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REVIEW

Surgery-centered integrated strategies for personalized hepatocellular carcinoma care

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ABSTRACT Hepatocellular carcinoma (HCC) remains a major global health burden characterized by late-stage diagnosis and high postoperative recurrence rates. This review presents a surgery-centered precision management framework integrating 3 synergistic components: early detection, precision surgery, and recurrence prevention. Early detection strategies incorporate multiparameter risk models including the gender, age, AFP-L3, AFP, and DCP (GALAD) as well as age, sex, AFP, and PIVKA-II (ASAP) scores, alongside circulating tumor DNA methylation-based liquid biopsy, thus enabling tumor identification at stages amenable to curative resection. Precision surgery optimizes patient selection through refined staging systems including the Chinese liver cancer staging (CNLC), and functional assessments including the albumin–bilirubin (ALBI) grade, whereas conversion therapy and minimally invasive approaches extend surgical eligibility to selected patients with intermediate-stage disease. To mitigate the risk of postoperative recurrence, distinguishing between early and late recurrence patterns and monitoring minimal residual disease are critical strategies. Perioperative systemic therapies, particularly immune checkpoint inhibitor-based combinations, show promise for eradicating micrometastatic disease. This integrated framework provides a cohesive, evidence-based approach to personalized HCC management aimed at maximizing curative potential and long-term survival.

KEYWORDS Hepatocellular carcinoma; early diagnosis; liquid biopsy; hepatectomy; tumor recurrence

Introduction

Hepatocellular carcinoma (HCC) is the sixth most common malignancy and the third leading cause of cancer-related mortality worldwide[1]. HCC most commonly develops in the setting of chronic liver disease, in which longstanding inflammatory states predispose individuals to malignancy. Although chronic hepatitis B virus (HBV) infection remains the predominant etiology in China and other East Asian countries, the epidemiological landscape is undergoing substantial transformation. Metabolic risk factors, including obesity and type 2 diabetes, are increasingly recognized as major contributors to non-viral hepatocarcinogenesis, particularly in the context of metabolic dysfunction-associated steatotic liver disease (MASLD)[1]. Despite considerable therapeutic advances over the past decade, the overall prognosis for people with HCC remains unsatisfactory. Inadequate early detection results in most patients presenting with intermediate or advanced-stage disease, thereby substantially limiting eligibility for curative-intent interventions. Even among patients receiving successful curative-intent treatment, postoperative recurrence remains a formidable obstacle: the 5-year recurrence rate approaching 70% significantly compromises long-term survival[2-4]. Clinical management of HCC therefore faces a triad of persistent challenges, comprising high incidence, high case fatality, and frequent postoperative recurrence, which are the principal barriers to improving patient outcomes.

Surgical treatment, encompassing partial hepatectomy and liver transplantation, provides the best opportunity for cure for eligible candidates with resectable disease and preserved hepatic functional reserve. However, treatment paradigms considerably differ between Eastern and Western practice. Western guidelines, as exemplified by the Barcelona Clinic Liver Cancer (BCLC) staging system, traditionally restrict surgical resection to patients with very early or early-stage disease, whereas transarterial chemoembolization (TACE) or systemic therapies are recommended for intermediate and advanced stages. In contrast, high-volume centers across East Asia frequently use a more aggressive surgical philosophy.

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Accumulating evidence from these institutions indicates that expanded resection criteria may confer meaningful survival advantages for carefully selected patients with intermediate or even advanced-stage HCC[5,6]. This divergence underscores the need for an integrated strategy to overcome the complex challenges of HCC. In high-incidence regions, a surgery-centered strategy, focusing on curative resection and complemented by enhanced early detection and adjunctive interventions, has emerged. This strategy, as summarized in **Figure 1**, involves 3 interconnected components: an early screening system to increase detection in early stages, a precision surgical system to optimize safety, and a recurrence prevention system to monitor minimal residual disease (MRD), thereby addressing the primary challenges of HCC.

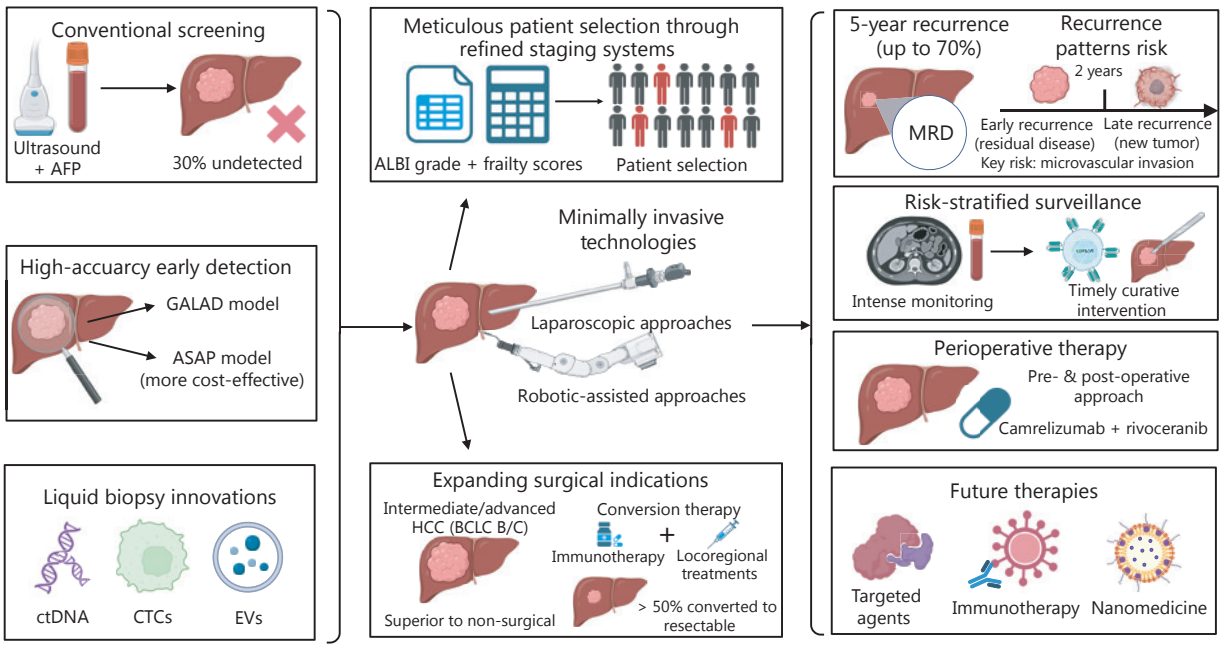


Figure 1 Overall framework of the surgery-centered integrated management strategy for hepatocellular carcinoma. This schematic illustrates the comprehensive clinical pathway integrating early detection, precision surgery, and recurrence prevention for individualized HCC management. The left panel depicts the early detection system, wherein conventional screening combining US and AFP has insufficient sensitivity, and therefore approximately 30% of early-stage cases remain undetected. High-accuracy early detection through multi-parameter models including GALAD and the more cost-effective ASAP score substantially enhances diagnostic performance. Liquid biopsy innovations using ctDNA methylation profiling, CTC enumeration, and EV analysis enable tumor identification at stages amenable to curative intervention. The central panel represents the precision surgery system, highlighting careful patient selection through refined staging systems incorporating ALBI grade and frailty scores for superior prognostication and candidate identification. Minimally invasive techniques including laparoscopic and robotic-assisted approaches facilitate safe tumor extirpation while preserving functional liver parenchyma. Expanding surgical indications for intermediate and advanced HCC in BCLC B/C stages is achieved through conversion therapy combining immunotherapy with locoregional treatments, thus enabling selected resection, which is superior to non-surgical approaches and converts initially unresectable disease to resectable status in more than 50% of responding patients. The right panel delineates the recurrence control system addressing the formidable challenge of post-operative recurrence, which affects as many as 70% of patients within 5 years. Recurrence patterns are categorized as early (occurring within 2 years and attributable to residual disease) or late (occurring beyond 2 years and associated with *de novo* tumor development, with MVI representing a key risk factor). Risk-stratified surveillance enables intense monitoring and timely curative intervention. Perioperative therapy promises a paradigm shift through approaches combining pre- and post-operative treatment with regimens such as camrelizumab plus rivoceranib. Future therapies including targeted agents, immunotherapy combinations, and nanomedicine platforms represent the expanding armamentarium for recurrence prevention. ALBI, albumin-bilirubin; AFP, alpha-fetoprotein; ASAP, age, sex, AFP, and PIVKA-II; BCLC, Barcelona Clinic Liver Cancer; CTC, circulating tumor cell; ctDNA, circulating tumor DNA; EV, extracellular vesicle; GALAD, gender, age, AFP-L3, AFP, and DCP; HCC, hepatocellular carcinoma; MRD, minimal residual disease; MVI, microvascular invasion.

In the context of this rapidly evolving HCC therapeutic landscape, this comprehensive review synthesizes current evidence across each domain and proposes an integrated clinical pathway incorporating multidisciplinary strategies. By aligning early detection, precision surgery, and systematic recurrence surveillance, we aim to provide an evidence-based framework for individualized HCC management that maximizes curative potential and optimizes long-term survival.

Early diagnosis and surveillance for HCC

Surveillance programs target individuals with elevated HCC risk, clinically encompassing patients with cirrhosis of any etiology and specific chronic HBV carriers, even before cirrhosis manifests[7]. Regular screening correlates with improved survival rates by facilitating earlier tumor detection[8]. Current guidelines typically recommend a standard approach of liver ultrasound (US) every 6 months, often combined with serum alpha-fetoprotein (AFP) measurement.

However, this combined US and AFP strategy has well-recognized limitations. US frequently has visualization limitations, particularly in patients with obesity or nonviral etiologies of cirrhosis. Moreover, AFP levels remain within normal in more than 40% of HCC cases, thus substantially restricting overall sensitivity[9]. Beyond these inherent technical limitations, adherence to surveillance protocols remains suboptimal in clinical practice. Factors including insufficient patient awareness, limited access to healthcare facilities, and resource constraints contribute to poor compliance. Consequently, an absence of regular screening in a substantial proportion of at-risk individuals perpetuates the low rates of early detection observed globally[10].

To address these shortcomings, various strategies are currently under investigation. In Asian centers, abbreviated magnetic resonance imaging (MRI) scans have been evaluated as alternatives to US, although cost and availability limit their widespread use[11,12]. In the Asia-Pacific region, integration of supplementary markers such as protein induced by vitamin K absence or antagonist-II (PIVKA-II), also known as des-gamma-carboxy prothrombin (DCP), alongside AFP has been proposed to optimize performance[13]. A recent prospective study has indicated that adding PIVKA-II to screening protocols enables the identification of early-stage HCC cases missed by AFP and US[14]. Despite these advances, establishing effective surveillance programs faces challenges, and a substantial number of patients are diagnosed in intermediate or advanced stages.

Liquid biopsy innovations

Beyond standard protein markers, the current exploration of liquid biopsy strategies is aimed at identifying HCC during its earliest phases. Carcinoma-derived DNA found in the bloodstream, known as circulating tumor DNA (ctDNA), carries tumor-specific genetic and epigenetic alterations. Notably, methylation patterns of ctDNA have emerged as particularly promising biomarkers for early HCC detection. An 11-gene plasma DNA methylation signature has been demonstrated to have high sensitivity in identifying HCC within high-risk cohorts[8]. Notably, this methylation panel has been reported to identify most early-stage cases missed by conventional AFP and PIVKA-II tests, thus underscoring its value as a complementary diagnostic tool.

A comprehensive model integrating gender, age, multi-target DNA methylation, AFP, and DCP (GAMAD) is undergoing prospective evaluation, thus reflecting a trend toward early tumor detection[15]. Investigations have also extended to other circulating biomarkers, including microRNAs and exosomal RNAs/proteins, which might indicate carcinoma[16]. Several microRNAs, such as miR-21 and miR-122, are present at abnormal levels in patients with HCC, although none have yet been used for routine clinical testing. Circulating tumor cells (CTCs) can also sometimes be detected in patients with HCC, but their utility for early diagnosis is limited by their extremely low abundance in early HCC stages[17]. Although these approaches remain in the research phase, they offer a glimpse into the future of early diagnosis, moving beyond traditional US and serum biomarkers.

Serum biomarkers and multi-parameter early detection models

The limited sensitivity and specificity of US and AFP require exploration of complementary biomarkers. PIVKA-II is elevated in a substantial subset of HCC cases, particularly those associated with HBV infection, and can detect cases with normal AFP levels. Similarly, the Lens culinaris agglutinin-reactive fraction of AFP (AFP-L3) is a recognized variant associated with malignant transformation.

To enhance early detection rates, researchers have developed multi-parameter risk models incorporating individual biomarkers. The GALAD score, which combines gender, age, AFP-L3, AFP, and DCP, has demonstrated high diagnostic accuracy, achieving an area under the receiver operating characteristic curve (AUROC) above 0.90 regardless of disease stage[18]. Global validation has confirmed its efficacy, even among patients with MASLD-related HCC. Concurrently, the ASAP score, combining age, sex, AFP, and PIVKA-II, introduced by Chinese investigators, has marked a major advancement. A detailed comparison of the specifications and diagnostic performance between the GALAD and ASAP models is presented in **Table 1**. ASAP, designed to overcome the high cost and limited availability of AFP-L3 testing in developing areas, excludes AFP-L3 while optimizing the statistical weights of AFP and PIVKA-II[19]. This simplified strategy maintains

Table 1 Comprehensive comparison of specifications and diagnostic performance between the GALAD and ASAP models

Feature	GALAD model	ASAP model	Clinical significance
Author and year	Johnson et al.[18], 2014	Yang et al.[19], 2019	ASAP is a more recent model developed specifically to optimize cost-effectiveness.
Model components	Five variables: gender, age, AFP, AFP-L3, DCP (PIVKA-II)	Four variables: age, sex, AFP, PIVKA-II	Key difference: ASAP excludes AFP-L3, thus decreasing complexity and cost.
Mathematical algorithm	Logistic regression (using $\log_{10}$ transformed biomarkers)	Logistic regression (using natural logarithm transformed biomarkers)	ASAP uses ln transformation to enhance detection sensitivity at lower biomarker levels.
Primary derivation cohort	UK (Western), Japan (mixed etiologies)	China (predominantly HBV-related HCC)	ASAP was originally optimized for HBV-endemic populations but has been validated globally.
AFP-L3 requirement	Mandatory (requires sensitive μTAS assay)	NA	ASAP avoids dependency on AFP-L3, which is costly and often unavailable in primary care.
Cost estimation (USD)	High (~$150–200 because of AFP-L3)	Moderate (~$40–60)	ASAP is suitable for large-scale population screening in developing regions.
Overall HCC detection	AUROC: 0.853–0.95	AUROC: 0.886–0.96	ASAP shows non-inferior or superior performance in head-to-head comparisons.
Early-stage HCC sensitivity	~60–85% (BCLC 0/A)	Comparable or higher	ASAP maintains high sensitivity without reliance on AFP-L3 elevation.
AFP-negative HCC detection	AUROC: 0.764	AUROC: 0.815	ASAP demonstrates superior detection in patients with AFP <20 ng/mL.
Specimen volume	Higher volume required for AFP-L3	Lower volume (<50 μL serum)	ASAP facilitates specimen collection, particularly in outpatient settings.

AFP, alpha-fetoprotein; DCP, des-gamma-carboxy prothrombin; PIVKA-II, protein induced by vitamin K absence or antagonist-II.

high diagnostic precision. In a multicenter case-control study focusing on hepatitis C (HCV)-related HCC, the ASAP score outperformed the GALAD score, particularly in detecting early-stage tumors (BCLC 0/A), with AUROC values of 0.898 *vs.* 0.860, as well as in identifying AFP-negative cases. These findings highlight the robustness of the ASAP score despite the exclusion of AFP-L3[20].

A comprehensive comparative analysis across various etiologies, including MASLD, has indicated that the ASAP score achieves a higher overall AUROC (0.886) than GALAD (0.853) in detecting HCC in all stages. Notably, in the challenging subgroup of patients with MASLD-related cirrhosis, the ASAP score has a clear diagnostic advantage[21]. These findings challenge the prevailing paradigm that incorporating additional biomarkers necessarily enhances diagnostic performance; instead, the mathematical optimization of key markers, specifically AFP and PIVKA-II, appears sufficient to develop cost-effective and accurate surveillance tools. However, because this analysis relied on retrospective data, and the ASAP score was developed within a Chinese cohort, further validation is required in diverse populations.

To address the increasing prevalence of MASLD-related HCC, Rodriguez et al.[22] have developed a machine learning-based prediction model using electronic health record data from a large racially and ethnically diverse cohort of more than 1.8 million patients in the Kaiser Permanente Northern California system. Although serum biomarkers were not used, 18 routinely captured clinical variables were integrated, including BMI; age; diabetes; and standard laboratory tests, such as platelets, albumin, aspartate aminotransferase/ALT, bilirubin, and INR. The model achieved an AUROC of 0.899 and showed high discrimination across all major ethnic subgroups, including Asian, Black, Hispanic, and White patients. This tool is therefore promising for surveillance in diverse high-risk MASLD populations.

Collectively, these emerging predictive models have led to a paradigm shift in HCC surveillance, by providing a detection sensitivity of 70%–85% for early-stage disease, which is markedly superior to that of AFP alone. Nevertheless, the translation of these findings into clinical practice warrants rigorous confirmation through large-scale, prospective, and multicenter validation studies across diverse populations, to definitively establish their utility and robustness in real-world settings.

Survival benefit of early detection

Early-stage diagnosis is fundamental to achieving long-term survival in patients with HCC, because it enables access to

potentially curative interventions, including surgical resection, liver transplantation, and ablation. Patients who receive curative-intent treatment for early-stage disease demonstrate substantially more favorable outcomes than those diagnosed at intermediate or advanced stages. Among patients with small, solitary tumors measuring less than 3 cm and preserved hepatic function, surgical resection achieves 5-year overall survival rates of 60%–80%[23]. A systematic review comparing resection with radiofrequency ablation for tumors as large as 3 cm has demonstrated comparable survival outcomes, with a modest advantage favoring resection for long-term local disease control[24]. These data underscore the critical importance of early detection in maximizing curative potential and optimizing long-term survival for patients with HCC.

The survival benefit of early intervention extends beyond patients with solitary tumors to those with early-stage multifocal disease. A multicenter study has demonstrated excellent long-term survival after resection in patients with binodular early-stage HCC, thus challenging the traditional paradigm in which multifocal disease uniformly precludes curative surgery[25]. In centers with established surveillance programs, a proportion of patients diagnosed with early-stage HCC who undergo prompt surgical intervention remain tumor-free for extended periods. The concept of statistical cure, defined as survival beyond a threshold at which the risk of cancer-related mortality approximates that of the age-matched general population, is applicable to a subset of these patients[26]. A recent study focusing on HBV-related HCC after hepatectomy has developed a predictive model for such a cure. Patients with very low-risk features, including a single tumor measuring ≤5 cm, no vascular invasion, and low AFP, were found to have a high likelihood of being statistically cured after 5 to 6 years of recurrence-free survival[27].

The implementation of an efficient early detection system would facilitate early intervention and therefore enhance patients' prognosis. By expanding eligibility for curative resection or ablation, early diagnosis contributes to improved survival outcomes, thereby providing a solid rationale for sustained investment in advanced screening strategies and biomarkers[28].

Precision surgery for HCC

Risk prediction and perioperative outcomes

Achieving a balance between oncologic efficacy and patient safety remains critical in hepatectomy, particularly given the prevalence of chronic liver disease. Although clinicians traditionally use the Child-Pugh class and the Model for End-Stage Liver Disease score to select suitable candidates, these tools are relatively coarse[29,30]. Recently, sophisticated models have emerged to enhance the prediction of outcomes, specifically severe complications, post-hepatectomy liver failure, and 90-day mortality. Among these, a notable individualized calculator combines the albumin-bilirubin (ALBI) grade with the aspartate aminotransferase-to-platelet ratio index, thereby outperforming the conventional Child-Pugh classification in predicting post-hepatectomy liver failure[31,32]. By synthesizing liver function, tumor burden, and patient-specific factors, these tools rigorously quantify operative risk. Furthermore, the effects of underlying etiology on long-term prognosis warrant greater recognition. In a European surgical cohort in which MASLD accounted for 27.3% of cases, patients with MASLD-related HCC exhibited comparable time-to-recurrence, whereas overall survival was significantly shorter after liver resection[33]. Multivariable analysis identified MASLD as an independent adverse prognostic factor together with portal vein thrombosis and a Model for End-Stage Liver Disease score ≥10. These data provide Western evidence that the etiology of HCC should be incorporated into risk prediction models.

The concept of textbook outcome has gained increasing prominence in hepatobiliary surgery. This composite measure defines an ideal postoperative trajectory encompassing complete tumor resection with negative margins, absence of major complications, short length of hospital stay, no unplanned readmission, and zero perioperative mortality[34]. In large-scale stratification of patients with HCC, variables such as the requirement for major resection, intraoperative blood transfusion, and poor performance status have been significantly associated with elevated likelihood of suboptimal outcomes[35-37]. Beyond tumor metrics, preoperative frailty and functional status have emerged as critical predictors. A multicenter analysis focusing on older cohorts has indicated that elevated frailty scores correlate with elevated complications and diminished overall survival post-resection[38]. Likewise, indices such as the Barthel index, which evaluates activities of daily living, are associated with failure to achieve ideal outcomes[39]. These data collectively underscore the importance of evaluating physiological reserve alongside tumor characteristics when determining surgical candidacy in patients with HCC.

Continuing refinements in perioperative management are aimed at enhancing patient safety. The use of advanced anesthetic monitoring techniques, the maintenance of low central venous pressure during transection, and the implementation of enhanced recovery protocols collectively mitigate surgical stress[40-42]. Innovation in surgical techniques is equally crucial. Techniques designed to minimize blood loss, such as the intermittent Pringle maneuver or use of novel transection devices, alongside vigilant postoperative monitoring, decrease the risk of liver failure[43]. Early postoperative elevations in liver enzymes are associated with subsequent complications, by reflecting the extent of intraoperative ischemia-reperfusion injury[44]. Ultimately, the goal of a precision safety management strategy is to use these tools to optimize patient selection and minimize hepatic injury, to ensure immediate postoperative safety while establishing a foundation for long-term outcomes.

Postoperative prognostic stratification and refined staging systems

Accurate prediction of long-term outcomes after resection is essential for guiding adjuvant treatment decisions and tailoring postoperative surveillance strategies. However, traditional staging systems have inherent limitations in prognostic stratification for surgical candidates. The BCLC classification, although widely used for treatment allocation, was developed primarily to guide therapeutic selection across the entire disease spectrum rather than to predict survival specifically after curative-intent resection. The tumor-node-metastasis (TNM) system provides anatomical staging based on pathological variables but lacks integration of hepatic functional reserve and tumor biological characteristics, both of which are critical determinants of postoperative outcomes[45-47]. To address these limitations, novel staging and prognostic scoring systems have been developed, predominantly from high-volume Asian centers, to achieve more precise risk stratification in patients undergoing surgical resection for HCC.

The Eastern staging system designed for resection candidates incorporates both tumor size and liver functional reserve. A prospective validation study in more than 4,600 patients has demonstrated this system's superior prognostic discrimination to the BCLC staging system. Patients with Eastern stage I, II, or III categorization show distinct survival outcomes after surgical resection. In contrast, the BCLC system often groups these heterogeneous patients into a single category, such as stage B or C[48,49]. These findings highlight the ability of a refined staging system to effectively differentiate between low-risk and high-risk surgical candidates, even among patients with intermediate or advanced classification according to the BCLC staging system.

Integrating serum biomarkers into staging protocols represents another strategy to refine prognostic stratification after resection. Serum AFP, an established independent prognostic marker for HCC, is incorporated into several composite scoring systems that complement conventional morphological criteria. In a multicentre analysis of 1,968 patients, the AFP model, a composite score incorporating tumor size, number, and AFP level, showed superior accuracy to the Milan criteria in predicting post-resection recurrence and survival, and further identified a subgroup at particularly high risk among patients exceeding both scoring systems[50]. Such tools assist clinicians in decision-making by helping them determine whether surgery is beneficial for patients who might fall outside conventional limits but exhibit favorable tumor biology, such as low AFP.

Endorsed by national guidelines, the China Liver Cancer (CNLC) staging system stratifies intermediate-stage HCC, thereby distinguishing surgical candidates, such as patients with CNLC stage IIa, from patients better suited for palliative therapy[5]. Robust statistical evidence from recent multicenter validation studies supports this granular approach. In head-to-head comparisons, the CNLC system exhibited homogeneity and monotonicity significantly superior to the BCLC system[51]. Moreover, CNLC achieved a higher C-index in predicting overall survival (0.674 *vs.* 0.667) and progression-free survival (0.692 *vs*. 0.679). It also had a lower Akaike Information Criterion, a marker of greater model goodness of fit[52]. These findings suggest that CNLC stratifies survival more accurately than BCLC and effectively mitigates the heterogeneity in the BCLC intermediate stage, thus providing a stronger evidentiary basis for selecting surgical candidates. The comparative prognostic performance of the CNLC *vs.* the BCLC staging system is summarized in **Table 2**.

Crucially, CNLC addresses certain ambiguities inherent in the BCLC framework. Even among patients meeting BCLC early-stage criteria, prognosis significantly varies. A comprehensive analysis of early-stage HCC across 5 distinct staging systems has revealed that patients with specific tumor characteristics, such as microvascular invasion (MVI) and elevated AFP levels, tend to have poor outcomes despite small tumor size[53]. Identifying these patients before or immediately after surgery enables clinicians to consider additional interventions, including intensified postoperative surveillance or adjuvant treatments. Ultimately, a personalized staging approach incorporating tumor biology, such as AFP levels and invasive features alongside liver function, would offer precise prognostic stratification. This personalized staging approach supports the development of individualized management strategies after resection.

Minimally invasive and anatomical approaches

Parallel advancements in surgical technique have enhanced patient selection, and consequently ensured both safety and efficacy during hepatectomy. Minimally invasive approaches, specifically laparoscopic and robotic surgeries, have become widely accepted modalities for treating HCC. Laparoscopic hepatectomy achieves oncological outcomes equivalent to those of open procedures while offering distinct advantages in recovery[54]. A propensity score analysis involving nearly 4,000 patients has linked laparoscopic resection to diminished infection rates and hospital stays, without compromising survival or increasing recurrence rates[55]. Another study on exophytic HCCs has confirmed that laparoscopic techniques yield long-term results similar to those of open surgery while limiting surgical trauma[56]. Moreover, in a study in 996 patients with HCC with MASLD from Europe and North America, minimally invasive liver resection has been associated with lower rates of major complications, post-hepatectomy liver failure, and postoperative ascites than open resection[57]. These findings have driven the expansion of minimally invasive techniques, even for complex resections in experienced medical centers.

Table 2 Comparative prognostic performance of CNLC *vs.* BCLC staging systems in hepatocellular carcinoma

Statistical metric	CNLC	BCLC	*P*-value
Discrimination (C-index)			
Overall survival	0.674 (0.610–0.726)	0.667 (0.613–0.715)	$P > 0.05$
Progression-free survival	0.692 (0.637–0.740)	0.679 (0.625–0.722)	$P > 0.05$
Homogeneity			
Likelihood ratio χ^2	159.2	158.7	$P < 0.001$
Monotonicity			
Linear trend χ^2	66.107	57.418	$P < 0.001$
Model fit			
Akaike Information Criterion	10,583.28	10,583.72	
Time-dependent AUC			
1-year survival	0.738	0.731	$P < 0.001$
3-year survival	0.679	0.666	$P < 0.001$

AUC, area under the receiver operating characteristic curve; BCLC, Barcelona Clinic Liver Cancer; CNLC, China Liver Cancer.

Surgeons continue to debate the relative merits of anatomic resection, which removes the tumor along with its entire anatomical segment, *vs.* non-anatomic wedge resection. Theoretically, anatomical resection eradicates microscopic tumor satellites and improves local control. However, this approach necessarily sacrifices more liver parenchyma. According to historical data, anatomical resection with adequate negative margins is particularly beneficial for tumors exhibiting MVI[58]. In a multicenter cohort, wider surgical margins have been independently associated with diminished recurrence risk in patients with microscopic vascular invasion[59]. In contrast, for diminutive and peripherally located tumors, parenchyma-sparing limited resection is often indicated, particularly in patients with cirrhosis, because this method preserves postoperative liver function more effectively than anatomical resection by minimizing the volume of resected non-tumorous parenchyma[60]. Therefore, the operative approach must be tailored according to tumor location and size. Deep parenchymal lesions are best managed with anatomical sectionectomy to ensure oncologically adequate margins. In contrast, superficial tumors smaller than 2 cm can frequently be treated with limited resection, a strategy that minimizes the loss of non-tumorous tissue[61].

Advanced intraoperative imaging, such as high-resolution ultrasonography and fluorescence-guided systems, allows surgeons to localize and delineate tumors with superior accuracy that substantially enhances resection precision[62,63]. Such technical refinements can improve surgical outcomes and help prevent tumor metastasis. For example, routine intraoperative US enables the detection of occult nodules and aids in precise determination of the transection plane. Hemorrhage control during liver transection is frequently achieved by maintaining low central venous pressure. When hepatic inflow occlusion *via* the Pringle maneuver is necessary, many experts use intermittent clamping to limit ischemia-reperfusion injury. Short, intermittent occlusion has been demonstrated not to harm postoperative recovery. Propensity-matched analyses have revealed no significant difference in long-term survival between surgeries performed with *vs.* without the Pringle maneuver[43]. Other adjunctive techniques, including selective hemihepatic inflow control and ischemic preconditioning, are also used to preserve liver function.

Ultimately, precision-oriented surgical strategies require rigorous patient selection and optimized operative techniques. This integrated approach combines minimally invasive modalities, efficient planning balancing anatomic and non-anatomic strategies, and standardized measures to protect liver function. Continued technical refinement and protocol standardization have significantly increased surgical proficiency; decreased perioperative morbidity; and fostered consistent, favorable outcomes after HCC resection.

Surgery for intermediate and advanced-stage HCC

The expansion of the criteria for surgical intervention beyond traditionally defined early-stage disease has marked a major paradigm shift in HCC management. Recent evidence, primarily from Asian institutions, suggests that rigorously selected patients in BCLC stage B or even stage C can achieve surgical outcomes superior to those of non-surgical

therapies[64]. Notably, propensity score-matched analyses have demonstrated that patients with large or multinodular tumors confined to the liver, and preserved hepatic functional reserve, attain a median overall survival of approximately 50 months after resection, significantly surpassing the 20-month survival observed with transarterial chemoembolization[65]. These findings highlight the inadequacy of the BCLC stage B category, which obscures the distinct survival potential of patients with favorable tumor biology. In contrast, stratification within the CNLC system offers superior discriminatory ability, by more accurately identifying patients who stand to significantly benefit from surgical intervention[51].

A similar trend has been found in meta-analyses on portal vein tumor thrombus (PVTT). Selected patients undergoing resection have demonstrated a significant survival benefit over those receiving non-surgical management, a finding challenging the prevailing notion that macrovascular invasion is an absolute contraindication to surgery. In reported cases in which PVTT is limited, for example, to a segmental or lobar branch rather than the main trunk, the 1-year survival after aggressive resection can reach 50%–70%. In contrast, the median survival without surgical intervention generally remains below 6 months[66]. For multinodular HCC, Western guidelines often discourage surgery, yet accumulating evidence supports resection in carefully selected candidates. In a multicenter cohort of 1,066 patients with multinodular disease, predominantly involving 2 or 3 nodules, hepatectomy achieved a 5-year overall survival rate of approximately 45%–50%[25]. Current data substantiate the viability of favorable long-term oncologic outcomes regardless of tumor burden, by establishing that large tumor size alone is not an absolute barrier to survival. Accordingly, surgical resection remains the preferred curative intervention for patients with confirmed technical resectability and adequate future liver remnant volume[67].

Expanding indications clearly require meticulous patient selection. To consider surgical intervention for cases beyond early stages, specific criteria must be met, including an absence of complete hepatic vascular outflow obstruction[68]; the feasibility of managing limited PVTT[69]; sufficient future liver remnant volume and functional reserve, as verified with volumetric imaging and indocyanine green clearance testing[70]; and adequate performance status. Notably, advanced age should not automatically preclude surgery. Evidence from octogenarian cohorts has demonstrated that, with careful preoperative optimization, the perioperative mortality rates are analogous to those seen in younger cohorts[71]. Similarly, mild to moderate portal hypertension, which was previously considered a barrier to resection, can now be managed in selected candidates through contemporary strategies, including concomitant splenectomy or portosystemic shunts when indicated, thereby achieving acceptable outcomes[72].

The reliance on retrospective, single-center data in many reports inevitably introduced selection bias, because surgery is often reserved for biologically favorable candidates. Nevertheless, the consistency of results across independent studies supports the Eastern guidelines advocating for an aggressive surgical approach for carefully selected BCLC B or C patients[73]. Western guidelines are beginning to acknowledge this evidence, although they still recommend caution. Consequently, multidisciplinary evaluation and rigorous evaluation of the risk-benefit ratio will be essential. In cases in which clinical and tumor characteristics indicate a high probability of cure or long-term control, such as a solitary large lesion, limited multifocal involvement, or resectable PVTT, and the operative risk is acceptable, hepatic resection is a justifiable procedure, even if the scenario falls outside the conventional BCLC framework. Clearly defining which patients in these advanced categories derive maximal benefit remains an ongoing challenge necessitating improved predictive models and prospective validation.

Conversion therapy, bridging, and sequential treatment

Modern HCC therapy has undergone a paradigm shift from single interventions to dynamic, multi-step plans. For example, in conversion therapy, also known as downstaging, patients with initially unresectable tumors receive upfront treatment designed to shrink the lesion or control its growth. Contemporary protocols often leverage systemic agents, such as tyrosine kinase inhibitors (TKIs) paired with immune checkpoint inhibitors, and locoregional modalities such as TACE, hepatic arterial infusion chemotherapy, or radiotherapy. The ultimate objective remains achieving resectability[74].

When significant tumor regression occurs, curative resection becomes a viable option. The efficacy of this strategy has been demonstrated by data from a multicenter study in 83 patients treated with TACE, lenvatinib, and anti-programmed cell death protein 1 (PD-1) immunotherapy. The conversion-to-resectability rate exceeded 50%, and patients proceeding to surgery notably achieved markedly longer survival than non-responders[75]. Even in complex scenarios involving advanced vascular invasion or limited extrahepatic spread, aggressive systemic therapy has shown efficacy occasionally permitting surgical intervention or transplantation[76].

Nonetheless, conversion attempts do not always succeed. However, early indicators, such as a substantial decline in AFP levels during neoadjuvant treatment, can effectively stratify patients likely to derive surgical benefit[77]. For borderline cases, the establishment of a treatment strategy through multidisciplinary team discussions is essential[78]. Although the role of hepatic arterial infusion chemotherapy (HAIC)-FOLFOX as a potent salvage strategy after systemic therapy failure has been substantiated by a randomized phase III trial by He et al.[79], the timing and sequence still require careful individualization. For example, some technically resectable patients might receive

neoadjuvant therapy to eliminate occult micrometastases and gauge tumor biology. Resection follows only if the disease remains stable or shows adequate control[80]. In contrast, patients undergoing resection might receive adjuvant systemic therapy to mitigate recurrence risks. A flexible treatment sequence requires close collaboration among surgeons, hepatologists, medical oncologists, and interventional radiologists.

For transplant candidates, multidisciplinary team planning necessitates the strategic integration of bridging and salvage strategies. Bridging therapy uses locoregional treatments, including TACE, ablation, or resection, to control tumor growth and prevent dropout while the patient awaits a donor, thus ensuring that the disease remains within transplant criteria. Salvage transplantation, defined as transplantation following recurrence after an initial resection, is an alternative curative pathway. Contemporary evidence has indicated comparable outcomes for salvage transplantation and primary transplantation; therefore, initial resection does not compromise future transplant eligibility[81]. Consequently, in regions where donor organs are scarce, performing upfront resection followed by rigorous surveillance is standard practice. If recurrence occurs, re-evaluation for transplantation is warranted if preserved hepatic functional reserve and tumor characteristics remain within established criteria[82].

Clinical practice guidelines for conversion therapy exhibit notable regional variations in recommendations. Initially unresectable HCC refers to disease precluding surgical resection because of surgical or oncological factors. Surgical unresectability refers to patient-related limitations including inadequate general condition or hepatic functional reserve, insufficient future liver remnant volume, and inability to achieve adequate resection margins. Oncological unresectability refers to tumor-related characteristics associated with prohibitively high recurrence risk, including macrovascular invasion, bile duct involvement, or extensive multifocal disease[80]. Notably, patients presenting with surgically resectable but oncologically unresectable disease, such as those with CNLC stage IIb/IIIa HCC, might have greater likelihood of achieving successful conversion than patients with concurrent surgical and oncological contraindications[81]. Conversion therapy involves administration of systemic and locoregional treatments before surgery to decrease tumor burden, induce tumor thrombosis retraction, and ultimately render initially unresectable disease amenable to curative-intent resection. Assessment of conversion therapy response requires standardized evaluation criteria. European Association for the Study of the Liver (EASL) and Japan Society of Hepatology (JSH) guidelines recommend response assessment with mRECIST, typically performed after 2 or 3 treatment cycles to evaluate sustained tumor response and biological behavior. Although major international guidelines, including those from EASL, American Association for the Study of Liver Diseases (AASLD), and JSH, unanimously endorse downstaging protocols for liver transplantation candidacy as a standard therapeutic strategy, recommendations regarding conversion to surgical resection substantially differ. The EASL and AASLD guidelines, citing the absence of high-level evidence demonstrating a survival benefit of conversion resection over continued systemic therapy, currently recommend performing conversion surgery exclusively within the context of prospective clinical trials. In contrast, the JSH guidelines recognize conversion surgery as a viable therapeutic option for patients achieving significant radiological response after systemic or locoregional treatment. The optimal timing of surgery and the appropriate interval between the cessation of systemic therapy and surgical intervention remain areas of ongoing investigation and multidisciplinary debate[9,83,84]. For patients who do not achieve successful conversion or who experience disease progression during treatment, alternative salvage strategies merit consideration. HAIC is an established salvage approach with demonstrated efficacy in patients with locally advanced disease refractory to first-line systemic therapy. Second-line systemic agents, including alternative TKIs or immune checkpoint inhibitor combinations, provide additional options for disease control. Dynamic monitoring of biomarkers including AFP, PIVKA-II, and DCP during treatment may facilitate early identification of primary progression and prediction of treatment failure, thereby enabling timely modification of therapeutic strategies.

In conclusion, surgical resection is a potentially curative intervention and a central component within the broader continuum of HCC care. Clinical decision-making requires a multidisciplinary team that longitudinally adapts individual treatment strategies according to tumor stage, hepatic functional reserve, and patient performance status. The therapeutic trajectory for a given patient may encompass systemic therapy, curative-intent resection, risk-adapted adjuvant treatment, structured surveillance, and salvage liver transplantation, as indicated. This surgery-centered iterative framework, positioning surgical intervention within an integrated treatment continuum rather than as an isolated modality, has emerged as the standard of care in high-volume hepatobiliary centers. Further improvements are needed across the whole care and disease continuum to address the persistent challenges of high recurrence rates and optimize long-term oncological outcomes.

Preventing and managing postoperative recurrence

Patterns of recurrence and the concept of minimal residual disease

Postoperative recurrence is the principal barrier to long-term survival after curative-intent resection for HCC. Approximately half of all patients experience recurrence

within 3 years of surgery, and the 5-year cumulative recurrence rates approach 70%[85,86]. Recurrence patterns are conventionally categorized as early or late, with a 2-year postoperative interval serving as the temporal threshold, although this cutoff remains debated[87]. Early recurrence is generally attributed to occult intrahepatic dissemination or intrinsically aggressive tumor biology of the index lesion, representing residual microscopic disease undetectable at the time of resection[88,89]. Clinical evidence has consistently linked early recurrence to adverse tumor characteristics, including microvascular invasion, satellite nodules, and elevated AFP concentrations[87]. In contrast, late recurrence is traditionally attributed to *de novo* carcinogenesis arising from the chronically diseased liver parenchyma, driven by persistent hepatitis viral infection, progressive fibrosis, or ongoing hepatic inflammation[87].

These observations have provided the conceptual foundation for MRD detection in HCC. MRD is defined as tumor-derived molecular abnormalities detectable through liquid biopsy after curative-intent treatment, when conventional imaging modalities and traditional laboratory methods do not identify residual disease, thus indicating the potential for tumor persistence and subsequent clinical progression[87]. The Chinese Expert Consensus on Solid Tumor MRD Detection formally recognizes ctDNA-based MRD assessment as a prognostically informative tool in HCC, although the evidence remains less robust than that for colorectal cancer, non-small cell lung cancer, and breast cancer. Current ctDNA-based MRD detection methods use next-generation sequencing platforms with either tumor-informed or tumor-agnostic analytical strategies. Tumor-informed approaches, which use somatic mutations identified through tissue sequencing to design personalized tracking panels, have superior sensitivity and specificity to tumor-agnostic methods, and are recommended as the preferred strategy[87]. The optimal recommended timing for landmark MRD assessment is within 1 month after curative-intent treatment, and should be followed by longitudinal monitoring to increase prognostic accuracy and enable early detection of molecular recurrence[87]. Notably, ctDNA detection, because it precedes radiological confirmation of recurrence by a median interval of 4 months, provides a clinically meaningful window for therapeutic intervention.

Despite these advances, several challenges must be addressed before MRD-guided treatment can be integrated into routine clinical practice. Current EASL guidelines stipulate that treatment decisions must rely on radiological confirmation of recurrence, because initiating adjuvant therapy solely on the basis of biochemical or molecular abnormalities without visible lesions is currently not supported, given the absence of demonstrated survival benefits[84]. Furthermore, emerging evidence suggests that the traditional dichotomy between early and late recurrence might be overly simplistic[87]. A multicenter cohort study has associated late recurrence not only with underlying cirrhosis but also with aggressive features of the index tumor, including multifocality, satellite nodules, larger tumor size, and vascular invasion; therefore, a subset of late recurrences might arise from dormant MRD rather than *de novo* carcinogenesis[87]. These findings underscore the clinical value of sustained, protocol-driven surveillance beyond 2 years, particularly for patients with high-risk tumor characteristics, because regular long-term follow-up has been associated with improved survival and elevated likelihood of receiving curative-intent treatment at the time of recurrence.

Risk factors for recurrence and prediction models

Recurrence after curative-intent hepatectomy remains a major obstacle to long-term survival in patients with HCC. Current evidence supports a multifactorial basis of relapse, wherein risk reflects the combined contributions of liver background, tumor burden, biological aggressiveness, and perioperative events. At the host level, extremes of body mass index have been associated with heightened recurrence[90], and a family history of liver cancer has also been reported as an adverse prognostic factor[91]. Virological activity further influences postoperative risk: higher HBV viral load and complex viral co-infections correlate with recurrence and reinforce the importance of sustained antiviral control[92]. Laboratory indices reflecting systemic inflammation and nutritive status, specifically preoperative albumin and the albumin-to-globulin ratio, provide additional prognostic value[93]. Platelet count shows a non-linear relationship with relapse, thus potentially reflecting both portal hypertension-related thrombocytopenia and platelet-associated pro-tumor mechanisms, and suggesting that thrombocytopenia and thrombocytosis are each associated with recurrence across cohorts[94].

In parallel, tumor-related factors remain central drivers of relapse propensity. Microvascular invasion is among the most robust pathological predictors of post-resection recurrence, and grading of MVI severity offers more granular stratification than a binary present or absent classification, even among patients with otherwise early-stage or solitary tumors[95]. Circulating biomarkers provide complementary biological signals: elevated PIVKA-II and AFP levels have consistently been associated with elevated recurrence risk[50,96]. Perioperative factors might further influence long-term outcomes. Narrower resection margins are associated with higher recurrence rates, particularly in the presence of MVI[97]. Postoperative infectious complications have been associated with worse long-term prognosis, potentially through systemic inflammation and immune perturbation[98].

These observations provide a rationale for prediction models that integrate variables across domains rather than relying on single risk markers. For example, the POLAR score, developed to estimate late recurrence by incorporating tumor-related characteristics, enables identification of patients who

remain vulnerable outside the conventional early recurrence window[99]. More broadly, composite models combining liver function measures, tumor features, and biomarkers can support individualized risk classification, and may inform clinically actionable decisions, such as tailoring surveillance intensity and prioritizing high-risk patients for adjuvant therapy trials. Although many models still require external validation across etiologies and practice settings, they represent a pragmatic step toward personalized prognostication after hepatectomy.

Surveillance strategies after resection of early detection of recurrence

Surveillance after curative treatment is crucial for early detection of recurrences when they are most amenable to therapy. Typical recommendations include cross-sectional imaging (US, contrast-enhanced CT, or MRI) and tumor marker tests (AFP ± PIVKA-II) every 3–4 months in the first 2 postoperative years and every 6–12 months thereafter for at least 5 years. In practice, adherence to such intensive follow-up can vary, yet studies have indicated that adherence leads to substantial differences in outcomes. In a multicenter analysis, patients who strictly followed a structured surveillance program had markedly more favorable post-recurrence survival than those with poor adherence to follow-up[100]. The benefit stems from timely detection of an asymptomatic recurrence, which allows for potentially curative interventions, including repeat resection, ablation, or transplant, rather than discovery of the recurrence at an advanced, incurable stage.

Modern follow-up strategies are evolving from rigid, uniform protocols toward risk-adapted paradigms. Risk stratification can be applied to tailor surveillance intensity. For example, a patient with multiple high-risk features, such as MVI and high AFP, might receive imaging every 2 to 3 months in the first year, whereas a low-risk patient could be monitored at standard 6-month intervals. Some centers incorporate dynamic biomarker monitoring into follow-up. For example, a rising AFP or PIVKA-II level might signal a recurrence months before it becomes radiologically apparent and therefore can prompt earlier imaging. Research on ctDNA-based surveillance is particularly promising. Some studies have demonstrated that postoperatively detecting ctDNA mutations or methylation markers can predict HCC recurrence in advance of conventional imaging. In the near future, such molecular surveillance could complement imaging and enable clinicians to identify recurrence at a nearly microscopic stage.

When a recurrence is identified, aggressive treatment can still salvage long-term survival in many cases. Approximately 20%–30% of HCC recurrences are amenable to potentially curative therapy, including repeat resection, local ablation, or even salvage transplantation. For example, repeat hepatectomy for an isolated intrahepatic recurrence has 5-year survival rates of approximately 50%, particularly for late recurrences[101]. These outcomes approach those of initial hepatectomy and indicate that secondary curative outcomes are often achievable. However, for success, the recurrence must be identified early, and the patient's liver function and performance status must remain sufficient. Therefore, the surveillance and recurrence-management plan is a critical component of the overall system in ensuring that the window of opportunity for curative treatment is not missed when recurrence occurs.

Adjuvant and sequential therapies to prevent recurrence

Given the high recurrence risk after resection and the ineffectiveness of traditional cytotoxic chemotherapy for HCC, numerous trials have explored alternative postoperative adjuvant therapies to eradicate residual disease and improve outcomes.

Adjuvant TACE has shown efficacy in select patient populations with high-risk features. The most compelling evidence has emerged from Asian studies. A phase II randomized trial has shown that adjuvant intra-arterial iodine-131-labeled lipiodol, compared with surgery alone, results in significantly prolonged recurrence-free survival in patients with HBV-related HCC and other risk factors. Recently, a meta-analysis and prospective studies have indicated that adjuvant TACE combined with TKIs, such as lenvatinib, might offer superior recurrence-free survival to that with TACE alone in patients with MVI, thus supporting the use of combination strategies in high-risk subgroups[102,103]. However, identifying the specific subgroups that benefit most remains a priority for ongoing research.

The systemic therapy landscape has shown both promise and setbacks. The STORM trial tested adjuvant sorafenib, but the absence of improvement in recurrence-free survival dampened enthusiasm for TKI monotherapy in the adjuvant setting[104]. With the advent of immunotherapy, the phase III IMbrave050 trial initially reignited excitement by demonstrating improved recurrence-free survival (RFS) with adjuvant atezolizumab plus bevacizumab at the interim analysis[105]. However, in updated results with longer follow-up, this benefit was not sustained: the hazard ratio for RFS rose from 0.72 to 0.90, and no significant overall survival benefit has been observed to date[106]. Similarly, the phase III KEYNOTE-937 trial evaluating adjuvant pembrolizumab did not meet its primary endpoints, thus further highlighting the challenges of pure adjuvant immunotherapy in HCC[107]. The EMERALD-1 phase III trial demonstrated that combining durvalumab and bevacizumab with TACE significantly improved PFS in unresectable HCC confined to the liver, a context distinct from the adjuvant setting. In contrast, the absence of a similar PFS benefit with durvalumab monotherapy with TACE underscores the critical role of anti-angiogenic therapy in potentiating

Table 3 Comprehensive comparison of key phase III clinical trials for perioperative and adjuvant therapy in hepatocellular carcinoma

Clinical trial	EMERALD-1	CARES-009	IMbrave050	KEYNOTE-937
Study design	Unresectable setting	Perioperative (neoadjuvant + adjuvant)	Adjuvant	Adjuvant
Phase	Phase III	Phase III	Phase III	Phase III
Target population	Global study	Predominantly in China	Global study	Predominantly in China
Experimental arm	Arm A: TACE + durvalumab + bevacizumab Arm B: TACE + eurvalumab + placebo	Perioperative camrelizumab + rivoceranib	Atezolizumab + bevacizumab	Pembrolizumab
Comparator	TACE + placebo	Surgery alone	Active surveillance	Placebo
Primary endpoint	PFS	EFS	RFS	RFS and OS
Latest hazard ratio (95% confidence interval)	0.77 (0.61–0.98)	0.59 (0.41–0.85)	0.90 (0.72–1.12)	RFS: 1.06 (0.88–1.26) OS: 1.08 (0.81–1.43)
Status	Ongoing	Ongoing	Ongoing	Completed
Conclusion	Positive result	Positive result	Benefit not sustained	Negative result

EFS, event-free survival; OS, overall survival; PFS, progression-free survival; RFS, relapse-free survival; TACE, transarterial chemoembolization.

immune checkpoint inhibition. The ongoing EMERALD-2 trial (NCT03847428) is further evaluating durvalumab, alone or with bevacizumab, *vs.* placebo as an adjuvant therapy after curative resection or ablation for HCC, to address a key unmet need. Concurrently, the EMERALD-3 study (NCT05301842) is investigating durvalumab alongside tremelimumab, with or without lenvatinib, in combination with TACE for patients with embolization-eligible HCC[108]. The comparative efficacy of critical phase III adjuvant and perioperative trials is summarized in **Table 3**.

In contrast to these adjuvant-only approaches, a paradigm shift toward perioperative therapy combining neoadjuvant and adjuvant treatment has emerged as a transformative therapeutic advance[109]. The phase III CARES-009 trial has recently demonstrated that perioperative therapy with camrelizumab (PD-1 inhibitor) and rivoceranib (VEGFR-2 inhibitor) results in significantly longer recurrence-free survival than surgery alone in high-risk patients[110]. Moreover, the remarkable major pathological response rate of 35.1% suggested that preoperative intervention might be crucial for eradicating micrometastases and enhancing anti-tumor immunity before surgical trauma occurs. The perioperative approach is therefore a superior strategy to traditional adjuvant monotherapy. In a multicenter, randomized, phase II trial, adjuvant sintilimab, compared with active surveillance, significantly prolonged RFS (median 27.7 *vs.* 15.5 months) and decreased the risk of recurrence or death by 46.6%. Whereas the IMbrave050 trial targeted a broader high-risk cohort, this study focused on the biologically aggressive MVI subgroup, thus underscoring the clinical necessity of refined patient stratification. Furthermore, the efficacy and manageable safety profile (grade 3/4 AEs, 12.4%) of fixed 6-month monotherapy provide a potent, economically viable alternative to complex perioperative combinations, particularly in resource-limited settings[111]. The success of sintilimab, in contrast to the neoadjuvant plus adjuvant regimen used in CARES-009, suggests that even monotherapy with a PD-1 inhibitor after surgery alone may provide substantial benefits for this specific high-risk MVI subgroup. Nevertheless, further phase III trials are required to validate the effects of different treatment durations, such as the 1-year regimen in this study, on overall survival.

Parallel to tumor-specific interventions, the optimization of underlying liver disease management is a fundamental pillar of postoperative care. For HBV-related HCC, the administration of potent nucleoside analogues is mandatory to achieve sustained viral suppression, a strategy substantiated to ameliorate long-term oncologic outcomes by mitigating the risk of late recurrence and preventing hepatic decompensation. In the context of HCV infection, achieving a sustained virologic response *via* direct-acting antiviral agents is recommended to preserve hepatic functional reserve and decrease the incidence of second primary tumors, although its effects on early recurrence remain an area of active investigation. Collectively, the landscape of recurrence prevention is evolving from a surveillance-centered model toward proactive adjuvant intervention.

Emerging therapies and future directions in recurrence prevention

Novel therapeutic avenues are currently under rigorous investigation to further enhance post-surgical prognosis. One

promising area involves sophisticated drug delivery systems engineered to target residual tumor cells with high precision. For example, bioabsorbable hydrogels loaded with chemotherapy nanoparticles can be applied directly into the resection cavity. In experimental models, this localized strategy has successfully eradicated microscopic residual disease and prevented local recurrence[112]. Simultaneously, the development of next-generation TACE materials, such as highly flexible embolic microspheres, allows for better navigation through tortuous tumor vasculature. This improvement enhances intra-tumoral drug saturation and might potentially lower relapse rates[113]. These advanced materials are aimed at maximizing cytotoxicity against tumor cells while sparing healthy tissue.

Targeting specific molecular drivers of HCC metastasis is another critical frontier. Preclinical inquiries have elucidated various genes and signaling pathways associated with aggressive phenotypes. For example, the serine/threonine kinase STK33 promotes tumorigenicity, whereas its inhibition has been shown to suppress tumor growth in preclinical xenograft model[114]. Moreover, blocking Krüppel-like factor 8 (KLF8), another molecule implicated in disease progression, triggers apoptosis in HCC cells and curtails their invasive potential[115]. Numerous microRNAs are also associated with recurrence. Downregulation of the tumor-suppressor miR-22 correlates with early relapse, whereas overexpression of others, such as miR-21 and miR-34a, drives oncogenesis.

Elucidation of the molecular landscape of HCC has fostered the development of novel therapeutic strategies. These emerging modalities encompass cancer vaccines targeting tumor-specific neoantigens and chimeric antigen receptor T-cell therapies directed against HCC-specific antigens, such as glypican-3. Concurrently, bispecific antibodies and oncolytic viruses are being engineered to potentiate anti-tumor immunity. Furthermore, nanomedicine provides a versatile platform for modulating the tumor microenvironment. Notably, bioengineered nanoparticles have been deployed to deliver immune checkpoint blockade directly to the liver, where they effectively reprogram the local immune milieu and have been found to suppress tumor growth in preclinical models[116].

Although most of these approaches remain in nascent stages, primarily laboratory research or early clinical trials, they presage the future of recurrence prevention. Combining localized therapies, such as optimized surgical techniques and targeted drug delivery, with systemic treatments, such as immunotherapies, is expected to lead to durable remission. Even biologically aggressive cases may eventually become curable. Continued exploration of HCC genomics, epigenetics, and immunology is expected to uncover new targets. Ultimately, these advances should revolutionize the management landscape by transforming recurrence from an inevitability into a preventable event.

Conclusions and perspectives

HCC remains a formidable global health challenge characterized by high incidence, substantial mortality, frequent postoperative recurrence, and persistently low rates of early-stage diagnosis. Addressing these interconnected problems requires an integrative strategy extending well beyond any single therapeutic modality. Accordingly, this review proposes a comprehensive, surgery-centered framework built upon 3 coordinated and mutually reinforcing pillars: early screening to identify tumors at a curable stage, precision surgical resection to achieve complete oncological clearance, and a systematic recurrence-prevention program to eradicate residual microscopic disease (**Figure 2**).

The future landscape of HCC prevention is undergoing a fundamental shift. Although antiviral therapies remain the cornerstone for mitigating viral risks, the escalating global burden of MASLD requires a novel preventive paradigm. Complementing pharmacological efforts, population-level lifestyle modifications addressing obesity and metabolic syndrome will be essential to curb MASLD-driven HCC. The integration of polygenic risk scores with clinical and metabolic biomarkers is anticipated to further refine individual risk stratification by enabling targeted intervention and facilitating a shift in clinical focus from reactive treatment to proactive disease interception. In parallel, advances in surveillance technology are reshaping the approach to early detection. The field is witnessing a transition from reliance on conventional imaging and serum AFP measurement toward molecular-level early warning systems. Breakthroughs in liquid biopsy technology, particularly multi-target ctDNA methylation profiling and fragmentomics, offer unprecedented sensitivity for detecting hepatocarcinogenesis at the earliest molecular stages. Integrating blood-based assays into structured surveillance for high-risk populations has potential to transform clinical outcomes by significantly enhancing early-stage diagnosis. However, clinical translation requires rigorous validation through prospective, multicenter cohort studies to demonstrate incremental utility over current standards and to optimize screening algorithms.

The emergence of conversion therapy and downstaging strategies is simultaneously redefining the therapeutic boundaries for patients presenting with initially unresectable advanced-stage HCC. The advent of highly efficacious systemic and locoregional regimens, including combinations of ICIs with TKIs, dual immunotherapy protocols, and HAIC, has enabled meaningful tumor regression in a substantial proportion of patients previously considered not to be surgical candidates. Accumulating evidence indicates that successful downstaging followed by R0 resection confers long-term survival comparable to that of primarily resectable disease. This concept of conversion surgery has expanded surgical indications by transforming resection

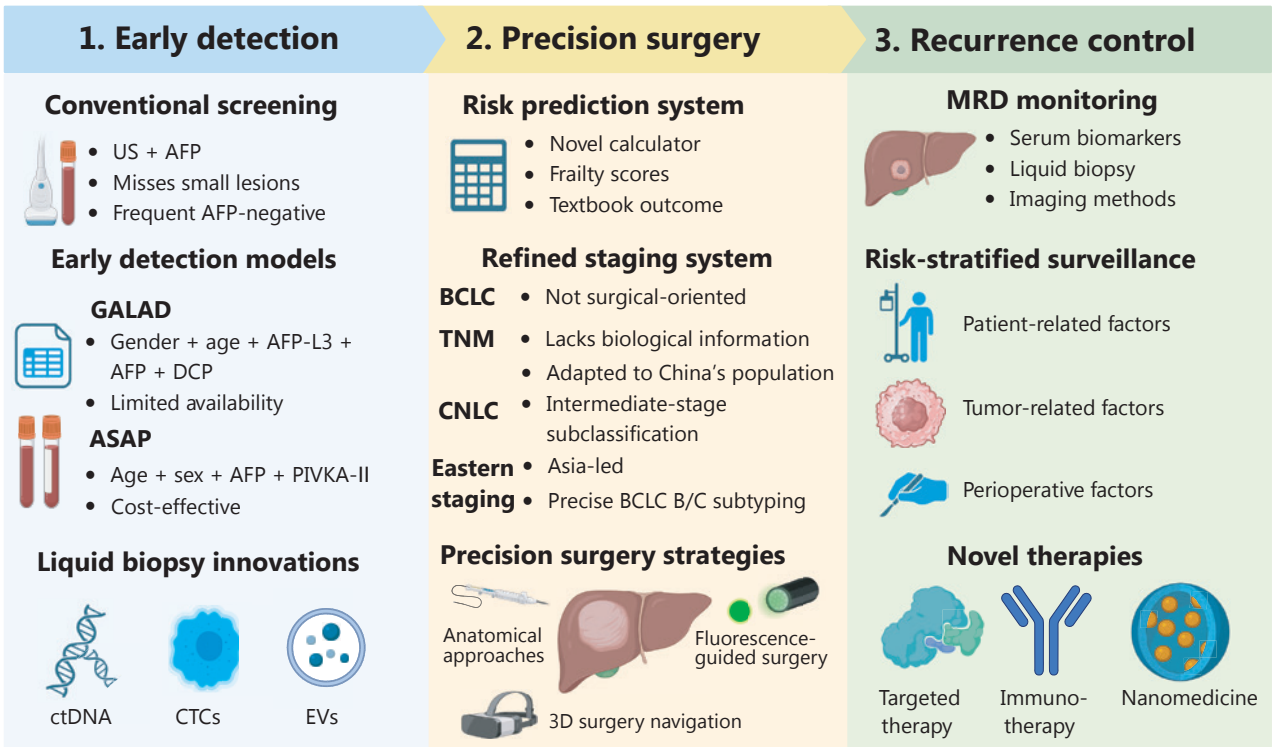


Figure 2 Clinical algorithm for surgery-centered precision management of hepatocellular carcinoma. This diagram delineates the specific elements of each domain of the integrated management strategy. The early detection domain encompasses conventional screening combining US with AFP measurement, which has inherent limitations including suboptimal sensitivity for small lesions and frequent AFP-negative cases in 30%–40% of early-stage HCC. Multi-parameter early detection models address these shortcomings through the GALAD score, integrating gender, age, AFP-L3, AFP, and DCP, alongside the more cost-effective ASAP model, incorporating age, sex, AFP, and PIVKA-II. Both achieve AUROC values exceeding 0.85 across various etiologies. Liquid biopsy innovations further augment surveillance capabilities through ctDNA methylation profiling, CTC enumeration, and EV analysis. The precision surgery domain highlights risk prediction systems incorporating novel calculators, frailty scores, and textbook outcome metrics to optimize patient selection. Refined staging systems address the limitations of the BCLC classification, which was not designed for surgical prognostication, and TNM staging, which lacks biological information. The CNLC system provides intermediate-stage subclassification adapted to China's population, whereas Eastern staging enables precise BCLC B/C subtyping. Precision surgical strategies encompass anatomical approaches, 3D surgery navigation, and fluorescence-guided techniques enhancing tumor localization and margin determination. The recurrence control domain delineates MRD monitoring through serum biomarkers, liquid biopsy platforms, and imaging methods enabling detection of molecular relapse preceding radiological confirmation. Risk-stratified surveillance protocols incorporate patient-related, tumor-related, and perioperative factors to tailor follow-up intensity. Novel therapeutic approaches spanning targeted therapy, immunotherapy combinations, and nanomedicine delivery systems represent the expanding armamentarium for adjuvant intervention. AFP, alpha-fetoprotein; ASAP, age, sex, AFP, and PIVKA-II; AUROC, area under the receiver operating characteristic curve; BCLC, Barcelona Clinic Liver Cancer; CNLC, China Liver Cancer; CTC, circulating tumor cell; ctDNA, circulating tumor DNA; DCP, des-gamma-carboxy prothrombin; EV, extracellular vesicle; GALAD, gender, age, AFP-L3, AFP, and DCP; HCC, hepatocellular carcinoma; MRD, minimal residual disease; PIVKA-II, protein induced by vitamin K absence or antagonist-II; TNM, tumor-node-metastasis; 3D, 3-dimensional; US, ultrasound.

from a treatment reserved for early-stage disease into a viable option across a broader spectrum of tumor burden. Future efforts should focus on identifying reliable predictive biomarkers of conversion response, by optimizing the timing and duration of preoperative systemic therapy, and establishing standardized criteria for resectability reassessment after downstaging, to ensure that surgical intervention is offered precisely when the balance between oncological benefit and operative risk is most favorable.

Precision liver surgery has evolved into a systematic intervention strategy predicated on balancing lesion clearance, organ protection, and damage control. Through individualized surgical planning integrating 3-dimensional volumetric reconstruction, intraoperative navigation, fluorescence imaging, and comprehensive functional reserve assessment, this approach achieves multi-objective optimization by minimizing surgical insult while maximizing long-term oncological benefit. Future advances will depend on interdisciplinary

convergence across medicine, basic sciences, and engineering, with priorities including the development of advanced imaging and navigation systems, artificial intelligence-driven regional hepatic functional assessment, and enhanced intraoperative decision-making precision.

Complementing the technical precision of surgery is the systematic integration of perioperative adjuvant therapies designed to eliminate micrometastatic disease and mitigate the risk of recurrence, which remains the predominant obstacle to long-term cure. The therapeutic armamentarium includes established locoregional approaches such as TACE and emerging immunotherapeutic strategies requiring patient selection according to individual tumor biology. Although data supporting perioperative ICI-based regimens in high-risk resected HCC represent a promising advance, the optimal combination and sequence of such protocols remain under investigation. Furthermore, the incorporation of ctDNA-based MRD monitoring into postoperative surveillance may facilitate a dynamic, personalized approach to adjuvant therapy, in which treatment intensity is modulated according to real-time molecular evidence of the residual tumor burden rather than static clinicopathological risk factors alone.

After curative therapy, an intensive, structured surveillance program is the essential final component of this integrated framework. The combination of high-resolution cross-sectional imaging and longitudinal liquid biopsy assessment facilitates the detection of recurrence in subclinical phases. Early identification is paramount, because it permits the implementation of salvage curative treatments, including repeat resection, radiofrequency ablation, or salvage liver transplantation, before tumor progression precludes these options. This rigorous approach to postoperative monitoring ensures that timely intervention preserves long-term survival outcomes even in the setting of disease relapse.

Much of the evidence supporting this integrated strategy has originated from Asian centers and retrospective cohorts, given the regional prevalence of HBV-related HCC. Although the fundamental principles of precision intervention and active surveillance have broad applicability, validation across diverse geographical populations and etiologies remains essential. Future multicenter prospective studies should specifically evaluate the reproducibility of these surgical and systemic approaches in Western cohorts, in which MAFLD and HCV are predominant drivers. A comprehensive management philosophy that treats surveillance, surgical excellence, and recurrence prevention as inseparable components of a unified care continuum will be essential. Ultimately, systematic implementation of this multimodal framework would offer the most robust pathway to translate scientific advances into tangible survival benefits and to increase the probability of durable cure for patients worldwide.

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Conflict of interest statement

No potential conflicts of interest are disclosed.

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