Editorial

DOI: 10.5582/ddt.2026.01068

The conversion window in hepatocellular carcinoma: When resectability alone is not an indication for surgery

Weiping Zhu[1,2], Lu Wang[1,2], Wei Tang[3,*]

[1] Department of Hepatic Surgery, Fudan University Shanghai Cancer Center, Shanghai Medical College, Fudan University, Shanghai, China;
[2] Department of Oncology, Shanghai Medical College, Fudan University, Shanghai, China;
[3] National Center for Global Health and Medicine, Japan Institute for Health Security, Tokyo, Japan.

SUMMARY: Effective systemic therapy has expanded the possibility of resection in hepatocellular carcinoma, while making its timing more uncertain. Technical feasibility alone cannot establish whether surgery adds value to an effective treatment sequence. In this context, the conversion window can be understood as a patient-specific interval in which achievable tumor clearance, preserved hepatic and systemic reserve, and sufficient evidence of disease control are considered together. These factors should be distinguished from the multidisciplinary team's overall determination of whether surgery is likely to provide additional benefit. Evidence from a randomized study supports consolidation in selected patients but does not define an optimal date for surgery. Retrospective associations between treatment duration and pathological response remain vulnerable to selection bias and cannot justify universal timing thresholds. Serial assessment should incorporate remnant liver function, treatment toxicity, drug interruption, uncertainty regarding residual disease, and patient preferences. Future trials and prospective registries should evaluate explicit timing strategies from the point of initial surgical eligibility, including patients who subsequently become ineligible, using survival, safety, and quality-of-life outcomes to inform individualized decisions.

Keywords: immunotherapy, hepatic reserve, treatment sequencing, pathological response, shared decision-making

Modern systemic therapy has made curative-intent resection conceivable for patients with hepatocellular carcinoma (HCC) that was previously considered unsuitable for surgery. Atezolizumab plus bevacizumab, tremelimumab plus durvalumab, and nivolumab plus ipilimumab have expanded effective treatment options, although pivotal trials of those regimens did not establish when responding patients should undergo hepatectomy (*1-3*). Recent reviews have described this changing surgical landscape (*4,5*). Its central difficulty is increasingly temporal: once resection becomes feasible, should effective therapy be interrupted, continued to gauge disease behavior, or followed by another local strategy? Answering this question requires evidence of benefit from a treatment sequence, beyond evidence that surgery can be completed.

Terminological progress provides a foundation. Japanese oncological resectability criteria distinguish resectable and borderline categories after technical and functional feasibility have been considered (*6*). The Japan Liver Cancer Association subsequently distinguished functional from oncological conversion (*7*), while the European Association for the Study of the Liver (EASL) guidance and the Barcelona Clinic Liver Cancer (BCLC) 2026 update support a multidisciplinary assessment incorporating liver function, tumor characteristics, and patient priorities (*8,9*). These frameworks clarify eligibility but do not specify an optimal date for surgery for every patient. Resectability describes whether microscopically margin-negative (R0) surgery can be performed with adequate remnant function; an indication requires judging whether that surgery offers sufficient additional benefit over the available alternatives. These judgments should remain distinguishable throughout treatment.

The evidence now extends beyond retrospective enthusiasm. A systematic review of 38 studies involving 4,042 patients documented substantial variation in conversion rates across treatment strategies (*10*), and a multicenter hepatic arterial infusion chemotherapy (HAIC)-based cohort associated preoperative response with favorable postoperative outcomes (*11*). Neither finding isolates the contribution of resection. Zhao and colleagues' quantitative bias analysis rated the comparative evidence as having very low certainty and they indicated its vulnerability to surgical-eligibility confounding and time-related bias (*12*). Patients who are eligible for surgery have already survived induction, retained hepatic reserve, and avoided disqualifying progression; these advantages cannot automatically be

credited to surgery.

TALENTOP materially advances this discussion (*13*). Following induction atezolizumab plus bevacizumab, 201 of 489 enrolled patients were randomized to resection followed by systemic therapy or maintenance treatment. Median time to treatment failure was 20.4 versus 11.8 months (hazard ratio: 0.60; 95% confidence interval: 0.39-0.91). This supports a treatment strategy that includes surgery for a selected population, rather than another comparison between responders who underwent surgery and unselected nonsurgical patients. Nevertheless, the trial involved locally advanced disease with macrovascular invasion and no extrahepatic spread; overall survival remained immature, and severe treatment-related toxicity was more frequent with the surgical strategy. The trial compared treatment strategies at a selected post-induction decision-making point, not alternative dates for surgery. It therefore strengthens the case for appropriate consolidation while leaving the timing question open.

Building on response-guided consolidation proposals (*14*), the conversion window may be viewed as a patient-specific interval during which R0 resection is feasible, hepatic and systemic reserve are adequate, and observed disease control supports consideration of surgery, subject to comparison with continued treatment and other options. This is a proposed decision-making framework, not a validated score or a claim that every responder benefits from resection. Crucially, such an interval can exist without an established surgical indication: the expected incremental benefit must still justify operative morbidity, interruption of systemic control, and the patient's recovery burden. Nor must every patient pass through such an interval.

Time contributes information, but elapsed time alone does not establish favorable biology. Sustained control without new lesions may increase confidence that surgery is reasonable, whereas early shrinkage can coexist with occult dissemination. Conversely, a requirement for prolonged response could exclude patients whose anatomy and disease distribution already justify intervention. TALENTOP eligibility included partial response or stable disease after induction, underscoring the contention that objective shrinkage should not become an obligatory surgical gate (*13*). The useful question is what another treatment interval is expected to clarify or improve, and whether that information is worth the risk of becoming ineligible. Waiting without an explicit purpose or reassessment date is difficult to defend. Apparent stability also reflects the sensitivity of surveillance and the timing of scans. It offers probabilistic reassurance rather than a biological certificate, and prolonged observation may select favorable patients without improving any individual patient's outcome. This distinction matters when clinicians attribute success to the duration of induction itself.

Figure 1 separates three inputs for this judgment: technical feasibility, confidence in disease control, and hepatic and systemic reserve. Surgical opportunity is

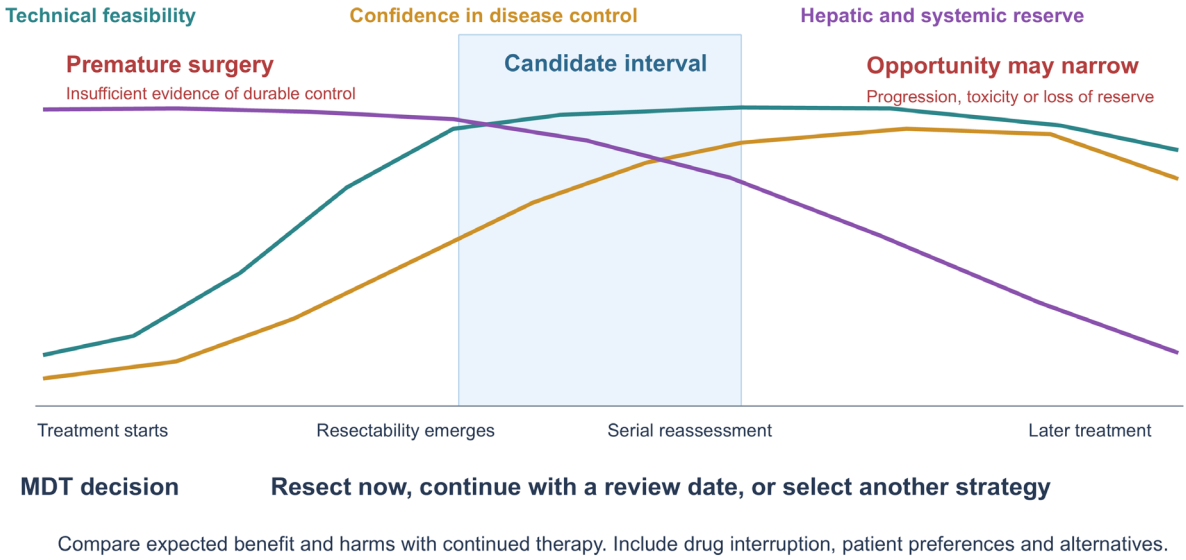


Figure 1. The conversion window in hepatocellular carcinoma. The schematic separates technical feasibility (teal), confidence in disease control (ochre), and hepatic and systemic reserve (purple) as inputs for a serial multidisciplinary team (MDT) assessment. The shaded candidate interval illustrates when these conditions may prompt consideration of resection; it does not itself establish an indication. The MDT compares expected surgical benefit and harm to continued treatment or alternative strategies, incorporating drug interruption and patient preferences. Premature intervention may not allow sufficient biological assessment, whereas progression, toxicity, or loss of reserve may narrow subsequent opportunities. Curves are qualitative illustrations, have no shared numerical scale, and do not represent patient data, validated thresholds, or a proven optimum. Reserve may remain stable or recover, and all trajectories depend on the patient and regimen. The framework is intended for prospective evaluation rather than prescription of a universal treatment duration.

the resulting assessment, rather than a fourth biological property. The schematic deliberately avoids numerical thresholds or a mathematically defined intersection. Technical feasibility may improve before disease behavior becomes sufficiently informative, while reserve may deteriorate with toxicity; however, reserve can also remain stable or improve after tumor control, antiviral treatment, or rehabilitation. Confidence may fall when new lesions appear. These trajectories are hypotheses for serial observation, not universal natural histories. Their paths should be expected to differ across HAIC, transarterial or radiation-based strategies, and systemic regimens (*5,15*).

An operational assessment should document what has changed since the previous multidisciplinary team (MDT) review. Imaging should address the distribution of viable disease, macrovascular involvement, new lesions, and the specific resection required, rather than tumor diameter alone. Response Evaluation Criteria in Solid Tumors (RECIST) and modified RECIST (mRECIST) findings should be interpreted alongside alpha-fetoprotein and des-gamma-carboxy prothrombin trends when informative; marker normalization is neither universally available nor proof of eradication. Child-Pugh status, albumin-bilirubin measures, portal hypertension, and future liver remnant volume and function should be reassessed with respect to the planned surgery, with indocyanine green testing where locally established (*8,15*). Frailty, nutritional status, treatment toxicity, and recovery expectations complete the assessment. A smaller tumor does not compensate for an unsafe remnant. The assessment should also retain the original reason for unresectability because improvement in tumor distribution, insufficient remnant function, and an unfavorable oncological profile represent different clinical problems. Patients initially eligible for resection who receive neoadjuvant therapy should not be pooled indiscriminately with those undergoing conversion. Otherwise, apparently similar treatment durations can describe fundamentally different decisions.

Background liver disease modifies these decisions through measured functional consequences, not through a geographical label. Viral suppression, cirrhosis severity, metabolic comorbidity, and prior liver-directed injury may alter the capacity to continue treatment or recover from hepatectomy (*8*). A worsening albumin-bilirubin trajectory should prompt investigation and reconsideration, but a single grade cannot define a universal closing date. Likewise, repeated local treatment should not be assumed to be inevitably harmful or automatically helpful. The MDT should explain whether the next intervention is intended to improve clearance, preserve parenchyma, or provide further evidence of disease control, and it should specify the finding that would trigger surgery or a change in strategy.

Perioperative drug management creates an additional interval within broader oncological decision-making. Bevacizumab prescribing information requires withholding treatment for at least 28 days before elective surgery and not resuming it for at least 28 days after major surgery and until adequate wound healing (*16*). This minimum is not a universal hepatectomy schedule; the extent of surgery, local protocol, and individual recovery may justify a longer interruption. Immune-related hepatitis and other unresolved toxicities require assessment rather than reliance on drug half-life alone (*15*). The MDT must anticipate disease behavior during treatment interruption and recovery, instead of declaring a window open on imaging and only addressing perioperative feasibility afterwards.

Recent timing data are useful precisely when their limitations remain evident. In a recent multicenter retrospective study, Li and colleagues analyzed 257 patients who underwent resection, stratified by treatment-to-surgery intervals of less than 12 weeks, 12-24 weeks, or more than 24 weeks (*17*). Major pathological response, defined using a study-derived residual viable tumor threshold of 15%, occurred in 41.3%, 66.2%, and 73.0% of patients, respectively. Although the authors favored 12-24 weeks, recurrence-free survival did not differ significantly across groups, and longer treatment did not clearly increase severe complications. These findings justify prospective evaluation; they neither prove a fixed optimum nor establish that later surgery is intrinsically unsafe. Patients who never survived to resection are particularly important to answering the question but were absent from this comparison.

Pathological response can support prognostic research without becoming a retrospective justification for a prospective decision. Another conversion cohort used a different major-response definition of at least 90% nonviable tumor, illustrating the need for pathological standardization (*18*). Both assessments require tissue obtained after surgery. Associations between pathology and outcome therefore cannot establish that delaying surgery to increase pathological response improves survival. Preoperative imaging and marker trajectories need to be validated with respect to clinically meaningful outcomes, including whether they identify a differential benefit from surgery. Circulating tumor DNA or tissue immune features may eventually add information, but they should not be compulsory gatekeepers while their value in decision-making remains unproven.

Clinical complete response presents a different uncertainty. Durable complete responses have been described after immunotherapy-based treatment (*19*), but absence of radiological activity cannot guarantee the absence of a viable tumor. In Aoki and colleagues' proof-of-concept study, only three of the 11 resected patients with a modified clinical complete response achieved a pathological complete response (*20*). Proposed "drug-off" (drug discontinuation) criteria included prior curative conversion and sustained marker normalization; they cannot be generalized into evidence that surgery may be

safely foregone after systemic therapy alone. Continued therapy, selected local consolidation, or structured observation may each be discussed, but a routine watch-and-wait policy lacks adequate comparative validation. The decision should reflect residual-disease uncertainty, the operative burden, and the patient's willingness to accept surveillance and possible retreatment.

These considerations make the MDT's conclusion more specific than "resectable." At each meaningful reassessment, it should record whether to proceed, continue treatment with a review date and explicit trigger, or pursue an alternative. The record should distinguish anatomical feasibility from the estimated benefit of acting now, identify the main uncertainty, and explain whether delay could resolve it. Patients should understand the plausible gains, the possibility of recurrence despite an R0 resection, the recovery period, and the potential need for subsequent therapy. Some will prioritize maximal local clearance; others will place greater weight on avoiding major surgery while control persists. Neither preference can be inferred from radiological response.

The next research step is to test dynamic strategies regarding the attainment of surgical eligibility. TALENTOP demonstrates the feasibility of randomization after induction, but it does not resolve early versus deferred resection across different regimens (*13*). Future trials should prespecify eligibility, induction exposure, reassessment intervals, permissible treatment interruptions, and the response or safety findings that trigger surgery. Overall survival, event-free outcomes, hepatic decompensation, perioperative morbidity, quality of life, and time without treatment would clarify the benefits and costs of the complete strategy. Pathological response should continue to be considered without displacing outcomes that matter to patients. A high resection rate alone cannot establish that a strategy is preferable. Comparative studies should also distinguish limited resections from major hepatectomy, since the same degree of tumor control can impose different operative costs. This would help determine whether preservation of future treatment options contributes to the value of consolidation.

Where randomization is impractical, prospective registries should identify all patients starting conversion treatment and a nested cohort at initial surgical eligibility. Treatment-to-resectability and resectability-to-surgery intervals should be reported separately, including missed opportunities and reasons for deferral. Target-trial emulation requires aligned eligibility, treatment assignment, and follow-up, with appropriate handling of treatment changes and time-varying confounding (*21*). Modeling surgery as a time-dependent exposure can address immortal time but cannot alone remove differences in evolving eligibility. The endpoint of interest is the outcome of a specified decision-making strategy among comparable patients, rather than survival conditional on eventually undergoing hepatectomy.

Dynamic resectability becomes clinically useful when it leads to a documented, revisable indication. The conversion window should make the tension between further biological information and ensuring safe surgery explicit, while avoiding the assumption that either immediate surgery or maximal response is invariably desirable. Modern therapy has expanded what surgeons can remove; evidence from a randomized study has now begun to clarify when adding resection can improve a treatment strategy. The remaining task is to determine for whom acting now offers more value than later reassessment, and how that judgment changes as tumor control and liver reserve evolve. Treating this as a prospective question will make the conversion window testable and help patients receive surgery when it is most likely to be of benefit.

Funding: None.

Conflict of Interest: The authors have no conflicts of interest to disclose.

References

1. Finn RS, Qin S, Ikeda M, *et al*. Atezolizumab plus bevacizumab in unresectable hepatocellular carcinoma. N Engl J Med. 2020; 382:1894-1905.
2. Abou-Alfa GK, Lau G, Kudo M, *et al*. Tremelimumab plus durvalumab in unresectable hepatocellular carcinoma. NEJM Evid. 2022; 1:EVIDoa2100070.
3. Yau T, Galle PR, Decaens T, *et al*. Nivolumab plus ipilimumab versus lenvatinib or sorafenib as first-line treatment for unresectable hepatocellular carcinoma (CheckMate 9DW): An open-label, randomised, phase 3 trial. Lancet. 2025; 405:1851-1864.
4. Kokudo N, Kokudo T, Song P, Tang W. Role of liver resection in the era of advanced systemic therapy for hepatocellular carcinoma. Glob Health Med. 2024; 6:170-173.
5. Hakoda H, Ichida A, Hasegawa K. Advances in systemic therapy leading to conversion surgery for advanced hepatocellular carcinoma. Biosci Trends. 2024; 18:525-534.
6. Akahoshi K, Shindoh J, Tanabe M, *et al.* Oncological resectability criteria for hepatocellular carcinoma in the era of novel systemic therapies: The Japan Liver Cancer Association and Japanese Society of Hepato-Biliary-Pancreatic Surgery Expert Consensus Statement 2023. Liver Cancer. 2024; 13:579-589.
7. Ichida A, Tateishi R, Hatano E, Taketomi A, Tanabe M, Nouso K, Minami Y, Murakami T, Shimada M, Hasegawa K. Definition of conversion therapy and neoadjuvant therapy for hepatocellular carcinoma: A consensus guideline from the Japan Liver Cancer Association. Liver Cancer. 2026; doi:10.1159/000552928.
8. European Association for the Study of the Liver. EASL Clinical Practice Guidelines on the management of hepatocellular carcinoma. J Hepatol. 2025; 82:315-374.
9. Reig M, Sanduzzi-Zamparelli M, Forner A, *et al*. BCLC strategy for prognosis prediction and treatment

recommendations: The 2026 update. J Hepatol. 2026; 84:631-654.
10. Xu H, Zhang H, Li B, Chen K, Wei Y. Systemic conversion therapies for initially unresectable hepatocellular carcinoma: A systematic review and meta-analysis. BMC Cancer. 2024; 24:1008.
11. Deng M, Zhong C, Li D, Guan R, Lee C, Chen H, Qin W, Cai H, Guo R, Chen Z. Hepatic arterial infusion chemotherapy-based conversion hepatectomy in responders versus nonresponders with hepatocellular carcinoma: A multicenter cohort study. Int J Surg. 2025; 111:135-145.
12. Zhao W, Zhang X, Zhong A, Jiang C, Cui R, Yu X, Lin S. Conversion hepatectomy and survival in initially unresectable hepatocellular carcinoma: A systematic review and meta-analysis with quantitative bias analysis. World J Surg Oncol. 2026; doi:10.1186/s12957-026-04498-x.
13. Sun HC, Zhu XD, Shen F, *et al*. Liver resection after atezolizumab and bevacizumab versus maintenance therapy for locally advanced hepatocellular carcinoma (TALENTOP): A multicentre, open-label, randomised, phase 3 trial. Lancet. 2026; 408:699-710.
14. Cheng Y, Xie K. When resectability emerges after systemic therapy in hepatocellular carcinoma: A proposed response-guided consolidation framework. J Hepatocell Carcinoma. 2026; 13:613934.
15. Wang Z, Sun H, Zhou J, *et al*. Chinese expert consensus on conversion and perioperative therapy of primary liver cancer (2024 edition). Hepatobiliary Surg Nutr. 2026; 15:72.
16. Genentech, Inc. Avastin (bevacizumab) prescribing information. *https://www.gene.com/download/pdf/avastin_prescribing.pdf* (accessed September 9, 2026).
17. Li S, Li M, Zhu F, Qin Y, Tang W, Yao J, Chen J, Liu L, Liang Z, Wei H, He Y, Wang G, Zhang J, Xiang B. Optimal timing of surgery after conversion therapy for initially unresectable hepatocellular carcinoma: A multicenter study integrating major pathological response and treatment duration. Front Immunol. 2026; 17:1911781.
18. Zeng ZX, Wu JY, Wu JY, Zhang ZB, Wang K, Zhuang SW, Li B, Zhou JY, Lin ZT, Li SQ, Li YN, Fu YK, Yan ML. Prognostic value of pathological response for patients with unresectable hepatocellular carcinoma undergoing conversion surgery. Liver Cancer. 2024; 13:498-508.
19. Scheiner B, Kang B, Balcar L, *et al*. Outcome and management of patients with hepatocellular carcinoma who achieved a complete response to immunotherapy-based systemic therapy. Hepatology. 2025; 81:1714-1727.
20. Aoki T, Kudo M, Nishida N, *et al*. Proposal of discontinuation criteria of atezolizumab plus bevacizumab after curative conversion therapy for unresectable early-to-intermediate-stage hepatocellular carcinoma: A multicenter proof-of-concept study. J Gastroenterol. 2025; 60:738-753.
21. Hernán MA, Robins JM. Using big data to emulate a target trial when a randomized trial is not available. Am J Epidemiol. 2016; 183:758-764.

Received September 6, 2026; Accepted September 22, 2026.

**Address correspondence to:*
Wei Tang, National Center for Global Health and Medicine, Japan Institute for Health Security, 1-21-1 Toyama, Shinjuku-ku, Tokyo 162-8655, Japan.
E-mail: politang-tky@umin.ac.jp

Released online in J-STAGE as advance publication September 25, 2026.