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Surgical indications for hepatocellular adenoma: Diagnostic uncertainty and molecular risk stratification

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SUMMARY: Surgical management of hepatocellular adenoma (HCA) is still guided principally by patient sex, tumor size, and growth, although molecular classification has revealed important biological differences. Retrospective studies have also exposed diagnostic discordance, complicating the interpretation of historical estimates of malignant risk. Molecular subtypes differ in their associations with hemorrhage and malignant transformation, but evidence that subtype-guided management improves outcomes remains limited. Proposals to observe selected men with small lesions have reopened the debate over routine resection. We examine how diagnostic confidence, molecular heterogeneity, and the limitations of available outcome data should inform surgical decisions. Any change in practice should be supported by validated estimates of clinical risk rather than molecular findings alone.

Keywords: hepatobiliary surgery, malignant transformation, hemorrhage risk, molecular pathology, clinical surveillance

1. Introduction

Hepatocellular adenoma (HCA) is a benign hepatocellular neoplasm that can cause hemorrhage or undergo malignant transformation. Molecular studies have clarified its heterogeneity, and yet management remains anchored in clinical risk factors. The European Association for the Study of the Liver (EASL) guidelines and the 2024 American College of Gastroenterology (ACG) guidelines recommend resection or definitive treatment in men regardless of tumor size. In women, lesion size, growth, and response to withdrawal of hormonal exposure or other risk-factor modification guide management; the ACG also emphasizes resection for β-catenin–mutated lesions irrespective of size (*1,2*).

These recommendations offer a workable clinical framework, but improved imaging and molecular characterization have made the limits of historical risk estimates more apparent.

2. Diagnostic uncertainty and the interpretation of historical risk

The recommendation for routine resection in men was influenced by Farges *et al*., who reported malignant transformation in 47% of men versus 4% of women in a tertiary-center series of 218 patients with histologically documented HCA (*3*). Those proportions describe a selected clinical cohort, not the prospective lifetime risk of malignancy in an unselected population.

More recent studies have demonstrated that diagnostic classification itself may be a major source of uncertainty. In a Dutch nationwide retrospective study of 66 men with an initial pathological diagnosis or differential diagnosis of HCA, an expert review supported by molecular analysis resulted in diagnostic reclassification in 33 patients (50%) (*4*). Importantly, the study also found clinically relevant differences in outcomes among patients ultimately classified as having HCA, uncertain HCA/hepatocellular carcinoma (HCC), or HCC.

In another nationwide study involving 222 patients undergoing resection for suspected HCA, Haring *et al*. reported postoperative diagnostic changes in 96 patients (43%). Male sex, smaller tumor size, and the absence of hepatobiliary contrast-enhanced magnetic resonance imaging were independently associated with diagnostic discordance (*5*).

The two Dutch studies used different definitions of diagnostic change and included selected patients. Reclassification should not be mistaken for malignant transformation during follow-up. Rather, these findings show how uncertainty at diagnosis may distort

Table 1. Key evidence informing the surgical indications for and risk stratification of hepatocellular adenoma

Study	Study design / population	Main findings	Implications and limitations
EASL (2016) and ACG (2024) (*1,2*)	Clinical practice guidelines	Men: resection or definitive treatment irrespective of size; women: observation after risk-factor modification for selected lesions, with the 5-cm threshold and β-catenin status guiding treatment	Current standard framework; molecularly individualized decisions remain not fully validated
Farges *et al.* (2011) (*3*)	Retrospective tertiary-center study; 218 histologically confirmed cases	Malignant transformation reported in 47% of men and 4% of women in this selected cohort	Influential historical evidence; selected population limits generalization
van Rosmalen *et al.* (2021) (*4*)	Nationwide retrospective pathological review; 66 men	Diagnosis reclassified in 33 patients (50%)	Demonstrates diagnostic uncertainty; selected pathology-registry population
Haring *et al.* (2023) (*5*)	Nationwide surgical cohort; 222 patients	Postoperative diagnostic change in 96 patients (43%)	Demonstrates discordance in a surgical cohort; cannot estimate population-wide error or malignant transformation rates
Nault *et al.* (2017) (*6*)	Multicenter molecular analysis; 533 HCAs from 411 patients	Molecular subtypes had different associations with bleeding and malignant transformation	Foundational biological evidence; not a prospectively validated treatment algorithm
Sempoux and Park (2026) (*7*)	Molecular pathology review	Updated classification integrates morphology and molecular characteristics	Improved diagnostic framework; direct treatment implications require outcome validation
Bioulac-Sage *et al.* (2026) (*8*)	Pathological series; 17 patients with resected sonic hedgehog HCA	Hemorrhage and microscopic vascular injury were also observed in small lesions	Supports size-independent biological features; does not quantify prospective clinical bleeding risk
Bioulac-Sage *et al.* (2026) (*9*)	Selected multicenter pathological series; 26 patients	Distinct HCA molecular subtypes coexisted within individual patients	Highlights inter-tumor heterogeneity; prevalence cannot be inferred from this selected series
Belledent *et al.* (2026) (*10*)	Narrative review focused on men	Proposes consideration of surveillance for selected men with lower-risk lesions	Emerging proposal, not a new guideline or prospectively proven standard

This table is a critical narrative synthesis of selected studies rather than a systematic review or quantitative meta-analysis. All numerical results refer to their respective study populations. *Abbreviations*: ACG, American College of Gastroenterology; EASL, European Association for the Study of the Liver; HCA, hepatocellular adenoma; HCC, hepatocellular carcinoma.

estimates of the risk attributed to HCA.

Before changing management on the assumption that a lesion is benign, clinicians must therefore consider how confidently HCA has been distinguished from well-differentiated HCC and other hepatocellular lesions.

3. Molecular heterogeneity and distinct clinical risks

In a multicenter analysis of 533 HCAs from 411 patients, Nault *et al*. linked molecular subtypes to patient characteristics, bleeding, and malignant transformation (*6*). Sempoux and Park subsequently described five principal molecular subtypes within the updated WHO framework, integrating morphology, immunohistochemistry, and molecular alterations (*7*).

The clinical consequences differ by subtype. Strongly activating CTNNB1 exon 3 alterations are associated with greater malignant potential, whereas sonic hedgehog–activated HCA and some CTNNB1 exon 7/8–mutated lesions have been linked to bleeding (*6,7*). Hemorrhage and malignant transformation should therefore be assessed as distinct outcomes rather than grouped under an undifferentiated high-risk label.

In a pathological series of 17 patients with sonic hedgehog–activated HCA, Bioulac-Sage *et al*. identified macroscopic hemorrhage and microscopic vascular injury in both small and large nodules (*8*). These findings suggest that hemorrhage-associated tissue changes are not restricted to tumors larger than 5 cm; however, the series does not measure prospective rates of clinically significant bleeding in small lesions.

Multiplicity adds another difficulty. In a selected series of 26 patients with inter-tumor heterogeneity, Bioulac-Sage *et al*. identified different HCA subtypes in the same liver, including subtypes associated with malignant progression or hemorrhage (*9*). Molecular analysis of one nodule may therefore fail to characterize the other lesions.

Molecular classification can inform assessment but has not been prospectively validated as a replacement for size, growth, imaging findings, or clinical context. Sampling error and overlap with well-differentiated HCC also limit the reassurance that immunohistochemistry or targeted sequencing can provide.

4. Reconsidering surgical indications without prematurely changing practice

Belledent *et al*. recently questioned universal resection in men and discussed surveillance for selected, carefully characterized low-risk lesions (*10*). Avoiding surgery in such patients could be beneficial, but the proposed selection criteria and surveillance approach have not been prospectively validated.

A biopsy without a detected high-risk mutation cannot exclude an unsampled malignant focus, and long-term outcomes of molecularly characterized, unresected HCA in men remain uncertain. Selective surveillance should thus be presented as a proposal for further evaluation, not as an alternative already endorsed by current guidelines. Table 1 distinguishes established recommendations from observational evidence and recent proposals.

5. Priorities for evidence-based risk-adapted management

Prospective multicenter registries should enroll consecutive patients with newly detected HCA, not only those referred for resection. Standardized multiphasic MRI, an expert pathological review when tissue is available, and clinically justified molecular testing would allow diagnostic confidence to be recorded alongside management decisions.

Clinically significant hemorrhage and malignant transformation should be prespecified as separate outcomes. Analyses should address size, growth, molecular subtype, hormonal and metabolic exposures, background liver disease, lesion multiplicity, treatment morbidity, and patient preferences. Comparisons of surveillance with intervention will also need to address confounding by indication and changes in diagnosis over time.

The relevant question is whether molecular data improve risk prediction and treatment decisions beyond established clinical and imaging variables. Any proposed model will require external validation in different populations and care settings.

Minimally invasive techniques may reduce the burden of liver resection, but technical feasibility is not itself an indication to operate on a benign lesion. Equally, molecular refinement does not establish that observation is safe.

The priority is to determine which patients are genuinely at risk of harm and which are more likely to be harmed by intervention. Surgical indications should evolve from more reliable diagnoses and validated outcome-based risk estimates, rather than from either tumor diameter or molecular subtype alone.

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