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REVIEW

When Resectability Emerges After Systemic Therapy in Hepatocellular Carcinoma: A Proposed Response-Guided Consolidation Framework

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Abstract: Immune checkpoint inhibitor–based combination therapies have increased the likelihood that a subset of patients with initially unresectable hepatocellular carcinoma (HCC) may achieve sufficient tumor regression to become technically resectable However, when resectability emerges systemic therapy, the optimal next step remains uncertain. Surgical resection may eradicate residual macroscopic disease, whereas continued systemic therapy may help maintain control of occult micrometastatic disease. In this review, we summarize the available evidence on surgical consolidation after conversion and propose a conceptual response-guided consolidation framework to support post-conversion decision-making. The current evidence base remains dominated by retrospective comparative studies, although early randomized data have recently emerged in selected populations. Overall, surgical consolidation appears feasible and may improve progression-related outcomes in carefully selected responders, but definitive survival benefit across all response categories remains unproven. Within the proposed framework, partial response appears to represent the most consistent clinical scenario supporting surgery, stable disease should be interpreted as a heterogeneous category requiring further biological and radiographic discrimination, and complete response remains the most uncertain setting in which surgery may not always be necessary. Beyond radiographic response alone, pathological response and biomarker-based predictive enrichment may help refine future selection strategies. We therefore suggest that post-conversion resectability should be viewed not simply as a technical surgical endpoint, but as a therapeutic decision point requiring multidisciplinary assessment of anatomical feasibility, response depth and durability, hepatic reserve, and biological risk. This proposed framework is intended as a practical interim model rather than an established clinical standard and requires prospective validation.

Keywords: hepatocellular carcinoma, conversion therapy, surgical consolidation, resectability, systemic therapy, response-guided framework, partial response, complete response

Introduction

The therapeutic landscape of hepatocellular carcinoma (HCC) has changed substantially in the era of immune checkpoint inhibitor–based combination therapies. Phase III trials have demonstrated improved objective response rates and survival compared with prior standards, thereby increasing the proportion of patients who achieve meaningful tumor regression.[1–3] As a result, a subset of patients with initially unresectable disease may become technically resectable after treatment, a process commonly referred to as conversion to resectability.[4–7]

While this development represents an important therapeutic advance, it has also created a new clinical dilemma. When systemic therapy renders disease technically resectable, should surgery be undertaken as consolidation to eradicate residual macroscopic disease, or should systemic therapy be continued to maintain tumor control? Current international guidelines acknowledge the possibility of downstaging and conversion, but provide limited direction regarding this specific post-conversion decision point.[8,9] Consequently, management remains heterogeneous across institutions and multidisciplinary teams.

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This uncertainty reflects the gap between technical feasibility and clinical decision-making. Although tumor shrinkage may permit R0 resection (complete macroscopic and microscopic removal with negative margins), it does not necessarily imply eradication of viable tumor cells or occult micrometastatic disease. At the same time, prolonged systemic therapy carries cumulative toxicity, financial burden, and uncertainty regarding optimal duration.[10–13] Against this background, a structured approach to post-conversion management is needed. In this review, we summarize the available clinical evidence on surgical consolidation after conversion and propose a response-guided, conceptual framework to support multidisciplinary decision-making when resectability emerges after systemic therapy in HCC.

Redefining Resectability in the Systemic Therapy Era

The advent of effective systemic therapies has fundamentally altered this landscape. Tumor burden and vascular invasion, and occasionally limited extrahepatic disease, may regress under treatment, converting disease previously deemed unresectable into technically resectable status. Downstaging and conversion are increasingly reported in contemporary cohorts, particularly with immune checkpoint inhibitor–based combinations.[4–7] Resectability has therefore evolved from a baseline classification to a dynamic state that may emerge during the course of therapy.

However, the emergence of technical resectability after systemic therapy does not necessarily indicate durable oncologic control. Technical resectability reflects the anatomical possibility of complete macroscopic removal, whereas biological eradication implies elimination of viable tumor cells and suppression of microscopic disease. These two concepts may not fully coincide. Post-conversion surgical series have shown that radiographic response does not uniformly predict pathological clearance, underscoring the distinction between technical feasibility and biological response.[14,15]

In the systemic therapy era, resectability should therefore be viewed not simply as a surgical endpoint, but as a therapeutic decision point. It marks a stage at which anatomical feasibility, depth and durability of response, hepatic reserve, and overall disease biology must be reconsidered together. This distinction forms the conceptual basis for a response-guided consolidation strategy.

Current Clinical Evidence for Surgical Consolidation After Conversion

Surgical Consolidation After Systemic Therapy–Induced Conversion

Evidence directly addressing whether surgical resection should be performed after systemic therapy renders hepatocellular carcinoma (HCC) technically resectable remains limited but is gradually accumulating.

Several multicenter retrospective cohorts have evaluated patients with initially unresectable HCC who achieved objective response or disease control following immune checkpoint inhibitor–based systemic therapy and subsequently met criteria for curative-intent resection.[10,14,16] In these studies, outcomes of patients undergoing surgical consolidation were compared with those of responders who continued systemic therapy without surgery.

Across analyses employing multivariable adjustment or propensity score matching, surgical resection after systemic therapy has been associated with improved progression-related endpoints. Hazard ratios for recurrence or progression in resected patients have generally ranged between approximately 0.5 and 0.7 in adjusted models.[10,13] Median recurrence-free survival frequently exceeded 18–24 months in surgical cohorts, compared with approximately 8–14 months among non-surgically managed responders.[5,10,17]

Overall survival findings have been more heterogeneous but directionally similar. In cohorts enriched for patients achieving partial response (PR), median overall survival in resected patients often exceeded 30 months, whereas patients continuing systemic therapy alone demonstrated shorter survival durations.[10,11,17] However, these comparisons are inherently subject to selection bias, as surgical candidates typically retained preserved liver function and favorable performance status.

Prospective evidence remains sparse. A recent phase III study enrolled patients with macrovascular invasion who achieved disease control after first-line immunotherapy-based therapy and were subsequently deemed resectable.[13] Participants were randomized to surgical resection followed by maintenance therapy versus continued systemic therapy alone. The primary endpoint of time to treatment failure favored the surgical arm (hazard ratio approximately 0.6), whereas overall survival data were immature at the time of reporting. Although limited to a defined subgroup, this trial represents the first randomized comparison in the post-conversion setting.

Collectively, available systemic therapy–based studies suggest that surgical consolidation after conversion is feasible and may improve progression-related outcomes in selected responders. Definitive survival benefit across all response categories, however, remains unproven.

Evidence From Multimodal Downstaging Strategies

Data from locoregional downstaging strategies provide additional, although indirect, insight into post-conversion management. In a retrospective TACE cohort of 831 initially unresectable patients, 82 were successfully downstaged to resectable disease; among these, patients who underwent salvage resection had longer median overall survival than those who continued TACE alone (49 vs 31 months; HR 0.337, 95% CI 0.184–0.616), suggesting that local curative treatment may confer additional benefit after successful downstaging.[18]

Similarly, retrospective studies of Y-90 radioembolization have shown that a subset of initially unresectable patients can be converted to resection or transplantation, with encouraging long-term survival observed in those who ultimately undergo curative-intent treatment.[19–21]

However, these studies involve heterogeneous treatment paradigms and highly selected populations, and they do not isolate the independent effect of systemic therapy–induced response. Accordingly, they should be viewed as supportive and hypothesis-generating rather than definitive evidence for the specific decision node of surgery versus continued systemic therapy after systemic conversion.[10,22]

Evidence Landscape

Overall, current data indicate that technical resectability can be achieved after systemic or multimodal therapy in a subset of patients. Surgical consolidation in selected responders is associated with favorable progression-related outcomes, but most evidence derives from retrospective analyses and remains vulnerable to selection bias. Randomized validation across broader response strata is limited, underscoring the need for structured, biologically informed decision-making after conversion. The principal direct comparative studies informing this decision point are summarized in Table 1.

A Response-Guided Consolidation Framework

When resectability emerges after systemic therapy in hepatocellular carcinoma, the central question is not merely whether surgery is technically feasible, but whether surgical consolidation is biologically and clinically justified. Given

Table 1 Direct Comparative Studies of Surgical Versus Non-Surgical Management After Conversion in HCC

Study	Design	Population	Response Category	Comparison	Key Endpoint(s)	Main Finding
TALENTop	Multicenter, open-label, randomized phase III trial	MVI-positive HCC without EHS that became resectable after induction atezolizumab plus bevacizumab	PR / SD	Resection followed by maintenance Atezo+Bev vs continued Atezo +Bev	TTF, OS	Surgical consolidation significantly improved TTF; OS data remained immature
GUIDANCE003	Multicenter retrospective study	Initially unresectable HCC after conversion therapy	PR / CR	Hepatectomy vs non-surgical management	OS, PFS	Hepatectomy was associated with improved survival in selected responders
Watch-and-Wait Study	Retrospective propensity score-matched study	Initially unresectable HCC with radiographic CR after conversion therapy	CR	Resection vs surveillance	OS, PFS	No clear OS advantage of surgery in CR; progression-related outcomes favored resection

Abbreviations: HCC, hepatocellular carcinoma; MVI, macrovascular invasion; EHS, extrahepatic spread; PR, partial response; SD, stable disease; CR, complete response; TTF, time to treatment failure; OS, overall survival; PFS, progression-free survival.

the heterogeneity of treatment response, residual tumor burden, and underlying disease biology, a uniform strategy is unlikely to be appropriate. Instead, consolidation decisions should be informed by both the depth and durability of response. On this basis, we propose a response-guided, conceptual framework structured around three principal response categories: stable disease (SD), partial response (PR), and complete response (CR). This framework is intended to support multidisciplinary discussion and hypothesis generation, rather than to function as a validated clinical algorithm.

Stable Disease: A Heterogeneous Category

Stable disease (SD) after systemic therapy should not be regarded as a biologically uniform state. Although SD does not meet formal criteria for objective response, it encompasses a broad spectrum of tumor behavior and does not necessarily indicate treatment resistance. In particular, SD with measurable tumor shrinkage may differ meaningfully from SD with slight interval growth or no meaningful change. Conceptually, SD accompanied by shrinkage may reflect biological sensitivity closer to partial response, whereas SD with interval enlargement may suggest emerging resistance.[23]

This distinction is increasingly supported by HCC-specific evidence. A recent study showed that patients with SD and tumor shrinkage could still derive benefit from surgery after immune-based therapy, whereas those with SD without shrinkage did not appear to benefit to the same extent.[24]

Accordingly, surgical consolidation in SD should remain individualized. SD alone should neither mandate nor automatically preclude resection; rather, decisions should integrate the direction and durability of tumor change, adequacy of hepatic reserve, technical feasibility, and the broader clinical context.

Partial Response: The Most Consistent Clinical Scenario

Partial response (PR) appears to represent the most clinically persuasive setting for surgical consolidation. Unlike SD, PR reflects unequivocal tumor regression and therefore provides stronger evidence of biological sensitivity to systemic therapy. Unlike complete response, however, PR still implies the presence of radiographically visible residual disease, leaving a clear target for local eradication.[10,24,25]

This combination of demonstrated systemic sensitivity and persistent macroscopic tumor burden is what makes PR particularly relevant to consolidation surgery. In this setting, resection is not intended to replace systemic therapy, but to complement it: systemic treatment has already shown activity against occult disease, while surgery may remove residual viable tumor that remains anatomically resectable As discussed in Section 3.1, the currently available post-conversion evidence most consistently suggests a progression-related benefit of surgery in responder populations, and this signal appears most persuasive in cohorts enriched for PR.[10,16,25]

Thus, in patients with preserved liver function, technically resectable disease, and acceptable operative risk, PR after systemic therapy may represent the most defensible context in which surgical consolidation can be considered. Nevertheless, PR alone should not be viewed as an automatic indication for resection; durability of response, vascular involvement, anticipated margin status, future liver remnant, and patient preference should all remain integral to multidisciplinary decision-making.

Complete Response: The Unresolved Scenario

Radiographic complete response (CR) introduces a different and less settled question. Although CR reflects maximal imaging response, radiographic disappearance does not uniformly equate to pathological eradication, and residual viable tumor may still be present despite imaging-defined CR.[11,14,15]

At the same time, the incremental value of surgery in CR populations remains uncertain. In the watch-and-wait versus resection study, patients who achieved radiographic CR had broadly comparable overall survival between strategies, although progression-related outcomes favored surgery; among those who achieved clinical complete response, survival outcomes were similar between surgical and non-surgical management.[11] An earlier multicenter study reached a similar conclusion, suggesting that salvage hepatectomy may not be essential for at least some patients with clinical complete response, particularly when surgical risk is substantial.[26]

Taken together, these findings suggest that CR is prognostically favorable but does not automatically imply that surgery is required. In selected patients with durable CR, preserved liver function, and favorable baseline characteristics, continued systemic therapy or close surveillance may be reasonable alternatives. Conversely, surgery may still be considered when uncertainty regarding residual viable disease persists or when baseline high-risk features raise concern for relapse. At present, the available evidence does not support a uniform recommendation either for or against surgical consolidation in CR populations.

Integrating Response with Clinical Context

Across response strata, consolidation decisions should integrate at least three domains: (1) depth and durability of response, (2) technical feasibility together with sufficient hepatic reserve, and (3) baseline tumor biology and patient-specific operative risk. Resectability should therefore be viewed as a therapeutic inflection point rather than an automatic trigger for surgery. Importantly, the available evidence suggests that the benefit of surgery is most convincing in biologically sensitive but residually measurable disease, whereas its value is less certain in imaging-defined complete response and absent in some biologically unfavorable SD subsets.[10–13,24,26]

This framework is intended to support multidisciplinary decision-making rather than define a rigid algorithm. Given that much of the current evidence remains retrospective and vulnerable to selection bias, individualized interpretation remains essential until more mature randomized data become available.[13,25] The proposed response-guided framework is illustrated in Figure 1.

Beyond Radiographic Response: Pathologic Depth and Predictive Enrichment

The preceding sections suggest that surgical consolidation may confer meaningful benefit in selected patients after conversion. However, reliance on categorical radiographic response alone is insufficient to determine which patients are most likely to benefit from surgery. If surgical advantage is concentrated in biologically favorable subsets, more precise indicators of residual disease and relapse risk are required.

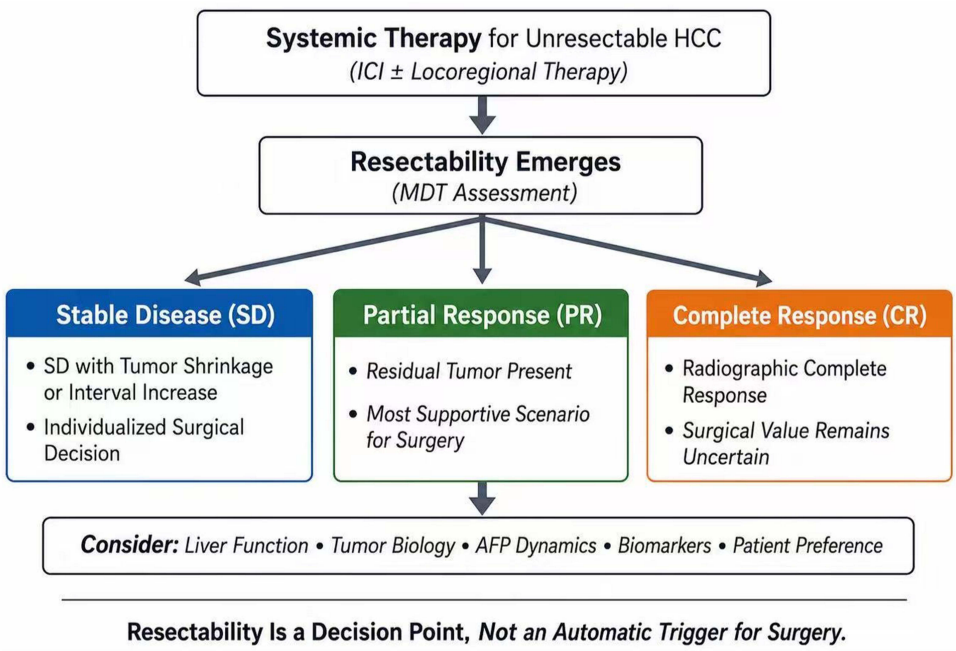

Figure 1 Response-Guided Consolidation Framework After Systemic Therapy–Induced Resectability in HCC.

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Pathologic Response and the Limits of Imaging

Across post-conversion surgical cohorts in HCC, pathologic response—particularly pathologic complete response (pCR)—has been consistently associated with favorable recurrence-free and overall survival. Patients achieving pCR demonstrate substantially lower recurrence risk than those with residual viable tumor.[27–29]

Importantly, radiographic complete response does not reliably predict pathological complete response. Residual viable tumor has been documented in a proportion of patients classified as imaging-defined CR, whereas extensive pathological necrosis may also be observed in some patients categorized as PR.[30,31] This discordance highlights a central limitation of imaging-based assessment: radiographic clearance does not necessarily indicate biological eradication. Similar observations have also been reported across HCC[27–29] and other solid tumors treated with modern systemic therapy, where pathological response may correlate more closely with long-term outcome than radiographic response alone.[32] At present, pCR remains a postoperative endpoint rather than a preoperative decision tool. Its principal value lies in underscoring the importance of biological response depth, rather than serving as a sufficiently accurate marker for surgical selection before resection.

Predictive Enrichment Beyond RECIST

If surgical benefit depends on residual viable disease and relapse risk, post-conversion decision-making should extend beyond RECIST-based (Response Evaluation Criteria in Solid Tumors) categorization alone. Several complementary strategies are under investigation, although none is currently validated for routine surgical selection in this setting.

Advanced imaging approaches, including diffusion-weighted MRI parameters and CT-based radiomic models, have been explored as surrogates of tumor viability, but standardized thresholds and prospective validation remain limited.[33]

Serum biomarker kinetics, particularly dynamic changes in alpha-fetoprotein (AFP), have also been associated with treatment response and pathologic regression; however, specificity remains insufficient for independent surgical decision-making.[15,31]

Molecular indicators, such as circulating tumor DNA and minimal residual disease assays, are increasingly being studied as markers of residual tumor burden. Early data in HCC and other malignancies suggest prognostic relevance, but integration into routine post-conversion algorithms remains investigational.[34,35]

Integrated predictive models incorporating baseline tumor characteristics, response depth, and biomarker data are also emerging, yet most have been developed in upfront resection or exploratory cohorts rather than specifically in post-conversion populations.[30,33,36]

At present, no single modality reliably predicts pathological clearance or definitively identifies patients most likely to derive incremental benefit from surgery after conversion.

Clinical Perspective

Given the limitations of imaging-based assessment and the prognostic significance of pathological response, post-conversion decision-making should move toward biologically informed risk stratification rather than reliance on categorical response alone. Prospective studies embedding translational biomarkers and standardized pathological endpoints are essential to validate predictive enrichment strategies in this setting.

Future Directions and Conclusions

The increasing frequency with which resectability emerges after systemic therapy marks a meaningful transition in the management of hepatocellular carcinoma. What was once a binary classification of resectable versus unresectable disease has evolved into a dynamic continuum shaped by treatment response. This evolution has created a new clinical decision point for which evidence-based guidance remains incomplete.

Current data suggest that surgical consolidation may provide meaningful benefit in selected responders, particularly those with biologically sensitive but residually measurable disease. However, the evidence base remains dominated by retrospective studies, despite the recent emergence of randomized data in selected populations.[10,11,13] Response definitions remain heterogeneous, and robust validation across predefined response strata is still limited. Accordingly, current

observations should not be interpreted as establishing a universal standard of care, and individualized multidisciplinary decision-making remains essential.

Future research should address three priorities. First, prospective trials specifically comparing surgical consolidation with continued systemic therapy across predefined response categories are needed. Second, standardized pathological reporting, including harmonized definitions of pCR and major pathological response, should be incorporated into post-conversion studies to improve correlation between radiographic and biological response. Third, translational integration is critical. Biomarkers capable of estimating residual viable disease, such as molecular minimal residual disease assessment or validated imaging surrogates, may enable more rational predictive enrichment.

Equally important is recognition of the multidisciplinary nature of these decisions. Hepatic reserve, operative risk, baseline tumor burden, and patient preference must remain integral components of management. Resectability should therefore be viewed not as an automatic trigger for surgery, but as a decision node requiring synthesis of anatomical feasibility and biological risk.

In summary, the post-conversion setting in HCC represents an emerging and clinically relevant domain in which treatment paradigms are still being defined. The response-guided framework proposed here should be regarded as a conceptual and pragmatic interim model to support clinical reasoning, rather than an established clinical standard. Prospective validation, randomized evidence, and biomarker-guided patient selection will determine whether surgical consolidation ultimately becomes a selective standard or remains an individualized strategy in the systemic therapy era.

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Disclosure

The authors report no conflicts of interest in this work.

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