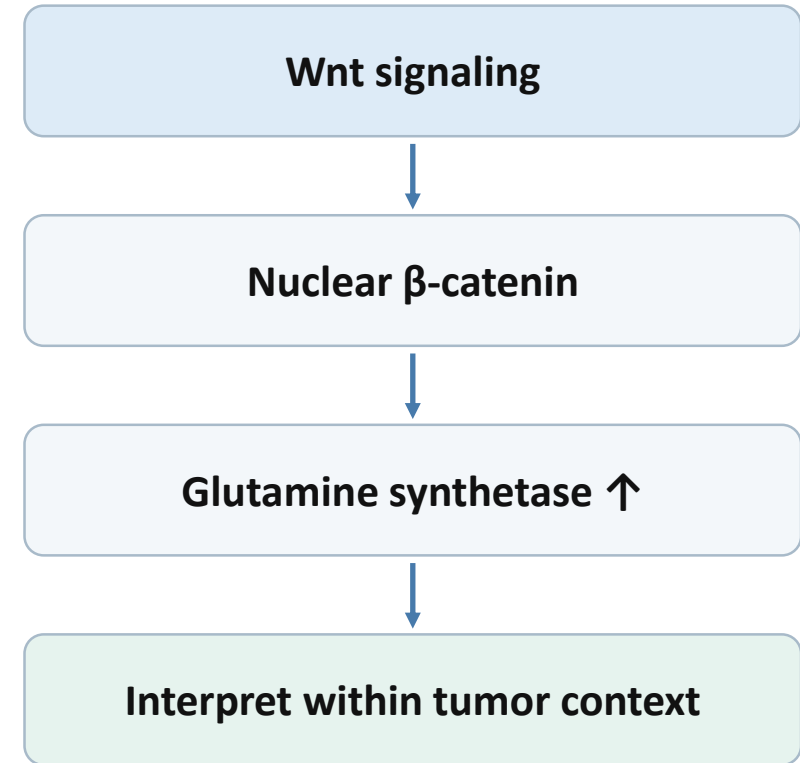
β -catenin: Interpret the compartment

- Nuclear localization supports Wnt-pathway activation.
- A stain's localization pattern is more informative than an unlabeled "positive".
- Staining must be assessed against internal controls and histologic context.



Glutamine synthetase as pathway readout

- Increased glutamine synthetase expression as a Wnt target-gene consequence.
- The finding supports pathway activity but is not exclusive proof of hepatoblastoma.
- Integrate with age, morphology, other markers, and imaging.



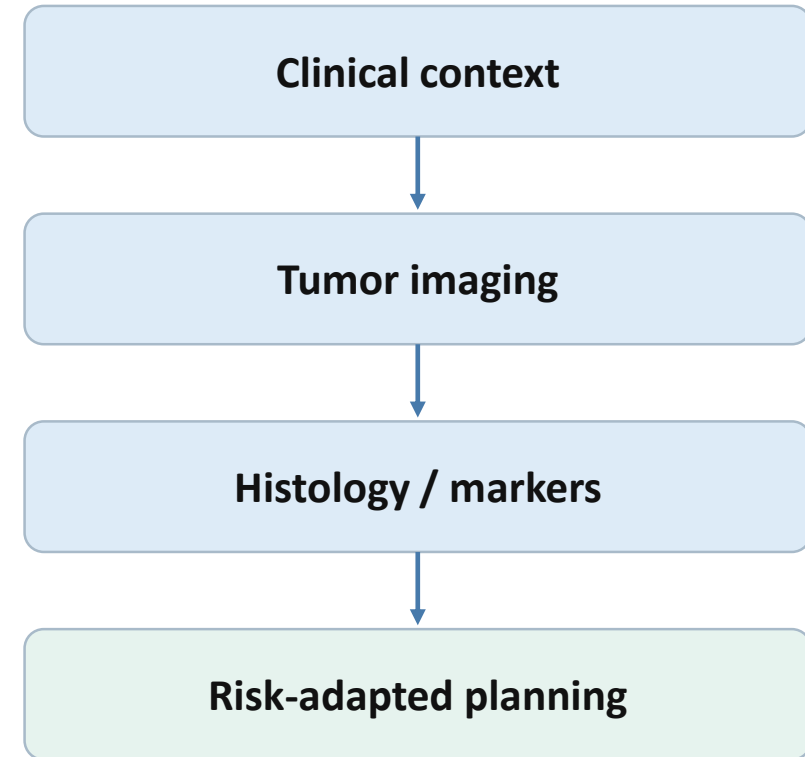
Molecular findings and their roles

- CTNNB1 or APC alterations explain a common oncogenic signaling theme.
- Additional molecular signatures are under study for biological stratification.
- Do not describe an exploratory molecular association as an established clinical decision rule.

Conceptual pathology model

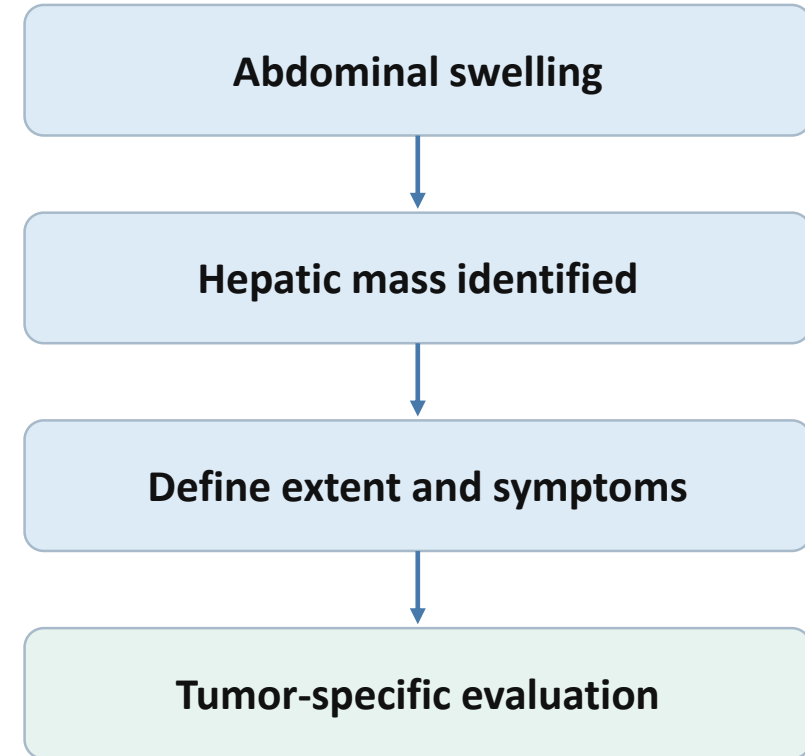
Diagnosis is a synthesis

- Clinical age and liver-mass presentation establish the diagnostic setting.
- Imaging defines anatomy; Pathology establishes tumor identity when tissue is obtained.
- Tumor markers and selected ancillary tests contribute separate information.



Presentation: A growing abdomen

- Abdominal swelling or mass is a typical initial finding.
- The child may otherwise appear well at presentation.
- A largely asymptomatic presentation does not imply localized disease.



Liver-related symptoms may occur

- Jaundice and pruritus are reported in a subset of patients.
- These findings reflect disturbance of hepatic or biliary function, not a unique tumor signature.
- Their absence cannot exclude hepatoblastoma.

The lung is an important metastatic site

- Approximately 20% have lung metastases by diagnosis.
- Distant disease changes risk assessment and management.
- Thoracic evaluation therefore matters in the initial staging work-up.

Serum AFP is useful but not specific

- Alpha-fetoprotein (AFP) is elevated in most children with hepatoblastoma.
- It is neither pathognomonic nor uniformly elevated.
- Benign conditions, other tumors, and normal infancy can affect interpretation.

AFP often elevated

Not cancer-specific

Not universally elevated

Why infant AFP requires care

- Serum AFP is physiologically high in neonates and declines with age.
- Use an age-adjusted reference range rather than an adult cutoff.
- An isolated AFP result never determines tumor histology or stage.

High neonatal baseline

Physiologic decline

Age-adjusted comparison

AFP can monitor response

- Serial values often parallel disease burden during treatment.
- Failure of a meaningful decline raises concern for inadequate response.
- Interpret kinetics together with imaging, treatment timing, and age.

Baseline

Serial AFP + imaging

Assess response together

Imaging answers an anatomic question

- Ultrasound can identify a hepatic mass and guide the initial work-up.
- Cross-sectional imaging delineates tumor distribution and major vascular relations.
- Imaging also informs whether complete resection appears feasible.

Ultrasound: Identify mass

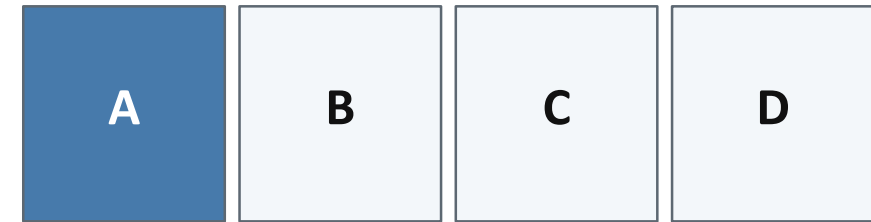
CT / MRI: Define anatomy

Chest evaluation: Lung spread

PRETEXT: Pretreatment hepatic extent

- PRETEXT is an imaging-based stratification of tumor extent before therapy.
- It uses four functional liver sections derived from segmental liver anatomy.
- The system assesses uninvolved contiguous sections and additional risk annotations.

Four-section conceptual representation

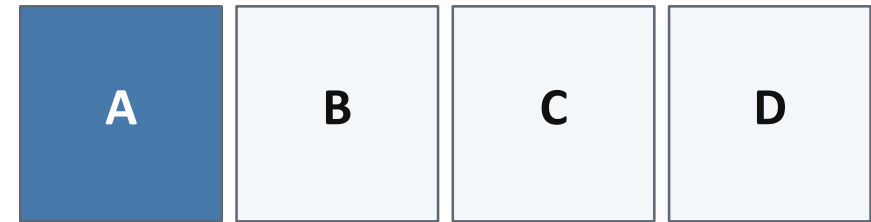


Schematic sections—not anatomical boundaries

PRETEXT I through IV

- Group I: Three adjoining hepatic sections remain tumor free.
- Group II: Two adjoining sections remain tumor free.
- Group III: One hepatic section remains tumor free.
- Group IV: No hepatic section remains tumor free.

Four-section conceptual representation



Schematic sections—not anatomical boundaries

PRETEXT vascular annotations

- V denotes major hepatic venous/inferior vena cava involvement.
- P denotes portal venous involvement.
- These features may constrain safe resection even when tumor volume appears limited.

V: Hepatic veins / IVC

P: Right + left portal veins

Major vascular relationships

Other PRETEXT annotations

- E: Contiguous extrahepatic extension; F: Multifocal disease.
- R: Tumor rupture; M: Distant metastases, commonly involving lungs.
- These are separate descriptors and must not be inferred from PRETEXT I–IV alone.

E: Extrahepatic extension

F: Multifocal • R: Rupture

M: Distant metastasis

PRETEXT and POSTTEXT are distinct

- PRETEXT records anatomic extent before treatment.
- POSTTEXT reassesses extent following chemotherapy.
- Both should use documented imaging findings rather than imagined tumor shrinkage.

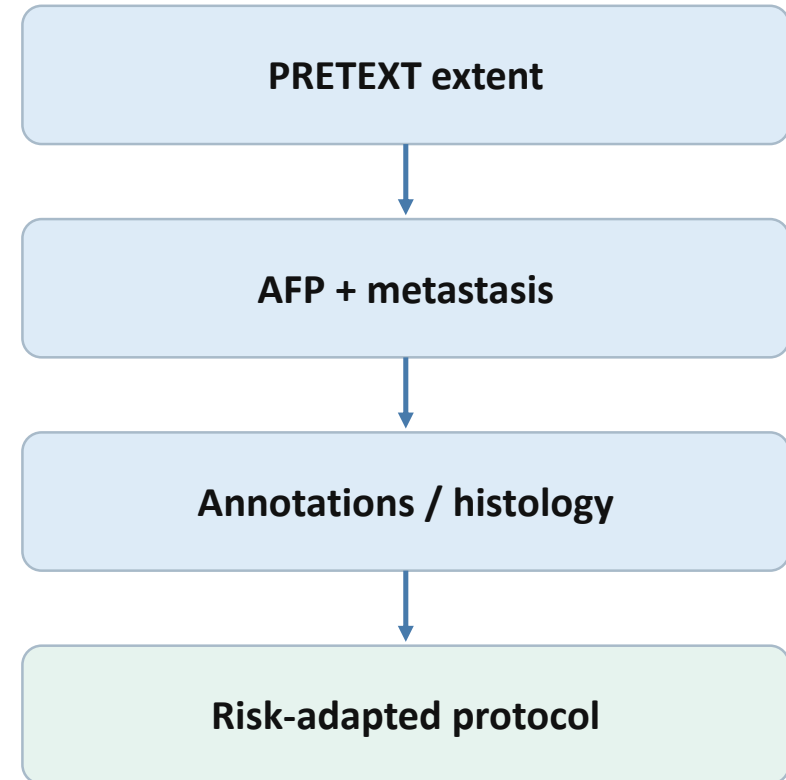
PRETEXT: Before therapy



POSTTEXT: After therapy

Risk stratification is multidimensional

- Important variables include PRETEXT category, metastatic disease, and serum AFP.
- Vascular involvement, tumor rupture, age, and histology provide further context.
- Contemporary risk group definitions are protocol-dependent.



Low AFP can be an adverse feature

- Unexpectedly low AFP at diagnosis is uncommon in hepatoblastoma.
- NCI links low AFP with adverse outcomes and certain primitive tumors.
- The exact threshold and interpretation depend on age and study protocol.

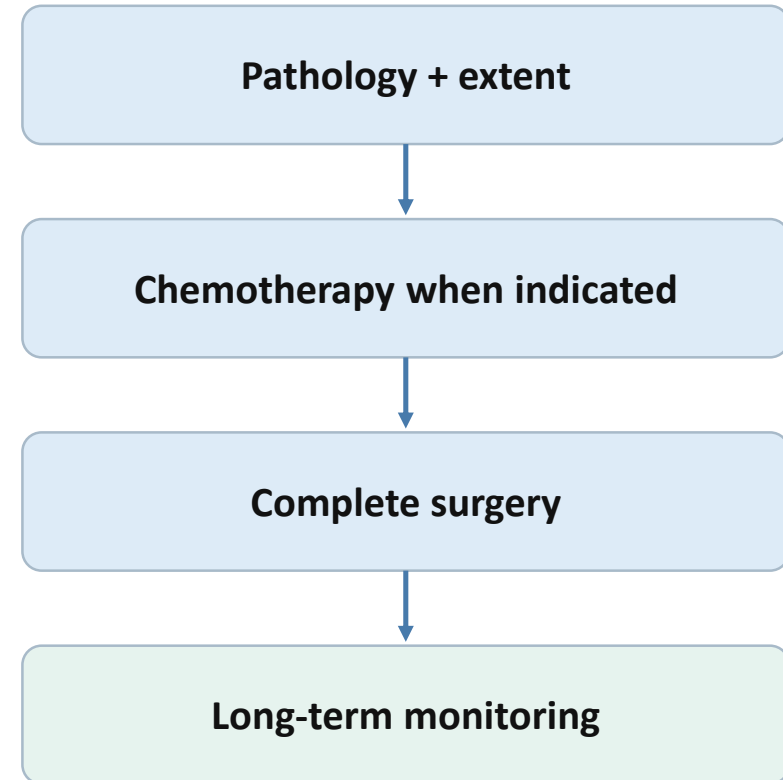
Unexpected low AFP

Reassess morphology

Check protocol risk criteria

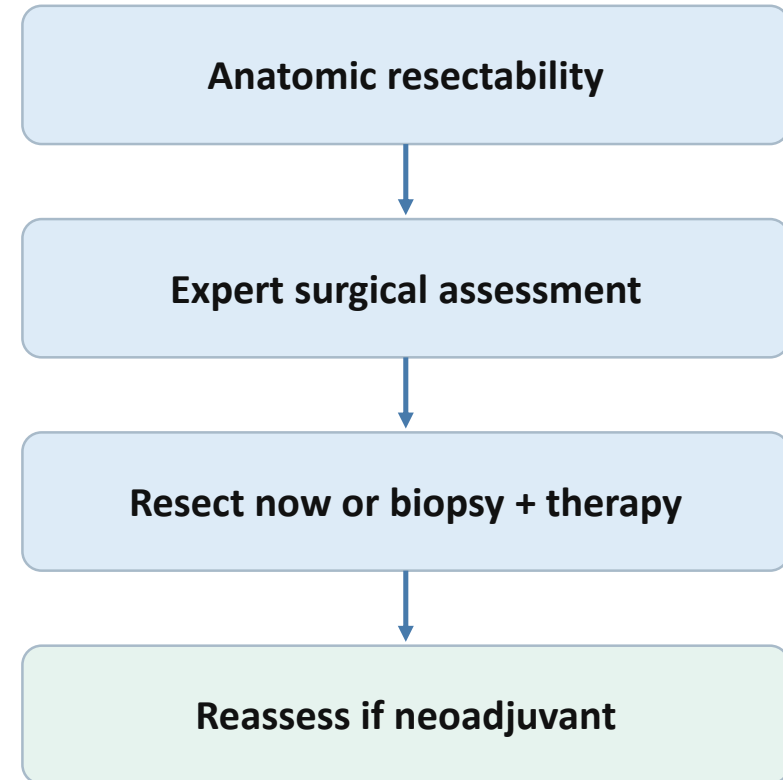
Surgery and chemotherapy are complementary

- Surgical resection plus chemotherapy as key treatments.
- Complete macroscopic tumor removal is central to cure.
- Treatment sequencing depends on resectability and disease extent.



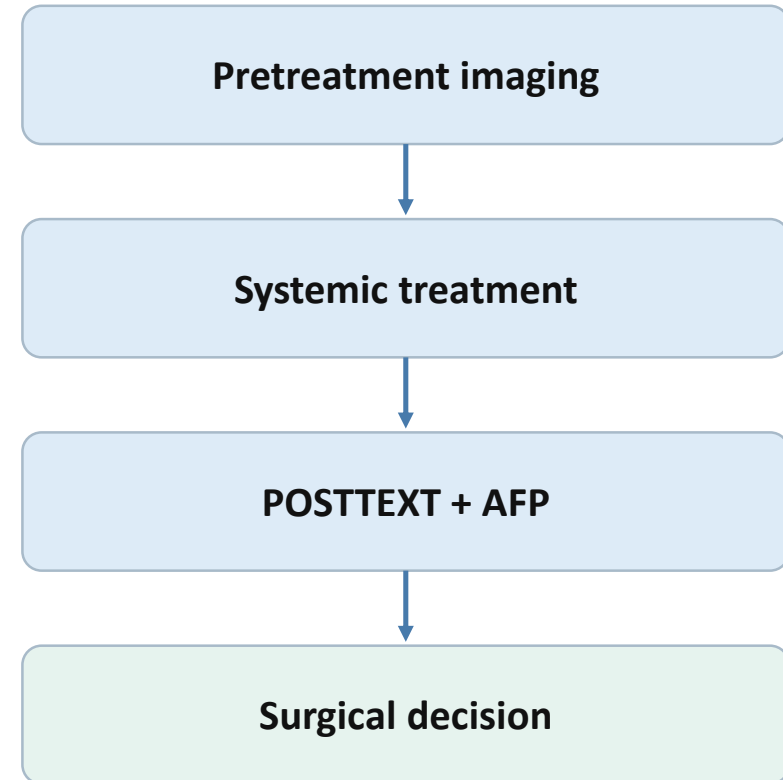
Primary resection is selective

- Some limited, safely resectable tumors undergo upfront surgery.
- Other patients require diagnostic biopsy and systemic therapy before resection.
- Decision-making belongs to an experienced pediatric liver tumor team.



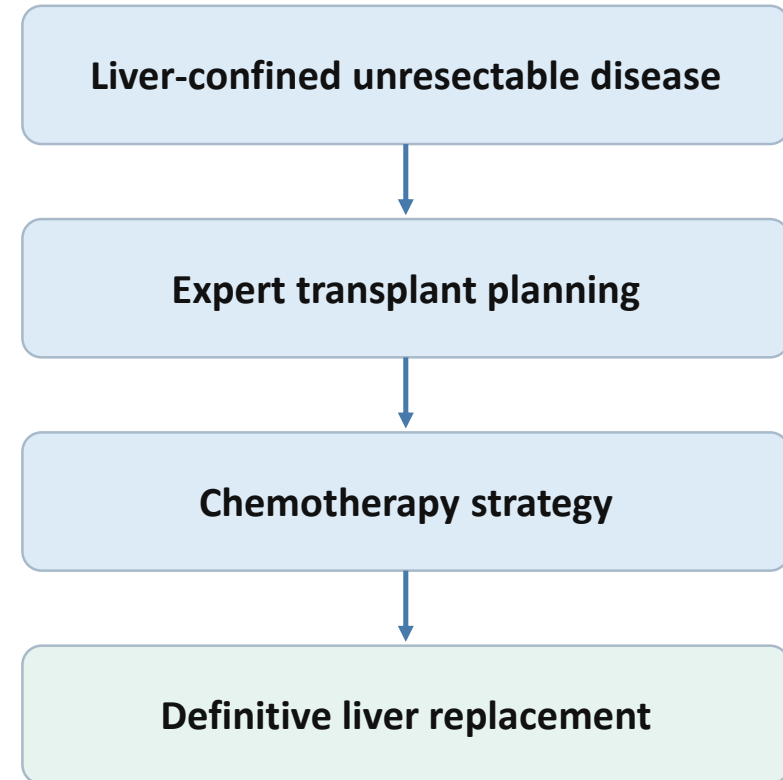
Neoadjuvant chemotherapy may convert resectability

- Chemotherapy can reduce mass and improve resectability.
- Imaging and AFP response contribute complementary reassessment.
- Pathologic classification of post-treatment tissue must account for therapy-related change.



Transplantation in selected unresectable disease

- Liver transplantation is an option for tumors that remain unresectable after chemotherapy.
- Major-vessel involvement and distribution affect operative planning.
- Advanced cases warrant early specialist evaluation rather than late salvage referral.



Outcome figures require context

- Robbins gives approximately 80% overall 5-year survival.
- NCI PDQ separately reports approximately 70% in its overall summary.
- These estimates come from different summaries; Do not interpret the difference as a direct trend.

Illustrative source-summary comparison

Robbins 11e: $\approx$ 80%

NCI PDQ: $\approx$ 70%

Different summaries, not a time series

Clinicopathologic scenario: A toddler

- A 20-month-old develops progressive painless abdominal swelling.
- Cross-sectional imaging shows a solid hepatic mass; The patient is otherwise well.
- What diagnoses, markers, and staging questions should be prioritized?

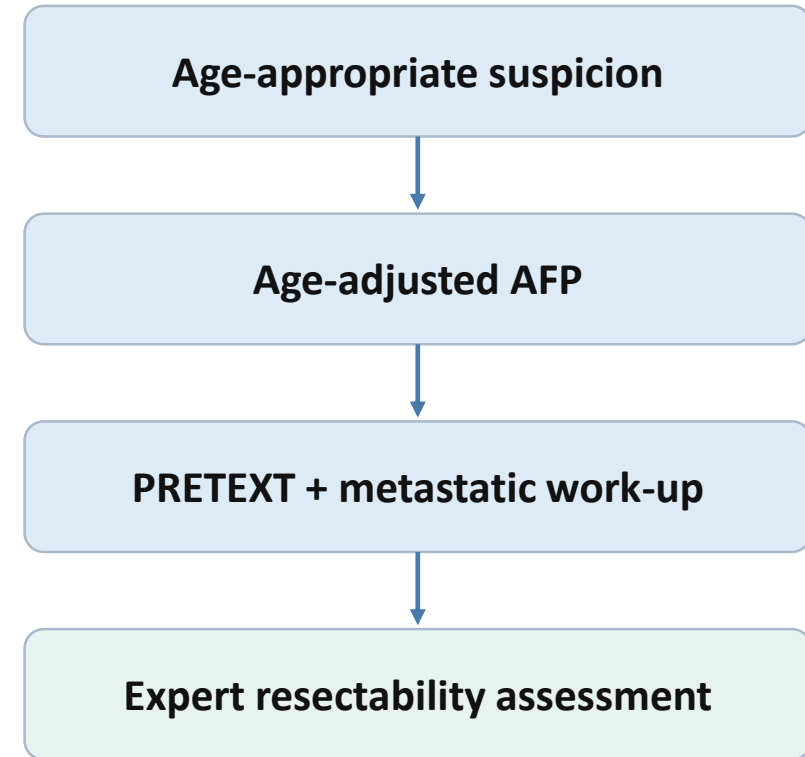
Diagnostic decision

Clinical mass in toddler

Which tests define identity and extent?

Interpretation of the toddler scenario

- Hepatoblastoma is a high-priority diagnosis in the age-appropriate setting.
- AFP assessment requires age-aware interpretation; Imaging defines PRETEXT and annotations.
- Histologic sampling or upfront resection follows a specialist resectability assessment.



Clinicopathologic scenario: Primitive cells

- A liver biopsy contains an extensive undifferentiated small-cell population.
- No convincing fetal-pattern epithelium appears in the initial cores.
- Which specific ancillary test is particularly consequential?

Diagnostic decision

Small-cell liver biopsy

Which entity requires exclusion?

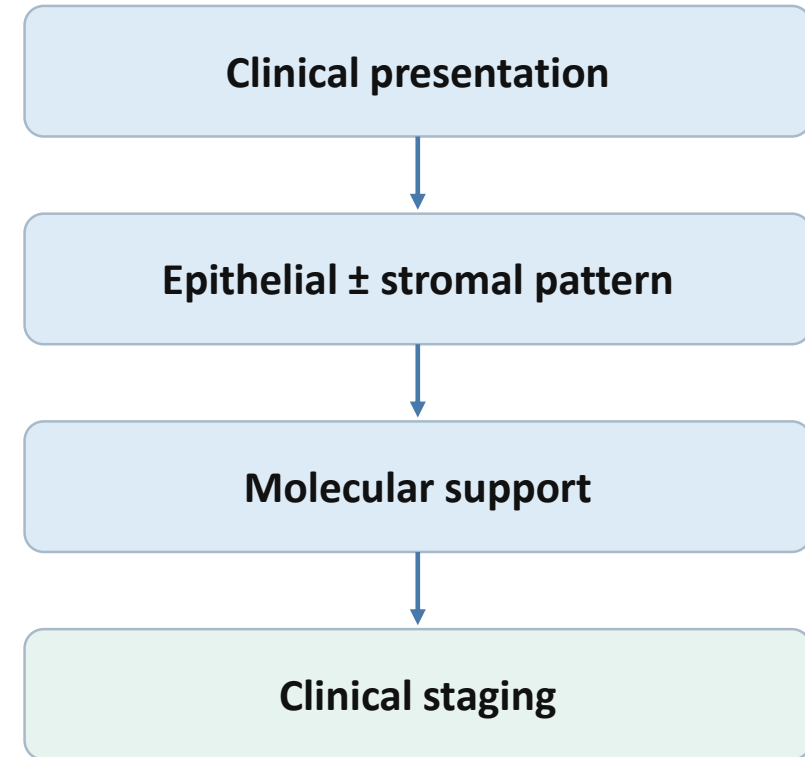
Interpretation of the primitive-cell case

- Assess SMARCB1/INI1 nuclear expression with appropriate internal controls.
- Loss raises strong concern for malignant rhabdoid tumor of the liver.
- Seek expert review and additional sampling as clinically appropriate.

Conceptual pathology model

Integrated diagnostic checkpoints

- Identify the clinical setting and embryonal/fetal hepatic morphology.
- Recognize divergent mesenchymal tissue and investigate primitive small-cell areas.
- Use Wnt markers as supporting evidence, not standalone proof.
- Communicate tumor extent and treatment-related interpretive limitations.



Key references

- Robbins, Cotran & Kumar. Pathologic Basis of Disease. 11th ed. Elsevier; 2026. Chapter 18, p 790.
- National Cancer Institute. Childhood Liver Cancer Treatment (PDQ®), Health Professional Version.
- National Cancer Institute. Childhood Cancer Genomics (PDQ®): Hepatoblastoma.
- International Pediatric Liver Tumors Consensus Classification, summarized in NCI PDQ.

Primary textbook + NCI PDQ

Slide-specific citations in speaker notes