Review

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# Management of dynamic therapeutic opportunity in hepatocellular carcinoma: Preserving liver function and enabling treatment transitions

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**SUMMARY**: Hepatocellular carcinoma (HCC) is governed by malignant progression and deterioration of the organ in which the cancer arises. Modern management has therefore outgrown static stage-to-treatment allocation. We define dynamic therapeutic opportunity as the time-varying set of clinically credible treatment options available to an individual patient, determined by hepatic reserve, oncological tractability, physiological reserve, prior therapeutic exposure, patient goals, and real-world deliverability. This framework does not replace validated staging systems or liver-function scores; it asks how each intervention changes the circumstances under which the next decision will be made. Evidence for curative-intent conversion remains dominated by selected cohorts, although the interim results of the randomized TALENTop trial provide the first prospective comparative signal supporting resection in a narrowly defined post-induction population. We review liver-sparing surgery, locoregional-systemic integration, conversion therapy, and modifiers such as frailty and metabolic dysfunction-associated steatotic liver disease. We then propose a trial architecture that complements tumor endpoints with hepatic decompensation, sustained ALBI deterioration, subsequent-treatment access, curative-intent transition, functional independence, and patient-reported outcomes. Modern HCC management should evaluate not only whether an intervention controls the present tumor but also whether it preserves, expands, or eliminates the patient's future set of clinically meaningful treatment options.

***Keywords***: treatment sequencing, transarterial chemoembolization, conversion therapy, frailty, ALBI grade, clinical trial endpoints

## 1. Introduction: HCC is not just a cancer

Hepatocellular carcinoma is the predominant form of primary liver cancer and remains a major cause of cancer death worldwide. Its management is unlike that of most solid tumors because prognosis reflects both tumor biology and the trajectory of chronic liver disease. A patient may die from cancer progression, portal-hypertensive complications, hepatic decompensation, treatment-related liver injury, or an interaction among these processes. Contemporary guidelines consequently integrate tumor burden, liver function, performance status, and patient preference rather than relying on anatomical stage alone (*1-4*).

This dual-risk structure creates a paradox. An intervention can suppress tumor growth and extend life, and yet it can also reduce hepatic or physiological reserve enough to make the next effective treatment unsafe. Conversely, a treatment that produces only modest radiological shrinkage may be valuable if it controls disease while preserving the circumstances required for later systemic therapy, ablation, radiotherapy, resection, or transplantation. The clinically relevant unit is therefore not the isolated treatment episode but the evolving treatment pathway.

We use the term "dynamic therapeutic opportunity" to describe the patient's time-varying set of clinically credible systemic, locoregional, and curative-intent options. "Reserve" is retained for internal capacities such as hepatic and physiological reserve; opportunity also depends on prior exposure, access, timing, and preference, and is therefore a state and set of options, not a score.

This Review develops that concept through a structured narrative review. PubMed/MEDLINE and key guideline, trial-registry and society sources were searched for English-language reports published from January 1, 2000 to August 13, 2026, with an emphasis on guidelines, randomized phase 3 trials, prospective

studies, large international cohorts, meta-analyses and concept-defining papers. Historical surgical reports published before 2000 were included when essential. This is not a systematic review and no claim of exhaustive evidence capture is made.

## 2. The Makuuchi legacy: Balancing curability and hepatic safety

A modern account should not portray historical HCC care as simply tumor-centered. The Makuuchi school established a different question: how much of the liver could safely be removed while retaining the possibility of a cure? Decision algorithms based on ascites, serum bilirubin, and indocyanine green retention at 15 minutes linked the extent of resection to functional reserve rather than tumor anatomy alone (*5,6*). Anatomical resection, portal vein embolization, future-liver-remnant assessment, and meticulous parenchymal preservation operationalized the principle that oncological ambition must be bounded by hepatic safety (*7,8*). A Japanese nationwide analysis of 15,597 resections later found lower operative mortality among patients who met Makuuchi's criteria than among those who exceeded them (*9*).

The framework was primarily optimized around the safety and oncological adequacy of an index intervention, although recurrence surveillance, repeat resection, and local treatment were integral to Japanese practice. What was not yet available was the present diversity of effective systemic and multimodal transitions capable of reopening local or surgical options. The contemporary extension is therefore not from episodic to longitudinal care, but from an established longitudinal surgical tradition to a much larger and more frequently changing treatment space.

This historical continuity matters. Dynamic opportunity management extends, rather than repudiates, liver-sparing surgery. The same logic that once constrained the volume of resection now needs to govern the intensity and repetition of TACE, the timing of systemic therapy, the management of portal hypertension, the prevention of sarcopenia, and the selection of conversion procedures (Figure 1).

## 3. Why static treatment allocation is no longer sufficient

Staging systems remain indispensable for prognosis, communication, and evidence-based recommendations. The 2026 BCLC update goes beyond stage allocation by formalising multidisciplinary deliberation, patient vulnerability, biological, psychosocial and contextual factors, and the CUSE framework for complexity, uncertainty, subjectivity, and emotion (*10*). EASL 2025, ESMO 2025, AASLD, the Japanese Society of Hepatology 2025, and the Chinese 2026 guidelines likewise require integration of tumor burden, liver function, comorbidity, local expertise, and patient context (*1-4,11,12*). Dynamic therapeutic opportunity is complementary rather than competitive: BCLC 2026 structures decisions under complexity, whereas the current framework focuses on the longitudinal state and set of options left by each intervention and on how that state should be measured in trials.

Static allocation is especially fragile in BCLC-B disease. Patients grouped together for having "intermediate stage" disease may have a solitary large tumor, multifocal disease within one vascular territory, diffuse bilobar disease, variable portal hypertension, and very different ALBI grades. The same label can therefore encompass patients suitable for selective embolization, systemic therapy, radiation, resection at expert centers, or a planned combination strategy. A one-time label cannot capture how

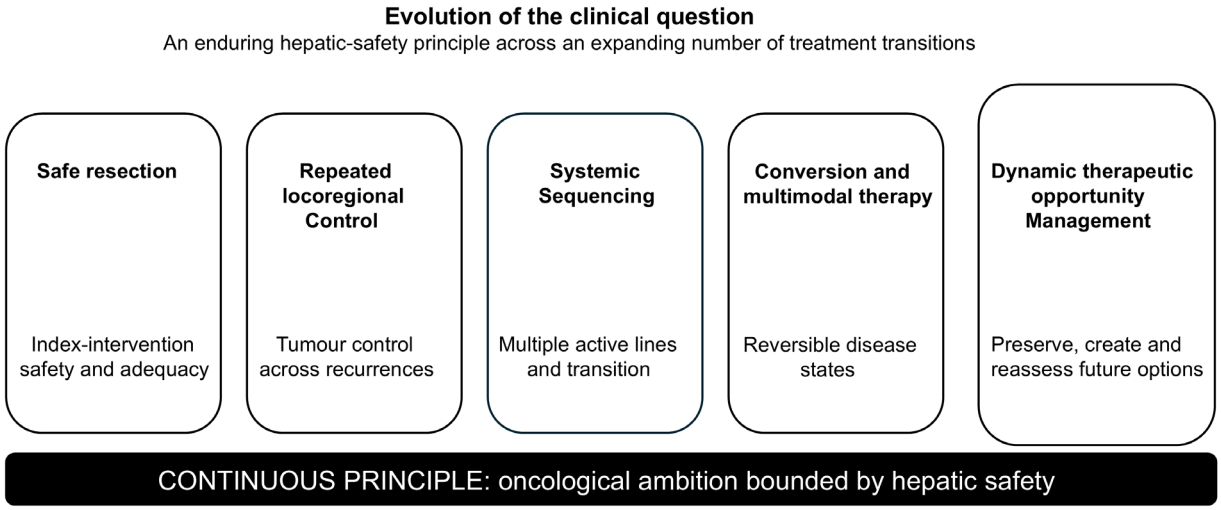


**Figure 1. Evolution of the clinical question in HCC management.** The Makuuchi-era principle of balancing oncological ambition with hepatic safety is not replaced; it remains a continuous thread as the decision horizon expands and the number of possible treatment transitions grows.

the disease state changes after the first intervention.

Dynamic management requires prospective transition rules. Before treatment begins, the team should specify when reassessment will occur, what constitutes adequate benefit, what degree of deterioration in liver function is unacceptable, when a switch or combination will be considered, and what findings will trigger re-review for curative-intent therapy. Without such rules, repeated treatment can become inertia disguised as continuity.

The practical implication is not continuous restaging for its own sake. Reassessment should be linked to a decision that can still be changed. For systemic treatment, early imaging may identify rapid progression, but biochemical toxicity, portal-hypertensive events, and functional decline may require action before radiological progression. For TACE, the relevant checkpoint may be after the first technically adequate treatment, when residual viable burden and the hepatic functional cost can be assessed together. For a patient approaching a local or surgical window, review may need to occur before maximal radiological response because waiting can consume liver function, allow resistant clones to emerge, or eliminate an operable interval. A dynamic model therefore replaces reactive rescue with planned decision windows.

## 4. Therapeutic opportunity as a dynamic clinical state

Dynamic therapeutic opportunity is the clinically credible set of options at a particular time. Four domains help identify what currently limits that set; none is sufficient alone.

Hepatic reserve includes synthetic function, portal-hypertensive status, prior decompensation, renal vulnerability, biliary injury, future liver remnant, and the liver's tolerance of embolization, radiation, surgery, and systemic therapy. Child–Pugh class remains clinically familiar but includes subjective components and coarse categories. The ALBI model, derived from albumin and bilirubin, provides an objective continuous measure and distinguishes among prognoses even within Child–Pugh A disease (*13*). Modified ALBI subdivisions improve granularity, but neither ALBI nor Child–Pugh captures portal hypertension, prior decompensation, or procedure-specific functional risk. Dynamic change is generally more informative than a baseline label alone.

Oncological tractability describes whether the cancer remains amenable to meaningful control. It includes burden, distribution, vascular invasion, extrahepatic spread, growth kinetics, AFP or PIVKA-II dynamics, response depth and durability, and the possibility of local clearance. Circulating tumor DNA (ctDNA) kinetics, Wnt/β-catenin activation, tumor mutational burden, microsatellite instability, and features of the immune microenvironment may eventually refine this domain. At present, however, these are investigational in HCC: Wnt/β-catenin-associated immune exclusion is biologically compelling but not uniformly predictive, and neither ctDNA nor molecular profiling should be used as a routine gatekeeper for immunotherapy or conversion outside the context of a validated assay or clinical study (*14-16*). Tractability is not synonymous with radiological response: stable disease with favorable biology may create a local-treatment window, whereas rapid regrowth after an impressive early response may signal limited surgical benefit.

Physiological reserve includes performance status, frailty, muscle quantity and function, nutrition, cognition, cardiopulmonary reserve, renal function, and comorbidity. ECOG performance status is useful but insufficient. Meta-analyses suggest that sarcopenia is common in HCC and is associated with worse survival across surgical, locoregional, and systemic therapies (*17,18*). Age alone should not determine treatment intensity; the relevant issue is resilience and recovery capacity.

Therapeutic optionality is the remaining space for treatment: the availability of active systemic therapy lines, the feasibility of embolization, ablation, or radiation, transplant or resection candidacy, cumulative toxicity, bleeding and vascular risk, organ function, previous drug exposure, and regional access. Patient goals, financial constraints, travel burden, and institutional expertise can narrow this space even when a treatment is technically available.

The framework is deliberately multidirectional. Tumor response can increase opportunity by reducing burden or vascular invasion. The same intervention can eliminate opportunity through decompensation, immune toxicity, vascular complications, or functional decline. Conversely, antiviral treatment, portal-hypertension management, nutrition, and rehabilitation may expand opportunity without directly shrinking the tumor.

Measurement should be parsimonious enough for routine care. At a minimum, each major reassessment should record tumor distribution and response, albumin, bilirubin, platelet count, renal function, portal-hypertensive events, ECOG performance status, weight or muscle trajectory, treatment toxicity, locally available next options, and patient priorities. Baseline values alone are insufficient: a change from ALBI grade 1 to 2a, a new episode of ascites, or a decline in walking capacity can be more decision-relevant than a stable categorical stage. The purpose is not to create a large checklist but to reveal which domain is becoming rate-limiting. Interventions can then be directed toward that domain—for example, selective rather than lobar embolization, treatment of portal hypertension, dose adaptation, prehabilitation, or an early switch to a non-overlapping mechanism (Figure 2 and Table 1).

## 5. Evidence reshaping treatment boundaries

### 5.1 Advanced HCC: Multiple effective first-line strategies

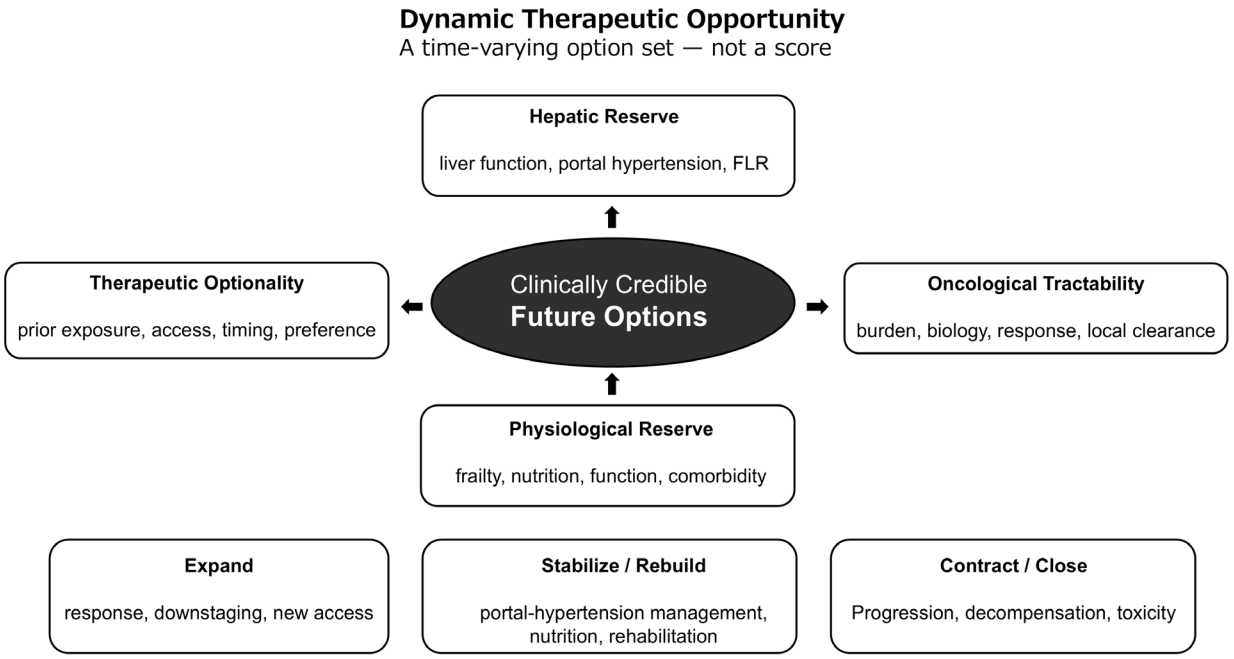


**Figure 2. Dynamic therapeutic opportunity as a time-varying set of options.** Any domain may become rate-limiting. Tumor response or new access can expand options; progression, decompensation, and toxicity can contract them; supportive care can stabilize or reopen them. The diagram is conceptual and does not imply a numerical score. FLR, future liver remnant.

**Table 1. From conventional efficacy endpoints to longitudinal opportunity endpoints**

| Endpoint | Primary construct | Strength | Limitation for HCC opportunity management | Recommended role |
|---|---|---|---|---|
| ORR / DoR | Tumor shrinkage / durability | Early antitumor signal; relevant to conversion | Response does not establish resectability, organ preservation or net benefit | Retain; link to predefined MDT reassessment |
| PFS / RFS | Time to progression or recurrence | Efficient comparison of disease control | Sensitive to assessment rules; may not predict OS or future eligibility | Retain; report with liver and subsequent-treatment data |
| OS | Time to death | Patient-important and regulatory standard | Affected by competing liver events, cross-over, and later therapy | Primary long-term outcome |
| ALBI deterioration | Dynamic liver-function change | Objective and repeatable | Does not capture portal hypertension or clinical decompensation alone | Core longitudinal measure with sustained-change definition |
| Hepatic decompensation | Ascites, bleeding, encephalopathy, jaundice | Directly clinically meaningful | Definitions and competing-risk methods remain inconsistent | Prospectively adjudicated opportunity endpoint |
| Subsequent-treatment access | Receipt of later systemic/ local therapy | Measures pathway preservation | Confounded by access, preference, and practice variation | Report reasons for receipt and non-receipt |
| Curative-intent conversion | Transition to resection, ablation or transplant pathway | Captures state change | Selection bias; definitions vary; not synonymous with ORR | Predefine criteria and central MDT review |
| PROs / functional independence | Patient experience and resilience | Captures benefit beyond imaging | Instrument choice and missing data | Co-primary supportive outcome in longitudinal trials |

The first-line systemic landscape has shifted from one dominant multikinase inhibitor to several mechanistically diverse combinations. IMbrave150, HIMALAYA, CARES-310 and CheckMate 9DW each established survival benefit over sorafenib or an investigator-choice TKI in their trial populations (*19-24*). The early crossing of the CheckMate 9DW survival curves may reflect delayed immune benefit together with early progression and treatment-related risk; the relative contribution of these mechanisms cannot be established from the curves alone. This uncertainty makes baseline hepatic and physiological vulnerability clinically relevant before dual-checkpoint blockade.

These trials do not create one universally best regimen. Therapy that includes bevacizumab requires careful assessment and management of bleeding risk and portal hypertension. Dual-checkpoint blockade avoids continuous anti-VEGF exposure but carries a distinct risk of severe immune-mediated toxicity. TKIs remain relevant when immunotherapy is contraindicated, for later-line therapy, or in healthcare systems where access differs. A treatment-opportunity perspective asks not only which regimen maximizes first-line efficacy but also which preserves a credible second-line pathway for the individual patient.

Evidence after modern immunotherapy is far flimsier than first-line evidence. Regorafenib, cabozantinib, and ramucirumab were validated mainly after sorafenib (*25-27*), while nivolumab-based evidence also arose in an earlier sequencing context (*28*). Post-immunotherapy practice therefore relies heavily on cross-trial reasoning and retrospective cohorts; randomized comparisons of complete sequences remain an unmet need. Such studies should document why subsequent treatment was or was not delivered, organ state at the transition, and whether the next therapy addressed resistance, toxicity, or a new curative-intent opportunity.

### 5.2 Intermediate and locally advanced HCC: From repeated embolization to selectively delivered and systemically integrated locoregional strategies

TACE transformed liver-limited HCC management but benefit depends on selection and technique. Unsuitability should be recognized before treatment or at the first meaningful reassessment when distribution, expected response, or hepatic vulnerability makes an embolization-led strategy unlikely to provide net benefit; refractoriness is declared only after inadequate response despite technically appropriate treatment. Repeated TACE has been associated with persistent ALBI deterioration, and a randomized-cohort secondary analysis documented 3-month ALBI-grade deterioration even after selective procedures (*29-33*). These data support reassessment, not an automatic prohibition: tumor burden, selectivity, recovery within 90 days, and alternatives must be considered together.

Randomized phase 3 trials now define a more complex boundary. EMERALD-1 improved PFS with durvalumab, bevacizumab, and TACE (*34*). LEAP-012 improved PFS, but failed to demonstrate a statistically significant overall survival (OS) benefit; the sponsors subsequently ended the study after a prespecified interim assessment indicated a low probability of meeting the protocol-defined OS threshold (*35,36*). At ASCO 2026, the conference-reported EMERALD-3 trial showed improved PFS with STRIDE plus lenvatinib and TACE *vs.* TACE alone (median 13.0 *vs.* 9.8 months; HR 0.70), with an immature, non-significant OS trend and substantially more grade 3–4 treatment-related adverse events (*37*). Full peer-reviewed reporting of hepatic trajectories, subsequent treatment, and mature OS remains essential. Together, these studies show that longer PFS does not by itself establish preserved survival, liver function, or future treatment access.

Selectively delivered strategies broaden the choice beyond TACE. In FOHAIC-1, modified FOLFOX hepatic arterial infusion chemotherapy (HAIC) improved median OS *vs.* sorafenib in predominantly high-burden, locally advanced HCC and enabled downstaging; another randomized trial in portal-vein invasion favored sorafenib plus FOLFOX-HAIC (*38,39*). These Asia-predominant data require attention to expertise, catheter risk, and external validity but support HAIC as a non-embolizing option when high tumor burden or a portal vein tumor thrombus makes repeated TACE unattractive.

Transarterial radioembolization (TARE) and stereotactic body radiotherapy (SBRT) can similarly concentrate treatment while limiting injury to the uninvolved liver. Randomized phase 2 comparisons reported longer time to progression with yttrium-90 TARE than with conventional or drug-eluting-bead TACE in selected patients (*40,41*). NRG/RTOG 1112 found that SBRT followed by sorafenib improved progression-free survival (PFS) and showed an adjusted OS advantage *vs.* sorafenib alone in locally advanced HCC, although the unadjusted primary comparison narrowly missed its prespecified significance threshold (*42*). These modalities are not intrinsically low-risk to the liver: dosimetry, treated volume, baseline function, and portal hypertension determine risk. Their opportunity value lies in avoiding repeated whole-territory ischemia, treating vascular invasion or focal residual disease, and creating a bridge to resection, ablation, or transplantation at expert centers.

Trials should therefore report selectivity, treated liver volume, procedure number, HAIC catheter complications, TARE dosimetry, SBRT dose-volume constraints, ALBI trajectory, decompensation, and subsequent-treatment eligibility. Technique is part of the causal pathway; none of these modalities is intrinsically organ-sparing.

### 5.3 Early and potentially resectable HCC: Perioperative uncertainty

Perioperative evidence is no longer uniformly negative. The early recurrence-free-survival advantage of adjuvant atezolizumab plus bevacizumab in IMbrave050 was not sustained with longer follow-up (*43,44*). By contrast, CARES-009, a randomized phase 2/3 trial in resectable HCC at intermediate or high recurrence risk, reported longer event-free survival with perioperative camrelizumab plus rivoceranib than with surgery alone (median 42.1 *vs.* 19.4 months; HR: 0.59), with grade 3 or worse treatment-related adverse events in approximately 38% of the patients (*45*). Generalizability beyond the trial population and mature OS remain unresolved.

The contrast is not a simple negative-versus-positive verdict. IMbrave050 cautions against adopting an advanced-disease regimen for purely postoperative use; CARES-009 suggests that perioperative timing, biological selection, and population may alter the result. Neoadjuvant exposure can test biology but can also delay surgery or cause immune and vascular toxicity. Trials must report the proportion reaching surgery, pathological response, postoperative liver function, recurrence patterns, and OS, and not EFS alone. (Table 2)

## 6. Conversion as an MDT-governed transition

Conversion is not a drug regimen. It is a transition from a disease state in which curative-intent treatment has an unfavorable or infeasible risk–benefit ratio to one in which such treatment becomes feasible. This definition separates conversion from neoadjuvant therapy, which begins with a planned operation, and from downstaging, which describes a change in measurable disease but does not by itself establish net surgical benefit.

Conversion evidence remains dominated by selected cohorts but is no longer entirely non-randomized. In the interim phase 3 TALENTop analysis, patients with locally advanced HCC, macrovascular invasion, and no extrahepatic spread in whom PR or SD was achieved after atezolizumab plus bevacizumab and who were already judged suitable for R0 resection were randomized to resection followed by therapy or continued systemic treatment. Median time to treatment failure was 20.4 *vs.* 11.8 months (HR 0.60); OS was immature (*46*). This is the first prospective comparative signal for surgery after induction in a narrowly defined population, not evidence that all responding or once-unresectable HCC should be resected. RACB and retrospective cohorts are informative for feasibility and selection but remain vulnerable to guarantee-time bias (*47-49*).

An MDT conversion review should use three safety gates. Biological safety asks whether response is durable rather than transient: sustained AFP or PIVKA-

**Table 2. Landmark evidence that changes treatment boundaries—and what it does not yet establish**

| Clinical problem / study | Primary construct | Liver/opportunity information | Implication for the framework |
|---|---|---|---|
| Advanced first line—IMbrave150 | Phase 3; atezolizumab–bevacizumab improved OS and PFS *vs* sorafenib | Selected Child–Pugh A population; later pathways not randomized | Establishes high-efficacy first line, not an optimal sequence |
| Advanced first line—HIMALAYA | Phase 3; STRIDE improved OS *vs* sorafenib | No continuous anti-VEGF exposure; immune toxicity can alter reserve | Offers a mechanistically distinct option; selection matters |
| Advanced first line—CheckMate 9DW | Phase 3; nivolumab–ipilimumab improved OS *vs* lenvatinib/sorafenib | Early crossing of curves and immune-related mortality require attention | Median OS alone does not describe early risk or future options |
| TACE combination—EMERALD-1 | Phase 3; durvalumab–bevacizumab–TACE improved PFS | OS and longitudinal hepatic-state data needed | Validates integration; does not yet prove preserved opportunity |
| TACE combination—LEAP-012 | Phase 3; improved PFS but no statistically significant OS benefit; study discontinued for low probability of meeting OS threshold | Liver-function trajectory and subsequent treatment incompletely reported | Demonstrates why PFS cannot stand alone |
| TACE combination—EMERALD-3 | Phase 3 conference abstract; STRIDE–lenvatinib–TACE improved PFS; OS immature | Grade 3–4 toxicity increased; longitudinal hepatic-state data awaited | Promising but requires full peer review and mature OS |
| Adjuvant—IMbrave050 update | Phase 3; early RFS benefit not sustained; updated HR 0.90 | One year of treatment after curative-intent therapy adds exposure and toxicity | Warns against premature extrapolation of intermediate endpoints |
| Perioperative—CARES-009 | Randomized phase 2/3; perioperative camrelizumab–rivoceranib improved EFS vs surgery | More treatment exposure and grade ≥ 3 toxicity; OS immature | Timing and selection may determine perioperative value |
| Conversion—TALENTop interim | Randomized phase 3; post-induction resection improved TTF *vs*. continued atezolizumab–bevacizumab | Only patients with PR/SD, macrovascular invasion, no extrahepatic spread, and R0-resectability | First comparative signal; not generalizable to all conversion candidates |

II decline, control of vascular invasion and extrahepatic disease, and radiological stability for approximately 3–4 months are reasonable expert-practice signals, not validated universal cut-offs. Washout safety addresses wound healing, bleeding, and immune injury. The bevacizumab label requires it to be withheld for at least 28 days before elective surgery; many hepatobiliary teams use approximately 4–6 weeks, but the exact interval should accord with the agent, procedure, toxicity, and institutional protocol (*50*). Active or recent immune-related hepatitis must be resolved and hepatic recovery demonstrated before surgery. Future-liver-remnant safety requires volumetric adequacy plus functional assessment appropriate to the center, such as ICG-R15 or 99mTc-galactosyl human serum albumin scintigraphy, rather than anatomy alone. R0 technical feasibility is therefore necessary but insufficient.

These gates resolve the apparent conflict between oncological tractability and marginal hepatic reserve. When tumor response makes local clearance attractive but reserve is borderline, the default is not maximal treatment intensity. The team should first ask whether the same oncological objective can be achieved with a smaller resection, ablation, SBRT, TARE, or staged strategy; treat portal hypertension and malnutrition; and repeat the functional assessment. If reserve remains the rate-limiting domain, preserving the effective systemic regimen or choosing lower-hepatic-cost consolidation may offer greater net benefit than immediate major hepatectomy.

Liver transplantation creates a distinct downstaging and bridging window because pre-transplant immune activation may persist after tumor control. Small series linked intervals shorter than 3 months between the last immune-checkpoint inhibitor dose and transplantation with severe rejection, and an individual-patient-data meta-analysis of 91 recipients reported rejection in 26.4%; a modeled median washout of 94 days corresponded to a rejection probability of 20% or less (*51,52*). These observational estimates do not establish a universal 90-day rule. Drug type, immune-related adverse events, urgency, donor timing, and immunosuppression protocol all matter, so ICI use for bridging or downstaging should trigger early transplant-center review and a documented, center-specific washout plan.

TALENTop also clarifies endpoint design. Its primary result concerns time to treatment failure, not mature OS, and applies only after induction response and resectability selection. Future studies should predefine the date of conversion eligibility, resectability criteria, central MDT review, competing local options, postoperative liver function, treatment-free survival, recurrence, and patient-reported recovery. Because randomization occurred only after induction response and confirmation of R0 resectability, TALENTop cannot estimate the intention-to-treat effect of an induction-to-conversion strategy in all initially unresectable patients.

The principal analytical challenge is guarantee-time bias: patients must survive, respond, and remain fit long enough to undergo conversion, so direct comparisons to non-converted patients will exaggerate benefit. Landmark analyses, target-trial emulation, and time-dependent exposure models can reduce but not eliminate confounding. Randomization at the moment of resectability may sometimes be feasible—for example, continued systemic therapy *vs.* local consolidation—but patient and clinician preferences will be strong. Even without randomization, prospective registries can improve inference by recording the first date on which conversion was considered, reasons for rejection, central review findings, and outcomes for all eligible patients, not only those who reached the operating room (Figure 3 and Table 3).

## 7. Aging, frailty, and MASLD are modifiers, not appendices

The HCC population is aging, particularly in countries with successful viral hepatitis control. Chronological age is a poor substitute for physiological reserve. Older adults with preserved function may tolerate intensive therapy, whereas younger patients with decompensated cirrhosis, sarcopenia, or cognitive impairment may have little recovery capacity. Comprehensive geriatric and nutritional assessment can reveal vulnerabilities that ECOG performance status misses.

Sarcopenia is especially relevant because it can be both a baseline risk and a treatment-emergent loss of reserve. A meta-analysis of 42 studies estimated a prevalence of 39% and an adjusted hazard ratio for overall mortality of 1.84 (*17*). Among patients receiving systemic therapy, the pooled prevalence of low skeletal-muscle mass was approximately 43%, with worse OS and PFS (*18*). These associations do not prove that reversing sarcopenia improves survival, but they justify routine screening, resistance exercise, nutritional support, and early rehabilitation as opportunity-preserving interventions.

MASLD changes both surveillance and treatment. HCC can occur without cirrhosis, and yet its absolute incidence in non-cirrhotic MASLD is generally too low for population-wide surveillance. Current guidance prioritizes cirrhosis and recommends stepwise fibrosis assessment: a simple blood-based score such as FIB-4 can identify low-risk patients, while an indeterminate or elevated result should prompt second-line assessment with vibration-controlled transient elastography (VCTE/FibroScan) or an equivalent validated method (*53,54*). These tools stratify fibrosis risk; they do not replace HCC staging or direct tumor treatment. Once HCC develops, cardiovascular, renal, and metabolic comorbidity can influence surgical risk, anti-VEGF eligibility, and recovery. These variables belong inside the core opportunity assessment, not in an etiological footnote.

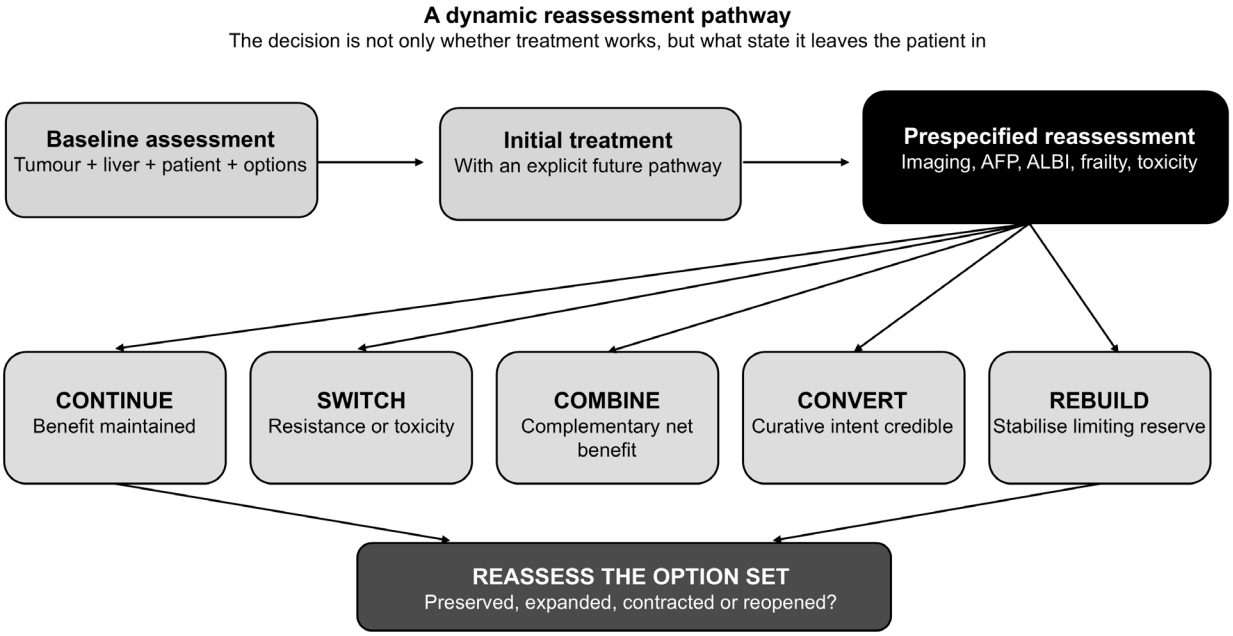


**Figure 3. Dynamic reassessment pathway.** Prespecified review can lead to continuation, switching, combination, conversion, or stabilization/rebuilding of a rate-limiting reserve. Each transition is followed by reassessment of the clinically credible set of options.

**Table 3. Illustrative decision matrix for dynamic therapeutic-opportunity reassessment**

| Scenario and trigger | Domain signal | Question for the MDT | Possible transition | Required clarification |
|---|---|---|---|---|
| A. After one round of technically adequate TACE: CR/PR, but ALBI 1 → 2b | Tumor improves; hepatic reserve may be rate-limiting | Is the decline persistent and attributable to TACE, and does expected benefit justify further embolization? | Trigger review of alternatives, including systemic therapy or focal ablation/SBRT; defer repeat TACE while recovery and selectivity are assessed. | ALBI recovery, portal-hypertensive events, treated volume, residual distribution, and available alternatives. |
| B. IImmune-checkpoint inhibitor + anti-VEGF for 6 months: SD, AFP falls, 20% shrinkage, ALBI 1 | Reserve stable; biology favorable; local-clearance potential | Does the distribution now permit a credible curative or consolidative option with acceptable hepatic cost? | Formal review for resection, SBRT, or TARE while comparing therapy to continued systemic control. | Durability, resectability/targetability, anti-VEGF washout. and FLR safety. |
| C. Third line: slow progression with new mild ascites | Cause and reversibility of hepatic deterioration are uncertain | Is ascites tumor-related, treatment-related or cirrhotic, and what is the immediate oncological risk? | Consider temporary interruption or dose adaptation while investigating and treating reversible causes; escalation may remain appropriate if tumor risk dominates. | Infection, portal-vein thrombosis, renal function, diuretic response, tumor kinetics, and current treatment benefit. |
| Conflict rule | Oncological tractability favors intensity, but hepatic reserve is marginal | Identify the rate-limiting domain and ask whether the same tumor objective can be achieved at lower hepatic cost. | Prefer smaller resection, ablation, SBRT/TARE, staged therapy or continued effective systemic treatment; defer major intervention if functional safety remains inadequate. | Document the alternative rejected, the locally defined safety threshold, patient preference, and the date for repeat MDT review; no universal numerical threshold has been validated. |

## 8. From an MDT meeting to longitudinal team-based care

Multidisciplinary care is associated with better treatment receipt and survival, although the supporting studies are observational and heterogeneous. A meta-analysis of 12 studies including 15,365 patients found an association between multidisciplinary care and improved OS, but heterogeneity exceeded 90% for several outcomes (*55*). This finding supports team care while cautioning against attributing all benefit to the meeting itself.

Three concepts should be distinguished. An MDT meeting is a time-limited case discussion; multimodality treatment combines interventions; longitudinal team-based care assigns responsibility for reassessment, supportive care, and transitions across the disease course. The last

model is the organizational counterpart to management of dynamic therapeutic opportunity.

Core membership may include hepatology, hepatobiliary surgery, transplant medicine, interventional and diagnostic radiology, radiation oncology, medical oncology, pathology, specialized nursing, nutrition, rehabilitation, geriatrics, and palliative care. Not every discipline must attend every discussion. What matters is a trigger-based process: review at diagnosis, after a prespecified number of treatment cycles or TACE sessions, at meaningful response, at hepatic or functional deterioration, at progression, and whenever curative-intent eligibility might change. The patient and family should be represented in the decision, directly or through structured elicitation of goals.

Implementation requires ownership. One clinician or nurse navigator should maintain the longitudinal problem list, confirm that reassessment occurs on schedule, and record the chosen transition together with the alternatives considered. The MDT output should state not only the recommended treatment but also the contingency plan: what finding would prompt continuation, switch, combination, conversion review, or supportive-care intensification. This reduces the risk that responsibility disappears between specialties. Institutions should audit the time from trigger to review, the proportion of eligible patients receiving the recommended next therapy, unplanned admissions for decompensation, and discordance between patient goals and delivered care. Such measures evaluate the care pathway rather than the frequency of meetings.

## 9. Redesigning endpoints around clinical-state preservation

OS remains the most consequential endpoint, but it is increasingly affected by long post-progression survival, cross-over, subsequent treatment, and competing liver-related events. ORR and PFS are valuable measures of tumor effect; they cannot by themselves show whether a therapy leaves the patient fit for the next intervention. Both the divergence between early and updated IMbrave050 results and the still-maturing survival data after TACE combinations illustrate the danger of treating an intermediate endpoint as a complete account of clinical value.

Hepatic decompensation should be treated as a major clinical event and not merely an adverse-event category. A 2025 proposal argued for its incorporation as a prognostically relevant intermediate endpoint during systemic therapy (*56*). Standardization is essential: ascites requiring treatment, variceal bleeding, overt encephalopathy, and clinically meaningful jaundice should be defined prospectively, with competing-risk methods that account for tumor progression and death.

We propose a two-layer endpoint architecture. The tumor layer includes ORR, duration of response, PFS, recurrence-free survival, pathological response, and OS. The opportunity layer includes time to first hepatic decompensation, time to sustained ALBI deterioration, maintenance of Child–Pugh A or ALBI grade 1/2a, access to second- and third-line therapy, time to loss of local-treatment eligibility, conversion to curative-intent treatment, treatment-free survival, functional independence, and patient-reported outcomes. A future composite such as "time with an effective treatment option remaining" is conceptually attractive but not ready for regulatory use because option availability varies by geography, expertise, and patient preference. This two-layer architecture operationalizes components of dynamic therapeutic opportunity without collapsing them into a single DTO score; components should be reported separately or combined only through a prespecified hierarchical or multistate analysis.

Endpoint collection should continue after protocol therapy. Without documenting subsequent treatment, local procedures, transplant evaluation, rehabilitation, and reasons for treatment non-receipt, trials cannot determine whether a therapy preserved opportunity or merely postponed radiographic progression.

This approach also changes statistical design. HCC pathways are naturally represented as multistate processes: compensated disease, treatment response, hepatic deterioration, progression, curative-intent transition, recurrence, and death. A conventional Kaplan–Meier curve collapses these clinically distinct transitions into one event time. Multistate models can estimate how an intervention changes the probability of preserving an opportunity-preserved state over time; joint models can relate repeated ALBI or functional measurements to progression and mortality.

A hierarchical composite analyzed with the win ratio could compare patient pairs in an order that reflects clinical priority: death first, then severe hepatic decompensation, then failure to achieve predefined curative-intent conversion, and finally progression (*57*). This prevents an earlier but less important radiological event from outweighing survival or organ failure, although the hierarchy, time windows, and conversion eligibility must be prespecified and sensitivity-tested. When proportional hazards are doubtful—as with early crossing under immunotherapy—restricted mean survival time (RMST) at clinically chosen horizons can express event-free time gained without assuming a constant hazard ratio (*58*). Win-ratio and RMST analyses should be complementary estimands, not post hoc devices used to rescue a negative primary endpoint.

## 10. A research agenda for dynamic HCC management

The framework is useful only if it generates testable work. Five priorities follow.

(*i*) Define dynamic therapeutic opportunity operationally using repeated, domain-specific variables

rather than an unvalidated summary score.

(*ii*) Standardize sustained ALBI deterioration and clinically adjudicated hepatic decompensation, with competing-risk analyses.

(*iii*) Require prospective trials of systemic therapy to capture subsequent local treatment, transplant assessment, and curative-intent conversion using predefined criteria.

(*iv*) Compare complete treatment strategies in pragmatic trials, including switch timing after TACE and sequencing after immunotherapy.

(*v*) Create a core longitudinal dataset incorporating frailty, sarcopenia, patient-reported outcomes, barriers to access, and reasons that eligible treatment was not delivered.

Methodologically, multistate and joint longitudinal-survival models are likely to be more informative than conventional analyses that treat each line as independent. Clinically, digital monitoring and imaging analytics may assist with repeated assessment, but they should be evaluated against decisions that matter: prevention of decompensation, timely transition, and preservation of curative-intent eligibility. AI and liquid biopsy are tools, not paradigms; their value depends on whether they improve those decisions.

Healthcare economics and equity must be built into this agenda. A sequence that is biologically attractive but unavailable after the first line does not preserve real-world optionality. Trials and registries should therefore report geographic region, insurance or reimbursement constraints, travel burden, referral delay, and access to transplant, radiation and interventional expertise. Cost-effectiveness models should value avoided decompensation, maintained independence, and access to later therapy rather than drug acquisition and progression alone. This is particularly important because the framework could otherwise widen disparities by favoring centers with the most treatment options. A valid opportunity assessment must report biological eligibility and actual deliverability as separate dimensions, identify reasons for the gap, and avoid attributing access-related non-receipt to the biological effect of the initial therapy.

## 11. Conclusion

The central question in contemporary HCC care is no longer merely which treatment is best for a given stage, but how each intervention changes the patient's future therapeutic possibilities. Preserving liver function is therefore not an ancillary goal and not the whole goal; it is one component of maintaining therapeutic opportunity.

The next paradigm will be defined by the ability to control cancer, prevent hepatic decompensation, preserve physiological resilience, enable treatment transitions, and repeatedly reassess curative-intent options. Static staging and established efficacy endpoints remain necessary, but they should be embedded within longitudinal, multidisciplinary management. The decisive measure of progress will be not only how long a treatment delays tumor growth but also how effectively it keeps meaningful treatment options open.

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